European Union Risk Management Plan
DACOGEN® (decitabine)

Data lock point for current RMP	30 April 2023	Version number	4.1

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RMP Version Number: 4.1
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QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	4.1
Rationale for submitting an updated RMP (if applicable)	Implementation of PRAC conclusions from the last PSUR assessment report (EMEA/H/C/PSUSA/00009118/202305) approved on 11 January 2024.

Summary of significant changes in this RMP:	• Safety concerns
	The following missing information were removed from Part II Module SVII:
	  • Use in severe renal impairment
	  • Use in hepatic impairment
	  • Use in severe cardiac disease (eg, uncontrolled angina or severe congestive heart failure [NYHA III-IV])
	• Removal of TFUQ for Cardiac, Hepatic and Renal Impairment in Part VII Annex 4
	• Update of epidemiology text in Part II Module SI
	• Update of postauthorization exposure data in Part II Module SV
	• Conversion of RMP to current company RMP template
	• Edits throughout to align with the changes above

Other RMP Versions Under Evaluation:

RMP Version Number	**Submitted on**	**Procedure Number**
None	Not applicable	Not applicable

Details of the Currently Approved RMP:

Version number of last agreed RMP:	3.3

Approved within procedure	EMEA/H/C/002221/II/0033
Date of approval (Competent authority opinion date)	23 January 2019 (EC decision)

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	decitabine
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic and Immunomodulating Agents, Pyrimidine Analogues (L01BC08)
MAH	Janssen-Cilag International NV
Medicinal products to which the RMP refers	DACOGEN® (decitabine)
Invented name(s) in the EEA	DACOGEN
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class cytidine deoxynucleoside analogue
	Summary of mode of action Decitabine (5-Aza-2'-deoxycytidine) selectively inhibits DNA methyltransferases at low doses, resulting in gene promoter hypomethylation that can lead to re-expression of silenced genes that can inhibit cellular proliferation, induce differentiation, or induce apoptosis.
	Important information about its composition Not applicable.
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labelling and Package Leaflet
Indication(s) in the EEA	Current: DACOGEN is indicated for the treatment of adult patients with newly diagnosed de novo or secondary AML, according to the WHO classification, who are not candidates for standard induction chemotherapy.
Dosage in the EEA	Current: DACOGEN is administered at a dose of 20 mg/m^2 body surface area by intravenous infusion over 1 hour repeated daily for 5 consecutive days (ie, a total of 5 doses per treatment cycle). The total daily dose must not exceed 20 mg/m^2 and the total dose per treatment cycle must not exceed 100 mg/m^2. If a dose is missed, treatment should be resumed as soon as possible. The cycle should be repeated every 4 weeks depending on the patient's clinical response and observed toxicity. It is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial remission may take longer than 4 cycles to be obtained. Treatment may be continued as long as the patient shows response, continues to benefit or exhibits stable disease, ie, in the absence of overt progression.
Pharmaceutical form(s) and	Current:

strengths	Powder for concentrate for solution for infusion. Each vial contains 50 mg of decitabine. After aseptic reconstitution with 10 mL of water for injection, each mL of concentrate for solution for infusion contains 5 mg of decitabine.	
Is/will the product be subject to additional monitoring in the EU?	☐ **Yes**	☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication(s)

DACOGEN (decitabine) is indicated for the treatment of adult patients with newly diagnosed de novo or secondary AML, according to the WHO classification, who are not candidates for standard induction chemotherapy.

The DACOGEN SmPC provides information for healthcare professionals on how to use the medicinal product safely and effectively and serves as the reference safety information for DACOGEN.

AML

Incidence:

The incidence of AML in Europe has been estimated by the HAEMACARE Project, a European Cancer Registry based project funded by the European Commission. The crude rate of AML in Europe is estimated to be 3.62 per 100,000 persons, while the age-standardized rate is 2.92 per 100,000 persons (Sant 2010). In the UK, HMRN estimated the incidence rate of AML to be 4.2 per 100,000 for the years 2010-2019 (HMRN). Similar rates are reported in the WHO GLOBOCAN database. An estimated 59,375 persons are diagnosed with leukemia each year in the European Union (EU) (International Agency for Research on Cancer 2008). Given that approximately 30% of all leukemias are AML, it is estimated that there are approximately 17,812 cases diagnosed each year. In 2010, the estimated incidence of AML in the US was 12,330 cases (male, 6,590; female, 5,740) (American Cancer Society 2010), with an estimated incidence of 2.7 per 100,000 persons. Incidence increases greatly with age and after the age of 55 years it increases exponentially (Deschler 2006).

Geographic differences occur in AML, with the highest rates reported in Australia, the US, and Western Europe, and the lowest rates seen in Kuwait and India (Deschler 2006). Registry data indicate that 4.8% of AML cases may be acute promyelocytic leukemia, which predominantly affects young adults. Secondary (or therapy-related) AML accounts for 10% to 30% of all AML cases (Østgard 2015; Leone 1999).

Prevalence:

In the UK, the 10-year prevalence of AML was estimated to be 7.4 per 100,000 (HMRN). For the EU, the 5-year prevalence was 4.7 per 100,000 (Visser 2012). The prevalence of AML in 2020 in the US was approximately 73,168 (SEER 2023).

Demographics of the Population in the Authorized Indication Age, Sex, Racial and/or Ethnic Origin and Risk Factors for the Disease

Sex: Incidence has been found to be slightly higher in males than females in most countries. In the UK, the annual incidence in males has been estimated to be 4.9 per 100,000 and 3.4 per 100,000

in females (HMRN). Incidence rates in US males (4.6 per 100,000 males vs 3.0 per 100,000 females) are similar to the incidence rates reported for males in the UK (Deschler 2006).

Age: The incidence of AML increases significantly with age. According to delay-adjusted SEER incidence rates, in 2020 the incidence was 1.2 cases per 100,000 in persons aged <50 years, 5.0 per 100,000 in those 50 to 64 years, and 19.4 per 100,000 in those 65 years and older (SEER 2023). A trial of the Southwest Oncology Group reported that the proportion of patients with favorable cytogenetics decreased dramatically with increasing age, from 17% in those younger than 56 years to 4% among those older than 75 years (Appelbaum 2006). The median age at presentation for patients with AML is 69 years (SEER 2023).

