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Market Authorisation Holder/Sponsor:

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EU RISK MANAGEMENT PLAN (RMP) for

Oral decitabine and cedazuridine

Version: 1.0

Data Lock Point for this RMP: 10 Sep 2021

Date of Final Sign Off: 17 Jul 2023

[redacted]

Signature	Electronically signed
	[redacted] MD, MPH / [redacted]
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	[redacted], MD, MSc./EU QPPV

EU Risk Management Plan for INAQOVI (oral decitabine and cedazuridine):

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data Lock Point for this RMP: 10 Sep 2021

Date of Final Sign Off: 17 Jul 2023

There are no previously submitted versions of this EU RMP that are still under evaluations by the Agency.

QPPV name: Emiel van Heumen, MD, MSc

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

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Abbreviation/Acronym	Definition
ADD	Average defined dose
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
AML	Acute myeloid leukaemia
APL	Acute promyelocytic leukaemia
ASR	Age-standardized incidence rates
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical classification system
AUC	Area under the curve
CALBG	Cancer and Leukaemia Group B
CDA	Cytidine deaminase
CHF	Congestive heart failure
CI	Confidence interval
CMML	Chronic myelomonocytic leukaemia
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPX-351	Liposomal combination of daunorubicin and cytarabine
CrCl	Creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	Electronic Common Technical Document
EEA	European economic area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDC	Fixed dose combination
FLT3	FMS-like tyrosine kinase 3
FSH	Follicle-stimulating hormone
GI	Gastrointestinal
GLP	Good Laboratory Practice
HBV	Hepatitis B virus
HCP	Health Care Professionals
HCV	Hepatitis C virus
hERG	human ether-a-go-go related gene
HIV	Human immunodeficiency virus
IARC	International Agency for Research on Cancer
ICD-O	International Classification of Diseases for Oncology
IDH	Isocitrate dehydrogenase
IV	Intravenous
HEK293	Human embryonic kidney cells
HMA	Hypomethylating agents
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IC50	Half-maximal inhibitory concentration
ILD	Interstitial lung disease

Abbreviation/Acronym	Definition
INN	International nonproprietary name
KIT	Proto-oncogene, receptor tyrosine kinase
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MDR	Multidrug resistance
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
NCE	New chemical entity
NCI	National Cancer Institute
NYHA	New York Heart Association
PD	Pharmacodynamic(s)
PDGF	Platelet-derived growth factor
PL	Package Leaflet
PK	Pharmacokinetics
PSA	Prostate-specific antigen
PSUR	Periodic Safety Update Report
PT	Preferred term
PV	Pharmacovigilance
QPPV	Qualified person responsible for pharmacovigilance
QTc	Corrected QT interval
QTcF	Corrected QT interval Fridericia
RMP	Risk management plan
SEER	Surveillance, Epidemiology, and End Results
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary of product characteristics
SMQ	Standard MedDRA query
ULN	Upper limit of normal
US	United States
USAN	United States Approved Name
VEGF	Vascular endothelial growth factor
WBC	White blood cell(s)
WHO	World Health Organization

1 PART I: PRODUCT(S) OVERVIEW

Table 1-1 Active Substance Information	
Active substance(s) (INN or common name)	INN, USAN: Decitabine INN, USAN: Cedazuridine
Pharmacotherapeutic group(s) (ATC code):	Antineoplastic agents, antimetabolites, pyrimidine analogues; cytidine deaminase inhibitor; ATC code: L01BC58
Name of marketing authorisation applicant	Otsuka Pharmaceuticals Netherlands B.V.
Medicinal products to which this RMP refers:	1
Invented name of the product in the European Economic Area (EEA)	INAQOVI
Marketing authorisation procedure	Marketing Authorisation Application Centralised
Brief description of the product	Chemical class: DNA hypomethylating agent (HMA)
	Summary of mode of action: Decitabine is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation and/or apoptosis. Cytidine deaminase (CDA) is an enzyme that is responsible for the degradation of nucleosides, including decitabine. High levels of CDA in the gastrointestinal tract and liver rapidly degrade these nucleosides and prohibit or limit their oral bioavailability. Cedazuridine is a new molecular entity that inhibits CDA. Oral administration of cedazuridine enhances the oral bioavailability of decitabine via inhibition of first pass metabolism of decitabine in the gut and liver by CDA.
	Important information about its composition: Decitabine and cedazuridine are synthetic chemicals INAQOVI is an oral FDC drug product that contains 35 mg decitabine and 100 mg cedazuridine
eCTD link to the proposed product information, as appropriate	Module 1.3.1 Combined Product Information
Indication(s) in the EEA: Proposed	The proposed indication for INAQOVI (oral decitabine and cedazuridine): INAQOVI is indicated as monotherapy for the treatment of adult patients with newly diagnosed acute myeloid

Table 1-1 Active Substance Information	
	leukaemia (AML) who are ineligible for standard induction chemotherapy.
Dosage in the EEA	The proposed dose of INAQOVI (oral decitabine and cedazuridine) is 1 tablet containing 35 mg decitabine and 100 mg cedazuridine orally without food once daily on Days 1 through 5 of each 28-day cycle for a minimum of 4 cycles until disease progression or unacceptable toxicity. Treatment should be continued as long as the patient continues to benefit.
Pharmaceutical Form(s)	Proposed: Oral Dosage Form (Tablets)
Pharmaceutical Strength(s)	Proposed: 35 mg decitabine and 100 mg cedazuridine
Is/will the product subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

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

Indication: INAQOVI is indicated as monotherapy for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy.

Brand names of concerned products: INAQOVI

Incidence:

Based on the most recent data available from the World Health Organization/International Agency for Research on Cancer (WHO/IARC)'s Cancer incidence in Five Continents series, AML incidence rates as reported by European cancer registries range between 4.5/100,000 in Belgian men to 1.9/100,000 in Ukraine women.[1] (Table 2.1-1). The IARC current data (2021) include the period 2008-2012 with data from 28 European countries with 127 cancer registries. The registries covered close to 50% of the European population and reported 89,391 newly diagnosed AML cases during that 5-year period.