Race: The incidence of AML has been found to be higher among white non-Hispanics than black non-Hispanics and Hispanics, particularly among the elderly (SEER 2023). Based on SEER data, the incidence of AML per 100,000 persons by age and race is as follows:

Age (years)	Non-Hispanic white	Non-Hispanic black	Hispanic
0-14	0.65	0.73	0.82
15-39	1.12	1.21	1.21
40-64	3.79	3.67	3.21
65-74	15.46	12.41	10.75
75+	27.49	18.77	19.19

Risk factors: Risk factors associated with AML are increasing age, male gender, previous cancer treatment involving radiation or chemotherapy, exposure to high levels of radiation, exposure to benzene, smoking, other blood disorders, and genetic disorders such as Down Syndrome (Mayo Clinic 2017).

Main Existing Treatment Options:

According to guidelines from the European LeukemiaNet (Döhner 2022), the ESMO (Heuser 2020), the British Society for Haematology (Dennis 2022), and the AML guidelines from the US NCCN (NCCN 2023), patient performance status, in addition to adverse features (eg, de novo AML without favorable cytogenetics or molecular markers; t-AML; antecedent hematologic disorder) and comorbid conditions, should be used to select treatment options, for patients >60 years old.

Standard therapy for patients with AML, aiming to attain a complete remission and improve survival, is combination induction chemotherapy, usually with an anthracycline (such as daunorubicin; 60 mg/m^2) for 3 days and cytarabine (100 to 200 mg/m^2 intravenous) for 7 days (3+7 chemotherapy). Alternatively, a dual-drug liposomal formulation that encapsulates cytarabine/daunorubicin (VYXEOS LIPOSOMAL) may be an alternative for 3+7 chemotherapy (Döhner 2022). Vyxeos liposomal is indicated in the EU for the treatment of adults with newly diagnosed, t-AML or AML with myelodysplasia-related changes (Vyxeos liposomal SmPC 2023). Intensive induction chemotherapy does not benefit older patients with AML. Hence, although younger AML patients may be able to tolerate induction chemotherapy, the potential risks in older patients outweigh the benefits.

For patients aged <60 years, there was improved survival for patients with newly diagnosed FLT3-mutation-positive AML when midostaurin 50 mg every 12 hours on Days 8 to 21 was added to standard chemotherapy as part of frontline treatment. Patients who received midostaurin with standard induction and consolidation therapy experienced a significant improvement in overall survival compared with those on the placebo arm (Döhner 2022; NCCN 2023).

If after initial therapy there is significant residual disease without a hypocellular marrow, recommended treatment includes: (1) cytarabine 1.5 to 3 g/m^2 every 12 hours for 6 days, (2) standard-dose cytarabine with idarubicin or daunorubicin, or (3) standard-dose cytarabine with daunorubicin and midostaurin. If there is significant cytoreduction with low residual blasts, standard-dose cytarabine with idarubicin or daunorubicin or standard-dose cytarabine with daunorubicin and midostaurin is recommended (NCCN 2023). For patients aged <60 years, additional post-remission therapy (ie, consolidation) may be needed to reduce the residual abnormal cells to a level that can be contained by immune surveillance and is based on risk status defined by cytogenetics and molecular abnormalities (NCCN 2023).

For patients 60 years or older, with unfavorable cytogenetic/molecular markers or antecedent hematologic disorder/t-AML, guidelines recommend lower-intensity therapy (azacitidine 75 mg/m^2 SC/intravenous on Days 1 to 7 or decitabine 20 mg/m^2 intravenous on Days 1 to 5) plus venetoclax dose ramp-up 100 mg Day 1, 200 mg Day 2, 400 mg orally once daily Days 3 to 28 (NCCN 2023; Döhner 2022). For those patients who are not candidates for intensive remission induction therapy, palliative therapy with hydroxyurea with supportive care measures are recommended for white blood cell count control (NCCN 2023; Döhner 2022).

Azacitidine has been approved for use in adult patients who are not eligible for hematopoietic stem cell transplantation with AML with 20%-30% blasts and multi-lineage dysplasia, according to WHO classification, or with AML with >30% marrow blasts according to the WHO classification (Vidaza SmPC 2023). Venetoclax (Venclyxto®) in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy (Venclyxto SmPC 2023).

Older patients with AML represent a difficult to treat population with an increased incidence of comorbidities, poor prognostic factors, and short survival time if left untreated. There is a continuing need to develop more effective treatment strategies for elderly patients (Sekeres 2020).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

The most common symptoms of AML include fatigue, shortness of breath, bruising or bleeding easily, fever, and infections (Mayo Clinic, 2017). AML can sometimes spread to other parts of the body including the lymph nodes, liver, and spleen.

Untreated AML is uniformly fatal, although treatment with supportive care alone can be associated with a median survival of 11 to 20 weeks (Deschler 2006). Treatment-related mortality has been decreased over time from an estimated rate of 13% to 18% in the 1990s to 3% to 4% in 2006-2009

(Othus 2014). Age has a modest effect on mortality in patients with an excellent performance status; however, a dramatic effect has been observed among those with a poor performance status. In a trial of the Southwest Oncology Group, 82% of patients older than 75 years with a performance status of 3 died within 30 days of induction (Appelbaum 2006). An assessment of 3,439 elderly persons with AML reported an overall median survival of 2.4 months. Fewer than 7% of patients were alive at 2 years of follow-up. Median survival ranged from 3.9 months among those who are 65 to 74 years of age to 1.4 months among those who are 85 years of age or older (Lang 2005). In Europe, the 5-year relative survival rate for all ages has been reported as 17.0% (95% CI: 16.1%-18.0%) and 47.4% (44.6%-50.1%) for ages 15-49; 15.4% (13.9%-17.0%) for ages 50-69 and 2.7% for ages 70+ (Maynadié 2013).

Important Co-morbidities:

Important comorbidities in the patients with AML include myelosuppression, infection, cardiac disorders, diabetes mellitus, and respiratory disorders.

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The nonclinical safety profile of decitabine has been characterized in safety pharmacology studies, genotoxicity studies, and single- and repeat-dose toxicity studies in various species. The nonclinical development adhered to the regulatory guidance for anticancer drugs (CPMP/SWP/997/96) and the regulatory guidance for nonclinical development of drugs (ICH M3). The program is also in agreement with the current ICH S9 guideline.

In in vitro studies (the ion channel encoded by the human ether-a-go-go related gene channel testing) and in vivo safety pharmacology studies (rodents and conscious monkeys after intravenous administration), decitabine exposure levels were markedly above target therapeutic exposure in humans and had no relevant effect on the CNS, or cardiovascular and respiratory systems.