Table 2.1-1 Age-standardized incidence rates (ASR) of AML during 2008-2012 based on 127 IARC registries in Europe.[1] Incidence rates in the nations in the highest and lowest ASR tertile, by sex

	Males		Females	
Country	**Cases**	**ASR per 100,000**	**Cases**	**ASR per 100,000**
Nations in highest tertile				
Belgium	2,040	4.5	1,614	3.3
France	2,105	4.5	1,746	3.1
Denmark	1,017	4.3	806	3.1
Italy	4,861	4.3	4,016	3.1
United Kingdom	11,226	4.2	8,965	3.0
Austria	1,689	4.1	1,403	2.9
Estonia	180	4.1	176	2.5
Germany	9,647	4.0	8,259	3.0
Netherlands	2,600	3.9	2,055	2.8
Nations in highest tertile				
Latvia	144	3.3	133	2.0

Table 2.1-1	**Age-standardized incidence rates (ASR) of AML during 2008-2012 based on 127 IARC registries in Europe.[1] Incidence rates in the nations in the highest and lowest ASR tertile, by sex**			
	Males		**Females**	
Azores	20	3.2	26	3.3
Croatia	536	3.2	477	2.1
Belarus	864	3.0	863	2.5
Poland	1,064	2.6	964	1.9
Russian Federation	619	2.6	761	2.2
Czech Republic	971	2.4	926	1.9
Bulgaria	672	2.3	564	1.8
Ukraine	3,155	2.3	3,379	1.9

To generate an overall estimate of the incidence of AML in Europe, Sant et al. evaluated 44 European cancer registries from 2000-2002 (an estimated 30% of the European population) for the HAEMACARE project and found an incidence of 3.6 per 100,000/year with an age-standardized incidence of 3.0 per 100,000/year.[2] Visser et al. similarly evaluated incidence of AML within 64 European cancer registries from 1995-2002 for the RARECARE project and found an incidence of 3.7 per 100,000/year (4.0/100,000 in men and 3.4/100,000 in women).[3] AML was 43% of all myeloid malignancies. Because the HAEMACARE and RARECARE projects amalgamate data from cancer registries that overlap with the IARC data, the results are highly comparable, and the similarity of these estimates suggests that incidence of AML in Europe has been highly stable for three decades or more. Notably, the classification of myeloid leukaemias including AML was standardized across registries since 2000 using the ICD-O-3 system, but under-reporting of AML was possible during the pre-2000 period.

Risk factors for the disease:

Age:

Age is a crucial risk factor for AML, which is primarily a disease of older adults (Figure 2.1-1). Within European nations, the median age of AML diagnosis is 65 to 70.[2] There is an early peak of incidence of AML among infants, with incidence declining until the onset of adulthood and then steadily rising with advancing age.[4]

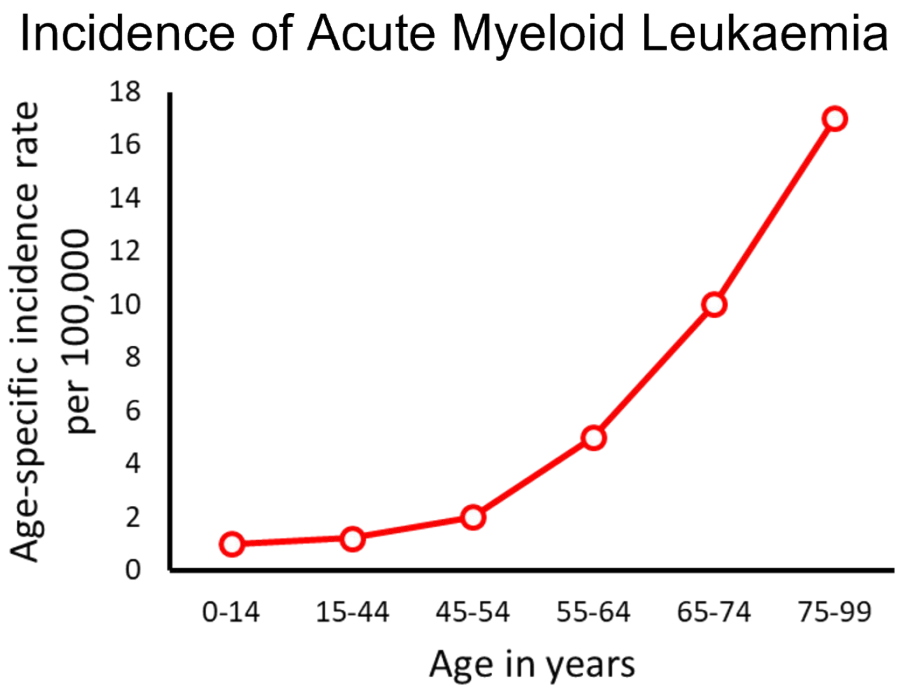

Figure 2.1-1 Incidence of AML by age. Adapted from Sant et al.[2]

Environmental exposures, sex, and other risk factors:

Exposure to carcinogens has been linked to AML in both children and adults. Carcinogens associated with AML include chemicals (formaldehyde, solvents such as benzene/toluene and other aromatic hydrocarbons, and pesticides), cigarette smoke, ionising radiation, and certain types of chemotherapy (most notably alkylating agents, anthracyclines, anthacenediones, and epipodophyllotoxins).

The early-life peak in AML has been associated with prenatal exposures, including gasoline-derived aromatic hydrocarbons[5] ionising radiation[6] cigarette smoke and/or maternal alcohol intake[7] and chemotherapy, especially chemotherapy using alkylating agents.[8] Down's syndrome has a 2-3% lifetime risk of AML, 100-200 times greater than the general population risk.[9] Many of these relationships between early AML and environmental exposures are weak, with data derived only from case-control studies (e.g., maternal alcohol or cigarette smoke exposure). Similarly, residency near high-intensity power lines based on electrical company wire coding grids was associated with childhood AML[6] but measured household electromagnetic wave intensity has been shown to be similar in children with AML and geographically matched controls.[10]

Those diagnosed with AML later in life are more likely to have AML arising from myelodysplastic syndrome (MDS) or treatment-related AML.[11] Such cancers confer a worse prognosis both because of the underlying tumor biology (increased cytogenetic abnormalities) and increased patient comorbidities and age. Relevant risk factors for de novo AML in older patients include carcinogenic occupational exposures (e.g., ionising radiation, synthetic fiber dust, industrial paints, benzene/toluene, more complex aromatic hydrocarbons, formaldehyde, industrial waste products such as dioxins, and pesticides).[12,13,14,15] A late-life diagnosis of AML in a relative is not a substantial risk factor for AML, although there are rare families with inherited bone marrow failure syndromes and increased risk for AML.[16]

Male sex is also an established although minor risk factor for AML, as it is for other hematological malignancies; the crude incidence rate in Europe is 4.0 versus 3.4 per 100,000/year in men versus women respectively.[3] The higher reported rates in men may be related to increased occupational exposure to industrial carcinogens or via lifestyle factors (increased cigarette smoking or alcohol consumption). No information in Europe is available on ethnicity as a potential risk factor for AML.