In all nonclinical species, similar toxicological profiles were observed characterized by myelosuppression (neutropenia, thrombocytopenia, and anemia) leading to fatal opportunistic infections in rabbits and dogs, as well as testicular degeneration in male dogs. Gastrointestinal toxicity was mostly seen at lethal dose levels or levels close to the lethal dose. Full reversibility was observed, with the exception of testicular alterations. Target organs of toxicity in animals have been predictive of human toxicity. For anticancer products, quantitative comparison of animal and human data is considered to have been appropriately achieved by comparing plasma exposure (area under the curve) at the animal's MTD vs exposure in patients. The exposure ratio (animal:man) for decitabine is slightly higher than 1 in all species. This is considered acceptable for a compound for treatment of adult patients with AML with limited life-expectancy.

Key Safety Findings	Relevance to Human Usage
Toxicity	
Repeat-dose toxicity	
In all nonclinical species, similar toxicological profiles were observed characterized by myelosuppression (neutropenia, thrombocytopenia, and anemia).	The most common toxicities of DACOGEN treatment are myelosuppression (neutropenia, anemia, and thrombocytopenia) and consequences of myelosuppression (infection, fever, fatigue, hemorrhage) and can be managed as part of routine practice in hematology clinics.
Reproductive toxicity	
Reports in the published literature indicate that decitabine has the potential to cause reproductive toxicity. Testicular seminiferous tubule degeneration was observed upon microscopic examination of primary and secondary sex organs in chronic animal toxicity studies. Additionally, DNA methylation is known to play an important role in spermatogenesis.	Decitabine has potential to affect male fertility. DNA methylation is known to play an important role in spermatogenesis. Considering the anticipated patient population (median age of patients with AML is 69 years) and the life expectancy of this population, this is considered of limited clinical relevance.

Key Safety Findings	Relevance to Human Usage
Teratogenicity	
Teratogenic effects (skeletal malformations) have been observed in 2 rodent species; these effects are not unexpected based on decitabine's mechanism of action and the crucial role of DNA methylation in embryogenesis. No placental transfer or milk excretion studies have been conducted with decitabine.	Methylation is an important process for embryogenesis as reflected by the effects of decitabine in nonclinical teratogenicity studies. Considering the anticipated patient population (median age of patients with AML is 69 years) and the life expectancy of the older AML population, this is considered of limited clinical relevance.
Genotoxicity	
Decitabine was genotoxic in multiple in vitro and in vivo models, as expected from its interaction with DNA.	Genotoxins may be mutagenic or carcinogenic. Considering the anticipated patient population (median age of patients with AML is 69 years), and their limited life expectancy, the relevance of genotoxicity is considered limited.
Carcinogenicity	
The carcinogenic potential of decitabine was evaluated in vivo in rats and mice, following mechanistic protocols. These mechanistic studies showed that decitabine might have divergent effects on the carcinogenicity process depending on the assay used.	The specific exclusion of formal 2-year GLP mice and rat carcinogenicity studies complied with regulatory guidance and standard practice for the assessment of an anticancer agent. Decitabine is considered as a potential carcinogen based on mechanistic rodent studies. Considering the anticipated patient population (median age of patients with AML is 69 years) and the life expectancy of the older AML population, this is considered of limited clinical relevance. Additionally, there were no secondary malignancies noted in clinical trials.
Acute toxicity	
The acute toxicity of decitabine in animals is mainly related to myelosuppression. Increasing the duration of the infusion reduced the lethal dose. Mortality was observed in mice after intravenous bolus injection at ≥225-450 mg/m^2 (75-150 mg/kg) and after 12-h intravenous infusion at ≥54 mg/m^2 (18 mg/kg), and in dogs after 12-h intravenous infusion at ≥100 mg/m^2 (5 mg/kg).	Patients are currently receiving doses far below the MTD. This was determined to be in excess of 2000 mg/m^2 per cycle, and current dosing is at 100 mg/m^2 per cycle, ie, 20 times lower. So the margin between the proposed dose and potentially lethal dose is very wide.

Key Safety Findings	Relevance to Human Usage
Mechanisms for drug interactions	
The initial enzyme in the activation of deoxycytidine nucleosides is deoxycytidine kinase. The major pathway for metabolism of decitabine is deamination by cytidine deaminase, so there is a theoretical potential for interaction with other agents, such as cytarabine, that compete for the same enzyme.	There are no known inhibitors of cytidine deaminase expected to be used in the target patient population. The currently available nonclinical data are inconclusive regarding the nature and potential for an interaction with other drugs (agents metabolized by deoxycytidine kinase and/or cytidine deaminase) and DACOGEN. DACOGEN is intended to be used as monotherapy in patients with newly diagnosed AML; therefore, the relevance of the theoretical interaction with co-administered agents, such as cytarabine, is considered limited.

Summary of Nonclinical Safety Concerns

None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

DACOGEN was approved in the US for the treatment of patients with MDS based upon the results of a pivotal Phase 3 trial, D-0007, which compared decitabine with supportive care. The decitabine regimen used in this and other supportive trials (Trials EORTC-06011, DACO-020, and ID03-0180) was 15 mg/m^2 decitabine administered as a 3-hour intravenous infusion every 8 hours for 3 consecutive days every 6 weeks (3-day regimen) or a 5-day regimen of 20 mg/m^2 decitabine administered as a 1-hour intravenous infusion daily for 5 consecutive days every 4 weeks. Using these data, decitabine was subsequently approved in more than 35 other countries.

The pivotal trial for decitabine treatment of patients with AML is DACO-016, a Phase 3, randomized, multicenter trial of decitabine compared with Treatment Choice consisting of the subject's choice (with physician's advice) of the current standard-care options of low-dose cytarabine or supportive care. These results are supported by a single-arm, Phase 2 trial, DACO-017, in patients with AML.

MDS and AML can be considered a continuum of the same myeloid malignancy. For this reason, and because of similar disease presentation, complications, and causes of death, clinical trials of decitabine in patients with MDS and AML are used for the evaluation of safety. Furthermore, extensive postmarketing experience in MDS has been included to provide a robust assessment of safety in subjects treated with DACOGEN.