Regional differences in incidence:

Regionally, the incidence of AML is lowest in Eastern Europe (as low as 1.9 per 100,000/yr in women in the Ukraine) and highest within Northern Europe (as high as 4.5 per 100,000/yr in men in Belgium) (see Table 2.1-1).[1] The lower incidence of AML within Eastern Europe may be due to under-reporting rather than differences in population genetic susceptibility or differential regional distributions of risk factors. Under-reporting of AML may be more likely among elderly patients who receive a less aggressive diagnostic work-up and may not be offered potential therapies depending on available healthcare resources. This is suggested by the younger median age of diagnosis seen in Eastern Europe (65 years old for Eastern Europe versus ≥68 years old for other regions) and in the lower rates of diagnosis of MDS seen within Eastern Europe compared to other regions.[2] Regional diagnostic variability can also be seen in the higher proportion of leukaemias reported as unknown cell type (ICD-10 C95) within Eastern Europe. This proportion was as high as 70% in the Czech Republic, 40% in the Russian Federation, and 25% in Ukraine compared to only 2% in Belgium and the Netherlands and 12% in Germany.[1] Nonetheless, the incidence range for AML within Europe is relatively narrow and the AML incidence data from Europe are roughly compatible with data from the U.S. as generated by the Surveillance, Epidemiology, and End Results (SEER) Program (U.S. SEER incidence 3.9 per 100,000/yr for the years 1992-2001).[17]

Prevalence:

Based on 54,619 cases, the RARECARE project estimated the prevalence of AML using the completeness index method at 11.0 per 100,000 subjects (standard error 0.17) as of January 1, 2008.[3] Among prevalent cases, 7.7 per 100,000 had been diagnosed with AML within the past 15 years, 4.7 per 100,000 had been diagnosed within the past 5 years, and 2.8 per 100,000 had been diagnosed within the past 2 years. These data suggest that up to 30% of prevalent AML cases are long-term survivors (>15 years), most likely those with childhood AML which has a good long-term prognosis. RARECARE estimates of incidence are comparable to IARC estimates although the cancer-registries are only partly overlapping. This suggests that the available population estimates may only be broadly representative of Europe.[18]

Main existing treatment options:

Treatment for AML is based on the medical fitness of the patient and the leukaemia genetic profile. Treatment of acute promyelocytic leukaemia (APL) is distinct, based on use all-trans retinoic acid and arsenic trioxide. Most patients with AML who are medically fit for intensive treatment achieve cancer remission after cytotoxic induction chemotherapy; however, most patients will relapse without stem cell transplantation or additional consolidative treatment. Therefore, post-remission treatment is given to prevent relapse and improve survival. For older patients and for patients medically unfit to receive intensive chemotherapy, standard therapy was modified with a lower-dose cytarabine or hypomethylating agents (azacitidine, decitabine) with or without venetoclax.[19] After remission is achieved, ongoing lower-intensity therapy is needed to maintain remission. A 1994 Cancer and Leukemia Group B (CALBG) trial of 600 adults showed that high- compared to low-dose cytarabine was associated with increased probability of complete remission after 4 years (44% for high- vs 24% for low-dose cytarabine), but this benefit was seen only in those younger than 60 years old.[20,21] More recently, improved tolerability has led towards increased use of hypomethylating agents. The 2019 HOVON-97 trial of 116 adults ≥60 years old with AML or MDS with blasts showed 64% disease-free survival after 12 months for subcutaneous azacitidine versus 42% for an observational control group.[22] For decitabine, early reports from the ECOG-ACRIN 2906 trial showed improved overall survival with decitabine for older adults with AML with a trend towards improvement with decitabine in disease-free survival.[23]

Recently, the liposomal combination of daunorubicin and cytarabine (CPX-351) in newly diagnosed, high-risk/secondary AML was shown to prolong outcome survival compared to conventional therapy.[24]

As next-generation sequencing has become more widely available, use of genetically targeted therapies for maintenance of remission based on cancer cytogenetics has become common. These therapies include the protein kinase inhibitor sorafenib for pathways involving KIT, VEGF, PDGF, RAS, and FLT3;[25] the tyrosine kinase inhibitors such as midostaurin for FLT3 and gilteritinib for relapsed FLT3-mutated AML;[26,27] the anti-CD33 conjugate gemtuzumab ozogamicin when CD33 is overexpressed;[28] and ivosidenib and enosidenib for IDH1 and IDH2-mutated AML.[29,30]

In summary, the primary treatment options for the target population for INAQOVI are as follows:

- Midostaurin added in patients with FLT3 mutations
- Gemtuzumab ozogamicin added to patients with favorable or intermediate risk disease who disease expresses CD33
- Azacitidine with or without venetoclax
- Decitabine with or without venetoclax
- Low dose cytarabine with or without venetoclax
- Liposomal cytarabine and daunorubicin for patients with secondary AML following an antecedent hematologic disease, prior chemotherapy, or cytogenetic abnormalities associated with MDS
- Ivosidenib and Enasidenib for relapsed IDH1 and IDH2 mutated AML, respectively
- Gilteritinib for relapsed FLT3-mutated AML
- Sorafenib in AML patients

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

Cases diagnosed between 1995-2002 and included in the RARECARE project (64 European cancer registries) had a 1-year observed overall survival rate of 57% and a 5-year observed overall survival rate of 29%.[3] Survival decreased with increasing age from 67% (95% confidence interval (CI) 61-72%) among those under 15 years old to 5% (95% CI 4-5%) among those aged 65 years and older.[3] These estimates are comparable to current U.S. SEER estimates which place the overall survival rate for AML at 29.5%.[31] Cytogenetic risk factors including CD33 expression, MDR1 gene mutation, and FLT3 gene mutation also substantially determine outcome and are used to guide treatment decisions.[32]

Important comorbidities:

Prognosis for AML is highly determined by age, and relevant comorbidities among patients receiving treatment for AML are age-related: coexistent congestive heart failure (CHF), coronary artery disease, chronic kidney disease, obesity, and dementia. As is the case for other cancers, the Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status have been associated with prognosis.

Additionally relevant comorbidities and factors include AML subtype, whether AML was treatment-related or arose out of MDS, and cancer genetics. Older patients are both more likely to have difficult-to-treat cancers with high-risk genotypes and more likely to have medical comorbidities that complicate treatment and place them at risk for treatment related adverse events (AEs). The 2017 European LeukemiaNet recommendations base prognostic and therapeutic recommendations on cancer cytogenetic abnormalities and define three strata of risk.[32] In a five-center retrospective study of 1,100 patients with AML age 20 to 89, the area-under-the-curve (AUC) for 1 year mortality was 0.69 for a model incorporating clinical factors and 0.76 for a model incorporating clinical factors and cytogenetics based on the LeuklemiaNet risk strata.[33] Among clinical factors, the most important in this model were age, prior cardiac comorbidities, low serum albumin (likely representing poor nutritional status and chronic disease), and high serum lactate dehydrogenase (likely representing cancer turnover).

2.2 Module SII: Nonclinical Part of the Safety Specification

The pharmacology, pharmacokinetics (PK), and toxicity of INAQOVI have been well characterised in a comprehensive series of in vitro and in vivo nonclinical studies that have evaluated decitabine alone, cedazuridine alone, or the combination of decitabine and cedazuridine. The toxicology program for INAQOVI followed the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S9 guidance titled “Nonclinical Evaluation for Anticancer Pharmaceuticals” (ICH 2009) and included comprehensive toxicity evaluation of both decitabine and cedazuridine as single agents in relevant species.

The safety pharmacology profile for cedazuridine (the new chemical entity [NCE] component of INAQOVI) has been evaluated in a program of Good Laboratory Practice (GLP) and non-GLP compliant studies. Cedazuridine was screened against a panel of 80 physiologically relevant cell receptors, ion channels, and transporters in radioligand binding assays (Study/Report No. 929053). Cedazuridine showed no significant inhibition of binding in any of these assays. Safety pharmacology studies were conducted with cedazuridine to determine its in vitro effects on the human ether-a-go-go related

gene (hERG) potassium channel current in stably transfected human embryonic kidney (HEK293) cells (Study/Report No. 100422.FJT) and on action potential parameters in isolated guinea pig papillary muscles (Report No. ER-849727-00), and to evaluate its potential in vivo effects on the cardiovascular (CV) system in monkeys (Study/Report No. 20123940). The cumulative data from these studies indicate that cedazuridine does not have any effect on the CV system as evidenced by an in vitro IC_{50} of >300 μM for inhibition of hERG channel current, no effects on any action potential parameters in isolated papillary muscles from guinea pigs, and a lack of effect on heart rate, arterial blood pressure, body temperature, and electrocardiogram (ECG) parameters in conscious telemetered monkeys when administered as a single oral dose of up to 200 mg/kg. In addition, CV assessments included as part of the toxicological assessments in a 7-day GLP toxicity study (Study/Report No. LFA00080) and a 4-cycle GLP toxicity study (Study/Report No. 201024863) in monkeys showed no abnormalities in the ECG data following repeat once-daily oral administrations of cedazuridine at doses of up to 200 mg/kg/day for 7 consecutive days. In a respiratory assessment study, a single oral dose of cedazuridine of up to 200 mg/kg was not associated with any effects on respiratory rate, tidal volume, or minute volume in conscious telemetered monkeys (Study/Report No. 20123940).

Results of safety pharmacology studies do not indicate a cause for concern regarding effects of cedazuridine on the respiratory system (based on evaluations in conscious monkeys) or the CV system (based on in vitro hERG and actional potential assay data and on in vivo evaluations in monkeys).

The toxicological profile of INAQOVI has been well-characterised in the nonclinical studies that have been conducted to date. Overall, the adverse effects that have been observed in nonclinical species (mice, rats, and monkeys) following oral administration of decitabine and/or cedazuridine largely reflect their anticipated pharmacodynamic (PD) activities. No unexpected findings have been noted.

The main repeat-dose toxicity findings from nonclinical studies were reversible myelosuppression (leucopenia, neutropenia, lymphopenia, and/or decreased platelet counts) due to decitabine, cedazuridine, or both (INAQOVI), thymic lymphoid depletion (reversible) and testicular effects (partially reversible) due to decitabine, and reversible reproductive tract effects due to cedazuridine. Standard genotoxicity studies for INAQOVI or decitabine were not conducted, the genotoxicity of decitabine is well known and is summarized in the DACOGEN Summary of Product Characteristics (SmPC).[34] Cedazuridine was mutagenic in *S. typhimurium* strain TA1535 both in the presence and absence of metabolic activation (only at the highest tested concentration)

and was genotoxic in human lymphocytes; however, the results of the in vivo micronucleus assay suggest that cedazuridine is not genotoxic in vivo. Based on its positive genotoxicity, decitabine may be expected to have carcinogenic potential. As such, there is a carcinogenic risk associated with exposure to INAQOVI. Moreover, based on its mechanism of action, decitabine is expected to result in adverse reproductive effects. The SmPC for decitabine (DACOGEN SmPC 2021) includes information on the effect of decitabine on postnatal development and reproductive capacity.[34] Histopathology findings in the male and female mouse reproductive tract following administration of cedazuridine were previously described and support potential adverse reproductive effects. Thus, there is a risk of reproductive and developmental toxicity associated with exposure to INAQOVI.

Based on margins of exposure for decitabine and cedazuridine, the cedazuridine epimer (the major circulating metabolite), in the pivotal nonclinical toxicology studies relative to the clinical exposure data from the pivotal Phase 3 study (Study No. ASTX727-02), systemic exposures to these analytes in the pivotal nonclinical studies (when cedazuridine was administered alone to mice or monkeys, when decitabine was administered alone to rats, and when the combination of decitabine and cedazuridine was administered to monkeys) were greater than clinical exposure levels. Thus, these data support the nonclinical safety conclusions for INAQOVI.