SIII.2. Clinical Trial Exposure

Exposure in Randomized Clinical Trials

The randomized clinical trials population includes 3 trials:

- Trial DACO-016
- Trial MDS EORTC-06011
- Trial MDS D-0007

In AML Trial DACO-016, subjects randomly assigned to the DACOGEN arm received DACOGEN 20 mg/m^2 given as a 1-hour intravenous infusion once daily for 5 consecutive days every 4 weeks (n=238) and subjects randomly assigned to the comparator arm of the trial received either supportive care (n=29, safety population) or 20 mg/m^2 cytarabine given SC once daily for 10 consecutive days every 4 weeks (n=208, safety population).

In MDS Trial EORTC-06011, subjects received either DACOGEN (15 mg/m^2 as a 4-hour infusion every 8 hours for 3 days every 6 weeks) plus supportive care (n=114) or supportive care only (n=114).

In MDS Trial D-0007, subjects received either DACOGEN (15 mg/m^2 as a 3-hour intravenous infusion every 8 hours for 3 days every 6 weeks) plus supportive care (n=83) or supportive care only (n=81).

Exposure to DACOGEN in the randomized clinical trials population is summarized in Tables SIII.1 through SIII.10 by duration, by age and gender, by dose, and by variable stratifications relevant to the product (eg, ethnic origin and renal impairment at baseline).

Table SIII.1 Exposure BY DURATION (by Indication); (The Randomised, Blinded Clinical Trials Population)

Indication: AML	Patients	Person-Months
Duration of Exposure	(N=238)	
< 1 Months	52	49.5
1 to < 3 Months	45	100.9
3 to < 6 Months	44	195.9
6 to < 9 Months	29	219.2
9 to < 12 Months	19	197.3
12 to < 24 Months	35	621.3
24 to < 48 Months[a]	14	384.1
Total person-months	238	1768.3
.		
Indication: MDS		
Duration of Exposure	(N=197)	
< 1 Months	6	3.9
1 to < 3 Months	56	116.8
3 to < 6 Months	46	212.4
6 to < 9 Months	40	305.1
9 to < 12 Months	36	393.5
12 to < 24 Months[a]	13	178.7
24 to < 48 Months	0	
Total person-months	197	1210.5

[a]Longest exposure for AML was 34 Months and for MDS was 23 Months
AML=acute myeloid leukemia; MDS=Myelodysplastic syndromes
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Table SIII.2 Exposure BY DURATION (Totals) (The Randomised, Blinded Clinical Trials Population)

	Persons (N=435)	**Person-Months**
Duration of Exposure[a]		
Cumulative up to 1 Months	58	
Cumulative up to 3 Months	159	
Cumulative up to 6 Months	249	
Cumulative up to 9 Months	318	
Cumulative up to 12 Months	373	
Cumulative up to 24 Months	421	
Cumulative up to 48 Months[a]	435	2978.8
Total person time	435	2978.8

[a] Longest exposure was 34 Months
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Table SIII.3 Exposure BY DOSE (by Indication)
(The Randomised, Blinded Clinical Trials Population)

	Persons	Person-Months
Indication: AML	**(N=238)**	
20 mg/m^2 Day1-5 Q4w	238	1768.3
Total	238	1768.3
Indication: MDS	(N=197)	
15 mg/m^2 TID Day1-3 Q6w	197	1210.5
Total	197	1210.5

AML=acute myeloid leukemia; MDS= Myelodysplastic syndromes; TID= three times daily; w=weeks
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Table SIII.4: Exposure BY DOSE (Totals)
(The Randomised, Blinded Clinical Trials Population)

	Persons (N=435)	Person-Months
20 mg/m^2 Day1-5 Q4w	238	1768.3
15 mg/m^2 TID Day1-3 Q6w	197	1210.5
Total	435	2978.8

TID=three times daily; w=weeks
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Table SIII.5: Exposure BY AGE GROUP AND GENDER (by Indication)
(The Randomised, Blinded Clinical Trials Population)

	Men		Women	
	Persons	**Person-Months**	**Persons**	**Person-Months**
Indication: AML	(N=135)		(N=103)	
< 18 years	0	0	0	0
18 - 59 years	0	0	0	0
60 - 64 years	2	16.9	1	1.9
65 - 69 years	43	309.9	25	275.4
70 - 74 years	35	230.1	40	315.6
75 - 79 years	40	276.3	23	153
> = 80 years	15	75.4	14	113.8
Total	135	908.6	103	859.7
Indication: MDS	(N=129)		(N=68)	
< 18 years	0	0	0	0
18 - 59 years	5	19	5	28.8
60 - 64 years	23	166.5	14	75.4
65 - 69 years	30	201.3	20	114.6
70 - 74 years	36	231.8	9	58.3
75 - 79 years	23	154	17	81.4
> = 80 years	12	67.8	3	11.5
Total	129	840.4	68	370

AML=acute myeloid leukaemia; MDS=myelodysplastic syndromes
AML: Randomised trial=DACO-016; MDS: Randomised trials=EORTC-06011 and D-0007
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Table SIII.6: Exposure BY AGE GROUP AND GENDER (Totals)
(The Randomised, Blinded Clinical Trials Population)

	Men (N=264)		Women (N=171)	
	Persons	**Person-Months**	**Persons**	**Person-Months**
< 18 years	0	0	0	0
18 - 59 years	5	19	5	28.8
60 - 64 years	25	183.4	15	77.3
65 - 69 years	73	511.2	45	390
70 - 74 years	71	462	49	373.9
75 - 79 years	63	430.3	40	234.4
> = 80 years	27	143.2	17	125.3

Table SIII.6: Exposure BY AGE GROUP AND GENDER (Totals)
(The Randomised, Blinded Clinical Trials Population)

	Men (N=264)		Women (N=171)	
	Persons	**Person-Months**	**Persons**	**Person-Months**
Total	264	1749	171	1229.7

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Table SIII.7: Exposure BY ETHNIC or RACIAL ORIGIN (by Indication)
(the Randomised, Blinded Clinical Trials Population)

	Persons	**Person-Months**
Indication: AML	**(N=238)**	
White	206	1540.4
Black or African American	0	0
Asian	32	227.9
Other[a]	0	0
NA	0	0
Total	238	1768.3
Indication: MDS	**(N=197)**	
White	77	427.9
Black or African American	4	20.8
Asian	0	0
Other[a]	2	11.7
NA	114	750.2
Total	197	1210.5

Note: The ethnicity information was not collected in trial EORTC, therefore those subjects were categorised into NA category.
[a] Other includes HISPANIC, MIDDLE EASTERN
AML=acute myeloid leukemia; MDS=Myelodysplastic syndromes
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Table SIII.8: Exposure BY ETHNIC or RACIAL ORIGIN (Totals)
(The Randomised, Blinded Clinical Trials Population)

	Persons (N=435)	**Person-Months**
White	283	1968.3
Black or African American	4	20.8
Asian	32	227.9
Other[a]	2	11.7
NA	114	750.2
Total	435	2978.8

Note: The ethnicity information was not collected in trial EORTC, therefore those subjects were categorised into NA category.
[a] Other includes HISPANIC, MIDDLE EASTERN
[TSIEXPETH01B rtf] [JNJ-30979754\Z_RMP\DBR_DEC2012\RE_DEC2012\tsiexpeth01b.sas] 01JUL2013, 22:47

Table SIII.9: Exposure BY SPECIAL POPULATIONS (by Indication)
(The Randomised, Blinded Clinical Trials Population)

	Persons	Person-Months
Indication: AML	**(N=238)**	
Renal impairment[a]		
Normal (CrCl >=50 mL/min)	197	1483.4
Mild-to-moderate (CrCl >=30 to <50 mL/min)	38	267.3
Severe (CrCl <30 mL/min)	1	14.7
Missing	2	2.9
Indication: MDS	**(N=197)**	
Renal impairment[a]		
Normal (CrCl >=50 mL/min)	164	1021.5
Mild-to-moderate (CrCl >=30 to <50 mL/min)	24	149.1
Severe (CrCl <30 mL/min)	0	0
Missing	9	39.9

[a] At baseline
CrCl=creatinine clearance
AML=acute myeloid leukemia; MDS= Myelodysplastic syndromes
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Table SIII.10: Exposure BY SPECIAL POPULATIONS (Totals)
(The Randomised, Blinded Clinical Trials Population)

	Persons (N=435)	Person-Months
Renal impairment[a]		
Normal (CrCl >=50 mL/min)	361	2504.9
Mild-to-moderate (CrCl >=30 to <50 mL/min)	62	416.4
Severe (CrCl <30 mL/min)	1	14.7
Missing	11	42.7

[a] at baseline
CrCl=creatinine clearance
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Exposure in All Clinical Trials

The all clinical trials population includes 6 trials:

- Trial DACO-016
- Trial MDS EORTC-06011
- Trial MDS D-0007
- Trial DACO-017
- Trial DACO-020
- Trial ID03-0180

Study DACO-017 was a Phase 2 multicenter, open-label, single-arm study of DACOGEN treatment with the 5-day dosing regimen as treatment for AML in subjects over 60 years of age. Treatment consisted of DACOGEN 20 mg/m^2 administered as a 1-hour intravenous infusion once daily on Days 1 to 5 of a 4-week cycle

Study DACO-020 was a multicenter, open-label, single-arm Phase 2 study of the 5-day dosing regimen in adult subjects with advanced stage MDS. Each treatment cycle consisted of 20 mg/m^2

DACOGEN administered as 1-hour intravenous infusion once daily on Days 1 through 5 of a 4-week cycle in an outpatient setting.

Study ID03-0180 was a single center study that explored 3 alternate dosing regimens. The Bayesian designed study incorporated 3 groups: A: 10 mg/m^2 as a 1-hour intravenous infusion for 10 days every 4 weeks, B: 20 mg/m^2 decitabine as a 1-hour intravenous infusion for 5 days every 4 weeks (5-Day dosing regimen), and C: 10 mg/m^2 as a SC injection twice per day for 5 days every 4 weeks.

Exposure to DACOGEN in clinical trials conducted in company supported indications (AML and MDS) is summarized in Tables SIII.11 to SIII.20 by duration, by dose, by age and gender, by race/ethnic origin, and by special population (eg, renal impairment).

Table SIII.11: Exposure BY DURATION (by Indication); (The All Clinical Trials Population Including Open Extensions)

Indication: AML	**Patients**	**Person-Months**
Duration of Exposure	(N=293)	
< 1 Months	64	60.6
1 to < 3 Months	58	130.9
3 to < 6 Months	55	246.9
6 to < 9 Months	35	263.3
9 to < 12 Months	23	238.6
12 to < 24 Months	41	721.5
24 to < 48 Months[a]	17	475.7
Total person-months	293	2137.5
.		
Indication: MDS		
Duration of Exposure	(N=389)	
< 1 Months	24	20.4
1 to < 3 Months	88	187
3 to < 6 Months	82	383
6 to < 9 Months	71	542.8
9 to < 12 Months	61	651.8
12 to < 24 Months	48	779.6
24 to < 48 Months[a]	15	451.6
Total person-months	389	3016.1

AML=acute myeloid leukemia; MDS= Myelodysplastic syndromes
[a]Longest exposure for AML was 38 Months and for MDS was 39 Months

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Table SIII.12 Exposure BY DURATION (Totals); (The All Clinical Trials Population Including Open Extensions)

Duration of Exposure	Patients (N=682)	Person-Months
< 1 Months	88	81
1 to < 3 Months	146	317.9
3 to < 6 Months	137	629.9
6 to < 9 Months	106	806
9 to < 12 Months	84	890.4
12 to < 24 Months	89	1501.1
24 to < 48 Months[a]	32	927.2
Total person-months	682	5153.6

[a]Longest exposure was 39 Months

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Table SIII.13: Exposure BY DOSE (by Indication) (The All Clinical Trials Population Including Open Extensions)

	Persons	Person-Months
Indication: AML	**(N=293)**	
20 mg/m^{2}Day1-5 Q4w	293	2137.5
Total	293	2137.5
Indication: MDS	**(N=389)**	
15 mg/m^{2}TID Day1-3 Q6w	197	1210.5
20 mg/m^{2}Day1-5 Q4w	192	1805.6
Total	389	3016.1

AML=acute myeloid leukemia; MDS= Myelodysplastic syndromes; TID= three times daily; w=weeks

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Table SIII.14: Exposure BY DOSE (Totals) (The All Clinical Trials Population Including Open Extensions)

	Persons (N=682)	Person-Months
20 mg/m^{2}Day1-5 Q4w	485	3943.1
15 mg/m^{2}TID Day1-3 Q6w	197	1210.5
Total	682	5153.6

TID= three times daily; w=weeks

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Table SIII.15: Exposure BY AGE GROUP AND GENDER (by Indication)
(The All Clinical Trials Population Including Open Extensions)