Table 2.2-1 SII-1: Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Repeat-dose Toxicity In mice, rats, and monkeys, similar toxicological profiles were observed characterised by reversible myelosuppression (leucopenia, neutropenia, lymphopenia, and/or decreased platelet counts) due to decitabine, cedazuridine, or both (INAQOVI) and thymic lymphoid depletion (reversible) due to decitabine.	The most common toxicities with decitabine, cedazuridine, or co-treatment with both (INAQOVI) is expected to be myelosuppression (leukopenia, neutropenia, lymphopenia, decreased platelet counts, anaemia, and/or thrombocytopenia) and consequences of myelosuppression (infection, fever, fatigue, haemorrhage) and can be managed as part of routine practice in haematology clinics.
Reproductive and Developmental Toxicity Based on its mechanism of action, decitabine is expected to result in adverse reproductive effects. The SmPC for decitabine (DACOGEN SmPC 2021) includes information on the effect of decitabine on postnatal development and reproductive capacity. Histopathology findings in the male and female mouse reproductive tract following repeated administration of cedazuridine support potential adverse reproductive effects; these effects were reversible in mice.	There is a risk of reproductive and developmental toxicity associated with exposure to INAQOVI due to the two active components, decitabine and cedazuridine. The potential reproductive risks, as well as information and a recommendation to women or men with female partners of childbearing potential are provided in the SmPC.

Table 2.2-1 SII-1: Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage	
Key Safety Findings (from nonclinical studies)	**Relevance to Human Usage**
Genotoxicity Standard genotoxicity studies for INAQOVI were not conducted, although the genotoxicity of decitabine is well known and is summarized in the SmPC for decitabine (DACOGEN SmPC 2021). Cedazuridine was mutagenic in *S. typhimurium* strain TA1535 both in the presence and absence of metabolic activation (only at the highest tested concentration) and was genotoxic in human lymphocytes; however, the results of the in vivo micronucleus assay suggest that cedazuridine is not genotoxic in a mouse micronucleus test, mouse comet assay, and rat pig-a mutation assay.	The potential genotoxicity, which includes mutagenicity or carcinogenicity, as well as information and a recommendation to women or men with female partners of childbearing potential are provided in the SmPC.
Carcinogenicity Based on its positive genotoxicity, decitabine may be expected to have carcinogenic potential. No carcinogenicity studies have been conducted with INAQOVI or with cedazuridine.	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.
Cardiovascular Results from nonclinical safety pharmacology studies do not indicate a cause for concern regarding effects of cedazuridine on the cardiovascular system (based on in vitro hERG and actional potential assay data and on in vivo evaluations in monkeys).	Any safety pharmacology concerns for INAQOVI are anticipated to be the result of potential effects of decitabine which has been in clinical use for many years. IV Decitabine has been in longstanding clinical use, and no new or more severe cardiac toxicities compared to IV decitabine were reported during the clinical trials. No safety issues were identified from safety pharmacology studies for cedazuridine.

Table 2.2-1 SII-1: Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage	
Key Safety Findings (from nonclinical studies)	**Relevance to Human Usage**
Respiratory Results from nonclinical safety pharmacology studies do not indicate a cause for concern regarding effects of cedazuridine on the respiratory system (based on evaluations in conscious monkeys).	IV Decitabine has been in longstanding clinical use, and no new or more severe pulmonary toxicities compared to IV decitabine were reported during the clinical trials. Single oral dose of cedazuridine of up to 200 mg/kg was not associated with any effects on respiratory rate, tidal volume, or minute volume in conscious telemetered monkeys. Any safety pharmacology concerns for INAQOVI are anticipated to be the result of potential effects of decitabine which has been in clinical use for many years. No safety issues were identified from safety pharmacology studies for cedazuridine.
Central Nervous System (CNS) Stand-alone nonclinical safety pharmacology assessment of INAQOVI (or decitabine or cedazuridine) on central nervous system function has not been conducted. Cedazuridine and cedazuridine-derived entities do not show a strong tendency to distribute into tissues and, following oral administration, are primarily distributed into the GI tract and metabolic/excretory tissues (e.g., kidney or urinary bladder). Cedazuridine-derived entities do not cross the blood brain barrier and are not significantly distributed into melanin-containing tissues.	Cedazuridine and cedazuridine-derived entities do not cross the blood brain barrier, and no CNS effects are anticipated.

2.3 Module SIII: Clinical Trial Exposure

Cumulatively, oral decitabine and cedazuridine has been administered to 288 subjects in clinical trials at the dose of 35 mg decitabine and 100 mg cedazuridine daily for 5 days every 28 days as of the data cutoff, 10 Sep 2021.

Of the 213 subjects enrolled for MDS, 208 subjects received oral decitabine and cedazuridine or IV decitabine. Five subjects were administered IV decitabine only and did not receive oral decitabine and cedazuridine. Of the 89 subjects enrolled for AML, 80 subjects received oral decitabine and cedazuridine or IV decitabine. Seven subjects were administered IV decitabine only and did not receive oral decitabine and cedazuridine. Two subjects were randomised but did not start treatment.

While exposure below is described for all subjects enrolled for MDS (N=213) and those exposed only to oral decitabine and cedazuridine for AML (N=80), the safety data was derived from those subjects who received oral decitabine and cedazuridine for a total of 288 subjects.

Table 2.3-1	**SIII.1: Clinical Trial Exposure to Oral Decitabine and Cedazuridine by Duration of Exposure (by Indication)**	
Duration of Exposure	**Persons**	**Person Time**
Indication - MDS		
≥ 1 Cycle	213	1347
≥ 3 Cycles	182	1296
≥ 6 Cycles	89	921
≥ 12 Cycles	20	377
Total [b]	**213**	**1347**
Indication - AML		
≥ 1 Cycle	80	480
≥ 3 Cycles	61	450
≥ 6 Cycles	41	372
≥ 12 Cycles	7	107
Total [b]	**80**	**480**

AML=acute myeloid leukaemia; MDS=myelodysplastic syndrome
[a]1 cycle = 28 days; partial cycles were calculated as full cycles.
[b]Totals for Persons and Person Time are not a sum total. The totals reflect the duration of exposure from Cycle 1 through ≥ 12 Cycles.