	Men		Women	
	Persons	**Person-Months**	**Persons**	**Person-Months**
Indication: AML	**(N=162)**		**(N=131)**	
< 18 years	0	0	0	0
18 - 59 years	0	0	0	0
60 - 64 years	6	27.3	4	36.2
65 - 69 years	52	366.3	30	317.3
70 - 74 years	40	250	44	347.6
75 - 79 years	47	337.2	30	218.7
> = 80 years	17	79	23	157.9
Total	162	1059.8	131	1077.7
Indication: MDS	**(N=263)**		**(N=126)**	
< 18 years	0	0	0	0
18 - 59 years	25	196.2	18	140.8
60 - 64 years	39	326.5	25	196.9
65 - 69 years	55	472.6	31	192.8
70 - 74 years	66	626	20	127.7
75 - 79 years	53	396.3	25	136.3
> = 80 years	25	162.7	7	41.4
Total	263	2180.2	126	835.9

AML=acute myeloid leukemia; MDS= Myelodysplastic syndromes
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Table SIII.16: Exposure BY AGE GROUP AND GENDER (by Totals)
(the All Clinical Trials Population Including Open Extensions)

	Men (N=425)		Women (N=257)	
	Persons	**Person-Months**	**Persons**	**Person-Months**
< 18 years	0	0	0	0
18 - 59 years	25	196.2	18	140.8
60 - 64 years	45	353.9	29	233.1
65 - 69 years	107	838.9	61	510.1
70 - 74 years	106	876	64	475.3
75 - 79 years	100	733.5	55	355.1
> = 80 years	42	241.6	30	199.3
Total	425	3240	257	1913.6

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Table SIII.17: Exposure BY ETHNIC or RACIAL ORIGIN (by Indication)
(The All Clinical Trials Population Including Open Extensions)

	Persons	Person-Months
Indication: AML	**(N=293)**	
White	256	1889.3
Black or African American	5	20.3
Asian	32	227.9
Other[a]	0	0
NA	0	0
Total	293	2137.5
Indication: MDS	**(N=389)**	
White	244	2015
Black or African American	13	78.7
Asian	5	37.6
Other[a]	13	134.7
NA	114	750.2
Total	389	3016.1

AML=acute myeloid leukemia; MDS= Myelodysplastic syndromes
Note: The ethnicity information was not collected in trial EORTC, therefore those subjects were categorised into NA category.
[a] Other includes Bulgarian, Hispanic, Mexican, Middle Eastern
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Table SIII.18: Exposure BY ETHNIC or RACIAL ORIGIN (Totals)
(The All Clinical Trials Population Including Open Extensions)

	Persons (N=682)	Person-Months
White	500	3904.3
Black or African American	18	99
Asian	37	265.4
Other[a]	13	134.7
NA	114	750.2
Total	682	5153.6

Note: The ethnicity information was not collected in trial EORTC, therefore those subjects were categorised into NA category.
[a] Other includes Bulgarian, Hispanic, Mexican, Middle Eastern
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Table SIII.19: Exposure BY SPECIAL POPULATIONS (by Indication)
(The All Clinical Trials Population Including Open Extensions)

	Persons	Person-Months
Indication: AML	**(N=293)**	
Renal impairment[a]		
Normal (CrCl >=50 mL/min)	245	1826
Mild-to-moderate (CrCl >=30 to <50 mL/min)	45	293.9
Severe (CrCl <30 mL/min)	1	14.7
Missing	2	2.9
Indication: MDS	**(N=389)**	
Renal impairment[a]		
Normal (CrCl >=50 mL/min)	326	2523.5
Mild-to-moderate (CrCl >=30 to <50 mL/min)	43	351.1
Severe (CrCl <30 mL/min)	1	11.5
Missing	19	130

[a] at baseline
AML=acute myeloid leukemia; MDS= Myelodysplastic syndromes; CrCl=creatinine clearance
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Table SIII.20: Exposure BY SPECIAL POPULATIONS (Totals)
(The All Clinical Trials Population Including Open Extensions)

	Persons (N=682)	Person-Months
Renal impairment[a]		
Normal (CrCl >=50 mL/min)	571	4349.4
Mild-to-moderate (CrCl >=30 to <50 mL/min)	88	645.1
Severe (CrCl <30 mL/min)	2	26.2
Missing	21	132.9