Table 2.3-2	**SIII.2: Clinical Trial Exposure to Oral Decitabine and Cedazuridine by Age Group and Gender (by Indication)**			
	Gender			
	Male		**Female**	
Indication - MDS				
Age Group	**Person**	**Person Cycles**	**Person**	**Person Cycles**
< 18 years	0	0	0	0
18-54 years	8	41	5	26
55-64 years	26	140	14	98
65-74 years	59	482	25	137
75-84 years	48	295	20	91
85 + years	7	34	1	3
Total	**148**	**992**	**65**	**355**
Indication - AML				
Age Group	**Person**	**Person Cycles**	**Person**	**Person Cycles**
< 18 years	0	0	0	0
18-54 years	0	0	0	0
55-64 years	2	23	1	5
65-74 years	16	121	12	72
75-84 years	26	141	16	84
85 + years	5	28	2	6
Total	**49**	**313**	**31**	**167**

AML=acute myeloid leukaemia; MDS=myelodysplastic syndrome

Table 2.3-3	**SIII.3: Clinical Trial Exposure to Oral Decitabine and Cedazuridine by Dose (by Indication)**	
Indication - MDS		
Cumulative ASTX727 Dose[a]	**Persons**	**Person Cycles**
0 mg - 675 mg	31	51
> 675 mg - 1350 mg	28	85
> 1350 mg - 2025 mg	36	145
> 2025 mg - 2700 mg	33	169
> 2700 mg - 3375 mg	24	152
> 3375 mg - 6750 mg	43	395
> 6750 mg	18	350
Total	**213**	**1347**
Indication - AML		
Cumulative ASTX727 Dose[b]	**Persons**	**Person Cycles**
0 mg - 675 mg	8	8
> 675 mg - 1350 mg	13	28
> 1350 mg - 2025 mg	7	21
> 2025 mg - 2700 mg	4	16
> 2700 mg - 3375 mg	8	41
> 3375 mg - 6750 mg	31	237
> 6750 mg	9	129
Total	**80**	**480**

AML=acute myeloid leukaemia; MDS=myelodysplastic syndrome
[a]Dosage was calculated to include 100 mg of cedazuridine and 35 mg of oral decitabine, and one full cycle of Oral Decitabine and Cedazuridine includes 5 days of 135 mg per day, for a total of 675 mg.
[b]1 cycle = 28 days; partial cycles were calculated as full cycles.

Table 2.3-4	**SIII.4: Clinical Trial Exposure to Oral Decitabine and Cedazuridine by Race (by Indication)**	
Race	**Persons**	**Person Cycles**
Indication - MDS		
American Indian or Alaska Native	0	0
Asian	4	21
Black or African American	6	24
Native Hawaiian or Other Pacific Islander	0	0
White	195	1244
More than One Race	0	0
Not Reported	5	28
Other[a]	3	30
Total	**213**	**1347**
[a] Three subjects who reported race as "Other" identified as South African/Portuguese, Cuban, and Unknown.		
Indication - AML		
American Indian or Alaska Native	0	0
Asian	0	0
Black or African American	0	0
Native Hawaiian or Other Pacific Islander	0	0
White	0	0
More than One Race	0	0
Not Reported	80	480

Table 2.3-4	**SIII.4: Clinical Trial Exposure to Oral Decitabine and Cedazuridine by Race (by Indication)**	
Race	**Persons**	**Person Cycles**
Other	0	0
Total	**80**	**480**
AML=acute myeloid leukaemia; MDS=myelodysplastic syndrome		

2.4 Module SIV: Populations Not Studied in Clinical Trials

There were a number of exclusion criteria in the ASTX727-02 EU (pivotal) clinical programme.

2.4.1 SIV.1: Exclusion Criteria in Pivotal Clinical Study Within the Development Programme

Table 2.4.1-1	**SIV.1-1: Exclusion Criteria in Pivotal Clinical Study ASTX727-02 EU**		
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
Prior treatment with more than 1 cycle of azacitidine or decitabine. Prior cytotoxic chemotherapy for AML except for hydroxyurea to control high white blood cell (WBC) counts.	This would have confounded the clinical end point of the study.	No	This population was excluded as previous treatment with HMA would have confounded the study clinical endpoint. However, these patients should not be excluded from treatment in general clinical setting when the drug is approved.
Treated with any investigational drug or therapy within 2 weeks of study treatment, or 5 half- lives, whichever is longer, before the protocol-defined first dose of study treatment, or ongoing clinically significant adverse events from previous treatment with investigational drug or therapy.	These subjects were excluded to eliminate the influence of delayed and ongoing adverse events related to previous therapies on safety assessment of INAQOVI	No	Exclusion of this population is to ensure better evaluation of potential adverse events related to INAQOVI during the clinical trial. No further evaluation in the pharmacovigilance plan is warranted. Physicians should make treatment decisions with INAQOVI based on the benefits and risks for each individual patient.
Cytotoxic chemotherapy or prior azacitidine or decitabine within 4	These subjects were restricted to minimize their influence on safety assessments and because of the potential	No	Physicians should make treatment decisions with INAQOVI based on the benefits and risks for each individual patient.

Table 2.4.1-1	**SIV.1-1: Exclusion Criteria in Pivotal Clinical Study ASTX727-02 EU**		
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
weeks of first dose of study treatment.	for confounding the clinical endpoints of the study.		
Poor medical risk because of other conditions such as uncontrolled systemic diseases or uncontrolled active human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). Hospitalisation for more than 2 days for documented febrile neutropenia, pneumonia, sepsis, or systemic infection in the 30 days before screening.	These subjects were excluded to mitigate the risk of study drop-out prior to completion of 2 cycles of treatment which was critical for the primary endpoint.	No	No further evaluation in the pharmacovigilance plan is warranted. Physicians would make treatment decisions with INAQOVI based on the benefits and risks for each individual patient. Other viral and bacterial infections are common complications of treatment and progressive AML.
Laboratory abnormalities, which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of INAQOVI, or compromise the integrity of the study outcomes.	These subjects were excluded to make sure that PK data was not confounded by other parameters.	No	No further evaluation in the pharmacovigilance plan is considered warranted. Physicians should make treatment decisions with INAQOVI based on the benefits and risks for each individual patient.
Known significant mental illness or other condition, such as active alcohol or other substance abuse or addiction, that in the opinion of the investigator predisposes the subject to high risk of noncompliance with the protocol.	This was done to maintain compliance with the study.	No	Exclusion of this population is to ensure study treatment compliance. However, physicians should consider the ability of individual patients to comply with an oral regimen. No further evaluation in the pharmacovigilance plan is warranted.
Rapidly progressive or highly proliferative	Patients with high WBC count may	No	High WBC count or leukocytosis is known to

Table 2.4.1-1	**SIV.1-1: Exclusion Criteria in Pivotal Clinical Study ASTX727-02 EU**		
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
disease (total WBC count of >15 × 109/L) or other criteria that render the subject at high risk of requiring intensive cytotoxic chemotherapy within the next 3 months.	develop rapidly progressive disease and may require chemotherapy, thus interrupting the first 2 PK cycles.		reduce long term survival in AML patients. Physicians should make treatment decisions with INAQOVI based on the benefits and risks for each individual patient.
Life-threatening illness or severe organ system dysfunction, such as uncontrolled congestive heart failure or uncontrolled chronic obstructive pulmonary disease, or other reasons that may compromise completion of the study or integrity of the study outcomes.	Subjects were excluded to minimize the risk of mortality and study drop out prior to completion of 2 cycles of treatment	Yes (uncontrolled cardiac, renal, hepatic)	This study is for patients with AML who are ineligible for intensive chemotherapy, and subjects for example with CHF and chronic obstructive pulmonary disease (COPD) were not excluded if they were assessed to be stable at screening baseline and their comorbid conditions were assessed to be maintainable by the investigator. Physicians should consider whether the benefits of INAQOVI treatment are expected to outweigh the risks of treatment.
Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, non-metastatic prostate cancer with normal prostate-specific antigen (PSA), or other cancer from which the subject has been disease free for at least 2 years.	These subjects were excluded to limit the impact of other active malignancies, which may interfere with adequate evaluation of safety and PK.	No	No further evaluation in the pharmacovigilance plan is warranted. Physicians should make treatment decisions with INAQOVI based on the benefits and risks for each individual patient.
Known or suspected hypersensitivity to decitabine or the components of cedazuridine.	Development of hypersensitivity is a contraindication due to patient safety.	No	Physicians would make treatment decisions with INAQOVI based on benefit and risks for each individual patient. Hypersensitivity to the active substance(s) or to any of the excipients is a contraindication in the INAQOVI EU SmPC.
Conditions that interfere with the	These subjects were excluded to ensure that	No	Patients with conditions that interfere with the absorption or

Table 2.4.1-1	**SIV.1-1: Exclusion Criteria in Pivotal Clinical Study ASTX727-02 EU**		
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
absorption or metabolism of INAQOVI.	PK data was not confounded by other parameters.		metabolism of INAQOVI, such as active, uncontrolled gastric or duodenal ulcers were excluded from the study to minimize the potential risk of reduced absorption of oral drug. No further evaluation in the pharmacovigilance plan is warranted. Physicians should make treatment decisions with INAQOVI based on the benefits and risks for each individual patient.
Women of child-bearing potential must not be pregnant or breastfeeding and must have a negative pregnancy test at screening. Women of non-childbearing potential are those who have had a hysterectomy or bilateral oophorectomy, or who have completed menopause, defined as no menses for at least 1 year AND either age ≥65 years or follicle-stimulating hormone (FSH) levels in the menopausal range.	It is common clinical practice to exclude pregnant women from anticancer clinical trials.	No	Based on its mechanism of action and findings in animals, decitabine (one of the active ingredients in the INAQOVI FDC tablet) is expected to cause foetal harm when administered to a pregnant woman. Decitabine alters DNA synthesis and is expected to result in adverse reproductive effects. In nonclinical studies with decitabine in mice and rats, decitabine was teratogenic, foetotoxic, and embryotoxic. The EU SmPC includes language regarding pregnancy and use of INAQOVI in the Fertility, pregnancy and lactation section. This risk is being appropriately managed and there are no plans to investigate further.
Subjects and their partners with reproductive potential must agree to use effective contraceptive measures during the study and for 3 months after the last dose of study treatment. Effective contraception includes methods such as oral contraceptives,	It is common clinical practice in anticancer clinical trial that patients do not conceive during active treatment as INAQOVI in animal studies is known to be teratogenic.	No	It is common clinical practice in anticancer clinical trial that patients do not conceive during active treatment. Based on its mechanism of action and findings in animals, decitabine (one of the active ingredients in the INAQOVI FDC tablet) is expected to cause foetal harm when administered to a pregnant woman or a man with female

Table 2.4.1-1	**SIV.1-1: Exclusion Criteria in Pivotal Clinical Study ASTX727-02 EU**		
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
double-barrier method (use of a condom AND diaphragm, with spermicide), or abstaining from sexual intercourse.			partner of childbearing potential. Decitabine alters DNA synthesis and is expected to result in adverse reproductive effects. In nonclinical studies with decitabine in mice and rats, decitabine was teratogenic, foetotoxic, and embryotoxic. Section 4.6 of the EU SmPC includes language regarding pregnancy and use of INAQOVI FDC in the Fertility, pregnancy and lactation section. This risk is being appropriately managed and there are no plans to investigate further.
Hepatic exclusion criteria included - Total or direct bilirubin ≥2 × upper limit of normal (ULN); AST/SGOT and ALT/SGPT ≥2.5 × ULN	Moderate and severe hepatic impairment was excluded for safety reasons and as recommended by National Cancer Institute (NCI).	Yes	Not applicable
Renal exclusion criteria included - serum creatinine ≥1.5 × ULN or calculated creatinine clearance or glomerular filtration rate <50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal.	Moderate to severe renal impairment was excluded for safety reasons and as recommended by NCI.	Yes	Not applicable

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

The INAQOVI clinical development programme is unlikely to detect certain types of adverse reactions especially adverse reactions related with a long latency, or those caused by prolonged or cumulative exposure.

With an overall oral decitabine and cedazuridine exposure of 288 subjects, any AE with incidence lower than 1/288 will not be detected. Once the drug is in the market post-

marketing pharmacovigilance surveillance and signal detection would detect uncommon and rare adverse drug reactions (ADRs).

2.4.3 SIV.3: Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programmes

Table 2.4.3-1 Exposure of Special Groups Included or not in Clinical Trial Development Programmes

Type of Special Group	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant comorbidities: • Patients with moderate or severe hepatic impairment • Patients with severe renal impairment • Patients with severe cardiac disease • Immunocompromised patients and/or with uncontrolled severe infection • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme for safety reasons.
Population with relevant different races	Race was not reported in the AML study because of local regulatory requirements
Subpopulations carrying relevant genetic polymorphisms	There was no specific genetic testing done for polymorphism in the INAQOVI clinical programme.

2.5 Module SV: Postauthorisation Experience

2.5.1 SV.1: Postauthorisation Exposure

2.5.1.1 SV.1.1: Method Used to Calculate Exposure

Estimates of patient exposure are based on the availability of monthly sales and "free goods" distribution figures per product. Due to the limitations of this approach, it is not possible to reliably estimate the number of patients treated with marketed oral decitabine and cedazuridine. The trade name of oral decitabine and cedazuridine being marketed in the US and Canada is INQOVI for Myelodysplastic Syndrome (MDS). The cumulative estimates have been calculated to 16 Jan 2022.

The following assumptions were used to arrive at an estimation of the number of patients treated with oral decitabine and cedazuridine.

- The Average Defined Dose (ADD) for oral decitabine and cedazuridine is 1 dose pack containing 5 tablets. One (1) tablet contains 35 mg of decitabine and 100 mg

cedazuridine and is taken orally once daily on day 1 through 5 of each 28-day cycle.

- Each patient received the ADD of 1 dose pack (5 tablets).
- Each patient received this dose for 4 cycles of treatment.
- Each patient received a total dose of 4 dose packs (20 tablets).

Sales figures for oral decitabine and cedazuridine were received from 07 Jul 2020 to 16 Jan 2022.

It is difficult to determine the number of patients treated with oral decitabine and cedazuridine during the post marketing experience. Therefore, the number of patients exposed is an estimation based on these sales data, an estimated [redacted] dose packs [redacted] sold. Taking into account the available sales data distributed by the marketing authorization holder (MAH) and the assumptions as described above, the cumulative number of patients exposed to commercial oral decitabine and cedazuridine is estimated to be 3,791.

A summary of the worldwide distribution of oral decitabine and cedazuridine cumulatively until 16 Jan 2022 is presented in Table 2.5.1.2-1.

2.5.1.2 SV.1.2: Exposure

The estimated cumulative number of patients treated with marketed oral decitabine and cedazuridine worldwide as of 16 Jan 2022 was approximately 3,791.

A summary of the worldwide distribution of oral decitabine and cedazuridine cumulatively until the 16 Jan 2022 is presented in Table 2.5.1.2-1.

Table 2.5.1.2-1 SV.1.2-1: Estimated Post marketing Exposure by Country/Region

Country /Region	Number of Dose Packs (Units)	Total Number of Tablets	Patient Exposure (Number of Patients[a])
Indication: MDS			
Australia	[redacted]		0
Canada			639
United States			3,152
Total (All Countries)			3,791
Indication: AML			
Australia	0	0	0
Canada	0	0	0

Table 2.5.1.2-1 SV.1.2-1: Estimated Post marketing Exposure by Country/Region			
Country /Region	**Number of Dose Packs (Units)**	**Total Number of Tablets**	**Patient Exposure (Number of Patients[a])**
United States	0	0	0
Total (All Countries)	0	0	0
[a]Algorithm: Number of Dose Packs ÷ 4 cycles = Number of Patients			

2.6 Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

This section is not applicable as INAQOVI is an antineoplastic agent and has no abuse potential.

2.7 Module SVII: Identified and Potential Risks

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

The summary of safety concerns identified for INAQOVI in this initial RMP submission are described in the sections below.

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

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

Known risks that do not impact the risk-benefit profile

The following risks are not considered to impact the risk-benefit profile: neutropenia, anaemia, thrombocytopenia, pancytopenia, febrile neutropenia, pneumonia, sepsis/septic shock, haemorrhage, urinary tract infection, other infections (excluding pneumonia and sepsis/septic shock, and urinary tract infection), and hypersensitivity including anaphylactic reaction. This assessment was based on the risks being well-characterised, recognised and managed within the scope of practicing Health Care Professionals (HCPs) for IV decitabine. Their recognition and management have been integrated within standard clinical practice, and they only require routine pharmacovigilance and routine risk minimisation measures. No safety data have emerged since initiation of the AML clinical trial programme that would suggest a quantitative or qualitative change for these identified risks.

Cardiomyopathy was assessed as a not important identified risk based on the very rare frequency of occurrence in spontaneous cases in IV decitabine, and the event does not lead to a treatment discontinuation of IV decitabine in majority of cases and is not considered an important risk for other Medicinal Products of the same class. A thorough review of the Cardiomyopathy standard MedDRA query (SMQ; narrow) was conducted for ASTX727-02 AML clinical trial. One subject reported a non-serious event of ejection fraction decreased assessed by the investigator as not related. A thorough review of the case by the Sponsor revealed the ejection fraction decreased was confounded by comorbid cardiac conditions.

Interstitial lung disease (ILD) was assessed as a not important potential risk based on lack of causal association between decitabine and ILD, currently unknown frequency of ILD in IV decitabine, and is not considered an important potential risk for IV decitabine. A thorough review of the ILD standard MedDRA query (SMQ; narrow) was conducted for ASTX727-02 AML clinical trial. One subject reported a non-serious event of pneumonitis assessed by the investigator as not related. A thorough review of the case by the Sponsor revealed pneumonitis was confounded by an ongoing concurrent acute infection.

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

Table 2.7.1.2-1 SVII.1.2-1: Summary of Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: None	
Risk Seriousness	None
Risk Frequency	None
Clinical and Risk-Benefit Impact	None
Important Potential Risk: None	
Risk Seriousness	None
Risk Frequency	None
Clinical and Risk-Benefit Impact	None
Missing Information: Use in severe renal impairment, moderate and severe hepatic impairment, and severe cardiac disease (e.g., uncontrolled angina or severe congestive heart failure [New York Heart Association [NYHA] III-IV])	
Clinical and Risk-Benefit Impact	Patients with a history of severe renal impairment, moderate and severe hepatic impairment, and severe cardiac disease were excluded from the clinical trials. The safety risk in this population has not been evaluated. The Company does not consider that there is any impact on the benefit-risk balance of INAQOVI.

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

This section is not applicable as there are no new safety concerns or reclassified risks.

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

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

Details of Important Identified Risk: None

Details of Important Potential Risk: None

2.7.3.2 SVII.3.2: Presentation of Missing Information

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Severe Renal Impairment**
MedDRA Terms	N/A. Verbatim: Use in severe renal impairment
Evidence Source(s)	Patients with severe renal impairment were excluded from clinical trials. Therefore, use in patients with severe renal impairment has not been studied. Caution should be exercised in the administration of INAQOVI to patients with severe renal impairment (Creatinine Clearance [CrCl] <20