[a] at baseline

CrCl=creatinine clearance

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Hypersensitivity to decitabine and any excipient of DACOGEN	
Reason for being an exclusion criterion	Development of hypersensitivity including anaphylactic reaction is an occasional but serious consequence of any chemotherapy including DACOGEN.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	The treating physician would be expected to weigh the benefit and risks for each individual patient. Hypersensitivity to decitabine or to any of the excipients is a contraindication in the DACOGEN SmPC Section 4.3 (Contraindications).
Lactation	
Reason for being an exclusion criterion	It is not known whether decitabine or its metabolites are excreted in breast milk.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	The use of DACOGEN in lactation is a contraindication in the SmPC.
Cardiac function impairment: Unstable angina or NYHA class III or IV congestive heart failure	
Reason for being an exclusion criterion	It is common clinical practice to not include subjects with these severe and potentially life-threatening cardiac conditions in trials on anticancer therapy.
Considered to be included as missing information: Yes/No	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Rationale (if not included as missing information)	The DACOGEN SmPC, Section 4.4 (Special warnings and precautions for use) adequately addresses this safety concern. “Patients with a history of severe congestive heart failure or clinically unstable cardiac disease were excluded from clinical studies and therefore, the safety and efficacy of Dacogen in these patients has not been established. Cases of cardiomyopathy with cardiac decompensation, in some cases reversible after treatment discontinuation, dose reduction or corrective treatment, have been reported in the postmarketing setting. Patients, especially those with cardiac disease history, should be monitored for signs and symptoms of heart failure.” This missing information has also been monitored for 12 years with a cumulative postmarketing exposure of >180,000 treatment courses through 30 April 2023. The anticipated safety profile is not expected to be different in those with a history of severe cardiac disease, compared with the target population. No additional pharmacovigilance activities are ongoing or planned in these populations. No new safety signals have been identified over the 12 years of postmarketing safety surveillance.
Renal impairment (creatinine >1.5 upper limit of normal range for DACO-017 or CrCl <40 mL/min for DACO-016)	
Reason for being an exclusion criterion	Early in the DACOGEN development program, the effects of renal clearance on decitabine PK and safety were not fully elucidated.
Considered to be included as missing information Yes/No	No
Rationale (if not included as missing information)	The DACOGEN SmPC, Section 4.4 (Special warnings and precautions for use) adequately addresses this safety concern. “Caution should be exercised in the administration of Dacogen to patients with severe renal impairment (Creatinine Clearance [CrCl] < 30 ml/min). Renal function tests should be performed prior to initiation of therapy and prior to each treatment cycle, and as clinically indicated.” This missing information has also been monitored for 12 years with a cumulative postmarketing exposure of >180,000 treatment courses through 30 April 2023. The anticipated safety profile is not expected to be different in those with a history of severe renal impairment, compared with the target population. No additional pharmacovigilance activities are ongoing or planned in these populations. No new safety signals have been identified over the 12 years of postmarketing safety surveillance.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Hepatic function tests abnormalities (bilirubin, alanine aminotransferase, aspartate aminotransferase) that are NCI-CTCAE (version 3.0) Grade 2 and above	
Reason for being an exclusion criterion	Early in the DACOGEN development program, the effects of hepatic function on decitabine PK and safety were not fully elucidated.
Considered to be included as missing information Yes/No	No
Rationale (if not included as missing information)	The DACOGEN SmPC, Section 4.4 (Special warnings and precautions for use) adequately addresses this safety concern. "Caution should be exercised in the administration of Dacogen to patients with hepatic impairment and in patients who develop signs or symptoms of hepatic impairment. Liver function tests should be performed prior to initiation of therapy and prior to each treatment cycle, and as clinically indicated." Section 5.2 (Pharmacokinetic properties) states that "results from a human mass-balance study and in vitro experiments indicated that the CYP enzymes are unlikely to be involved in the metabolism of decitabine." "Thus, decitabine exposure is not likely to be affected in patients with impaired hepatic function." and "Based on model simulation, PK parameters were independent of time (ie, did not change from cycle to cycle) and no accumulation was observed with this dosing regimen". This missing information has also been monitored for 12 years with a cumulative postmarketing exposure of >180,000 treatment courses through 30 April 2023. The anticipated safety profile is not expected to be different in those with a history of hepatic impairment, compared with the target population. No additional pharmacovigilance activities are ongoing or planned in these populations. No new safety signals have been identified over the 12 years of postmarketing safety surveillance.
Uncontrolled viral or bacterial infection (uncontrolled viral infection includes HIV)	
Reason for being an exclusion criterion	It is common clinical practice to not include subjects with uncontrolled and potentially life-threatening infections in trials on anticancer therapy.
Considered to be included as missing information Yes/No	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Rationale (if not included as missing information)	Severe infections are a typical symptom of progressive MDS or AML. Myelosuppression and AEs related to myelosuppression are common in both treated and untreated patients with AML. Complications of myelosuppression include infections.
Chronic respiratory disease that requires continuous oxygen	
Reason for being an exclusion criterion	It is common clinical practice to not include subjects with severe and potentially life-threatening pulmonary conditions in trials on anticancer therapy.
Considered to be included as missing information Yes/No	No
Rationale (if not included as missing information)	There are no specific data available for use of DACOGEN in patients with chronic respiratory disease that requires continuous oxygen. The treating physician would be expected to weigh the benefits and risks for each individual patient.
CNS leukaemia	
Reason for being an exclusion criterion	It is common clinical practice to not include subjects with known CNS involvement in trials on anticancer therapy.
Considered to be included as missing information Yes/No	No
Rationale (if not included as missing information)	Exclusion of this population is to assure a more homogeneous clinical trial population, and one that is not based on safety, per se. In addition, induction strategies recommended for AML with CNS involvement in treatment guidelines from ESMO and NCCN are broadly the same as those for AML without CNS involvement. The safety of DACOGEN is not expected to be different in this population.
Pregnancy	
Reason for being an exclusion criterion	It is common clinical practice to not include pregnant women in anticancer trials.
Considered to be included as missing information Yes/No	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Rationale (if not included as missing information)	There are no adequate data on the use of DACOGEN in pregnant women. However, studies have shown that decitabine is teratogenic in rats and mice. The potential risk for humans is unknown. The DACOGEN SmPC Section 4.6 (Fertility, pregnancy and lactation) states that DACOGEN should not be used during pregnancy and in women of childbearing potential who are not using effective contraception.

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

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

With an overall exposure of 682 subjects, any ADR with incidence lower than 1/227 would be difficult to detect. However, postmarketing pharmacovigilance surveillance and signal detection would detect such uncommon ADRs.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Population with relevant different ethnic origin	Of the 293 subjects with AML exposed to DACOGEN in the all clinical trials population, 86.4% (209/293) were white and 13.6% (33/293) were Asian. A review of population PK data indicated that race had no apparent effect on exposure to decitabine. However, 95% of the patients included in the analysis were white.
Subpopulations carrying relevant genetic polymorphisms	Decitabine is metabolized by cytidine deaminase present in the liver as well as in granulocytes, intestinal epithelium and plasma to its metabolite, 5-aza-2'-deoxyuridine. Decitabine also undergoes anabolism, ie, phosphorylation to triphosphate which is the active moiety incorporated into the DNA. In vitro metabolism trials suggest that decitabine is not a substrate for the human liver

	CYP450 enzymes. No pharmacogenomic assessments of the effect of genetic polymorphisms on the metabolism, safety, or efficacy of DACOGEN have been conducted.
Elderly	The age of subjects recruited in clinical trials of DACOGEN across the AML and MDS indications is as follows: Of the 682 subjects, 117 (17%) were <65 years of age, while 565 (83%) of the subjects were ≥65 years of age, including 227 (33%) ≥75 years of age. Of the 293 subjects with AML, 97% were ≥65 years of age and 40% were ≥75 years of age; Of the 389 subjects with MDS, 72% were ≥65 years of age and 28% were ≥75 years of age. Based on subgroup analyses, there was no relationship between the frequency of AEs and increasing age (<65, 65 to 69, 70 to 74, 75 to 79, ≥80 years). Similarly, there was no relationship between the nature, severity, seriousness, or outcome of AEs and increasing age. A population PK investigation of the PK properties of decitabine in 59 subjects with AML or MDS was performed. The population PK analysis revealed no significant parameter dependency on age.
Gender	Of the 293 subjects with AML exposed to DACOGEN in the all clinical trials population, 162 (55%) were men and 131 (45%) were women. Among the 389 subjects with MDS exposed to DACOGEN in the 3-Day or 5-Day dosing group, 263 (68%) were men and 126 (32%) were women. Based on subgroup analyses, there was no relationship between the frequency of occurrence of AEs and gender. Similarly, there was no noteworthy difference in the nature, severity, seriousness, or outcome of AEs occurring in men vs women. A population PK investigation of the PK properties of decitabine delivered by the 20 mg/m^2 1-hour or 15 mg/m^2 3-hour infusions in 59 subjects with AML or MDS was performed. Clearance for women was 12.1% (95% CI: 0.5%, 25.6%) lower than for men, but inter-individual variability for models with and without gender effect were similar, and the size of the effect was

	small relative to the interindividual variability. Hence, the observed difference in clearance is considered to be of no clinical relevance.
Patients with relevant comorbidities:	
Patients with severe hepatic impairment	Use in patients with hepatic impairment has not been established. The PK of decitabine have not been formally studied in patients with hepatic impairment.
Patients with severe renal impairment	Use in patients with severe renal impairment has not been established. The PK of decitabine have not been formally studied in patients with renal insufficiency.
Use in severe cardiac disease (eg, uncontrolled angina or severe congestive heart failure [NYHA III-IV])	Patients with a history of severe congestive heart failure or clinically unstable cardiac disease were excluded from clinical trials and therefore the safety and efficacy of DACOGEN in these patients has not been established.
Immunocompromised patients	Not included in the clinical development program.
CNS leukemia	Subjects with overt evidence of CNS leukaemia were excluded from clinical trials. The safety profile in this group is not expected to be different from that in the target AML population. Moreover, CNS involvement in older patients with AML is rare. Furthermore, decitabine is known to cross the blood-brain barrier and thus could have activity in patients with CNS AML.
Uncontrolled Infections (Including HIV)	Not included in the clinical development program.

Summary of Missing Information Due to Limitations of the Clinical Trial Program

None

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by a patient.

Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. The assumed dose for decitabine is 20 mg/m^2 administered by continuous intravenous infusion over 1 hour repeated once daily for 5 days. Assuming an average body surface area of 1.73 m^2 (De Jong 2004), this corresponds to 173 mg/cycle. It is further assumed that there are 4 cycles per treatment course (the median cycles per treatment course was 4 in DACO-016, the pivotal AML trial). The cumulative exposure to decitabine is presented below.

SV.1.2. Exposure

The cumulative exposure from 02 May 2006 to 30 April 2023 is provided in Table SV.1.

Table SV.1: Cumulative Exposure to Decitabine (02 May 2006 to 30 April 2023)

Region	Number of Vials	Grams	Estimated Treatment Courses[a]
EU	665,249	33,262	48,037
Non-EU	1,849,328	92,467	132,647
Total	**2,514,577**	**125,729**	**180,684**

[a] Old algorithm applied for the period from launch to 31 October 2012 (234 mg/cycle x 3 cycles = 702 mg per course) and new algorithm applied from 01 November 2012 onwards (173 mg/cycle x 4 cycles = 692 mg per course).

Based on the 2,514,577 vials distributed worldwide from 02 May 2006 to 30 April 2023, the estimated exposure to decitabine is 180,684 treatment courses.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

DACOGEN is an antineoplastic agent and has no abuse potential. Therefore, potential illegal use is unlikely.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

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

Not applicable.

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

Not applicable.

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Not applicable.

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

Not applicable.

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

No new safety concerns have been identified since this RMP was last updated.

Removal of the missing information "Use in severe renal impairment", "Use in hepatic impairment" and "Use in severe cardiac disease (eg, uncontrolled angina or severe congestive heart failure [NYHA III-IV])" is based on the PRAC conclusions resulting from the last PSUR assessment report (procedure number: EMEA/H/C/PSUSA/00009118/202305) related to the PSUR covering the period 02 May 2020 to 01 May 2023. Whilst a targeted questionnaire for spontaneous reports in patients with a history of renal impairment, hepatic impairment and cardiac disease was in place for these populations, PRAC noted that there were no specific questions in the questionnaires which would bring additional information to what is already covered in the routine process. Therefore, PRAC recommended that the questionnaires and the associated missing information are to be removed from the EU RMP. The anticipated safety profile is not expected to be different in those with a severe renal, hepatic impairment and severe cardiac disease compared with the target population. No additional pharmacovigilance activities are ongoing or planned in these populations. No new safety signals have been identified over 12 years of postmarketing safety surveillance.

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

Important identified risks

None

Important potential risks

None

Missing Information:

None

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

Important Identified Risks: None

Important Potential Risks: None

SVII.3.2. Presentation of the Missing Information

Not Applicable.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN
(Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Adverse Reaction Follow-up Questionnaires for Safety Concerns

Safety Concern	Purpose/Description
None	

Other Forms of Routine Pharmacovigilance Activities

Activity	Objective/Description	Milestones
None		

III.2. Additional Pharmacovigilance Activities

None.

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
None				

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
None				

PART V: RISK MINIMIZATION MEASURES
(Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Not applicable as there are no important identified risks, important potential risks, or missing information for DACOGEN.

V.2. Additional Risk Minimization Measures

Not applicable.

V.2.1. Removal of Additional Risk Minimization Activities

Activity	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable.	

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Not applicable.		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for DACOGEN (decitabine)

This is a summary of the risk management plan (RMP) for DACOGEN. Over 12 years' market experience with DACOGEN has demonstrated a favorable benefit-risk profile for the indication specified in this RMP and, therefore, there are no important risks or uncertainties (missing information) associated with this product.

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

Important new concerns will be included in updates of DACOGEN's RMP.

I. The Medicine and What it is Used For

DACOGEN is authorized for acute myeloid leukemia (AML) (see SmPC for the full indication). It contains decitabine as the active substance and it is administered intravenously.

Further information about the evaluation of DACOGEN's benefits can be found in DACOGEN's European public assessment report (EPAR), including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/dacogen

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Not applicable, as there are no important identified risks or important potential risks for DACOGEN.

II.A. List of Important Risks and Missing Information

There are no important identified risks, important potential risks, or missing information for DACOGEN.

II.B. Summary of Important Risks

There are no important identified risks, important potential risks, or missing information for DACOGEN.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of DACOGEN.

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for DACOGEN.

PART VII: ANNEXES

Table of Contents

Annex 4 Specific Adverse Drug Reaction Follow-up Forms

Annex 6 Details of Proposed Additional Risk Minimization Measures (if applicable)

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

None

Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable.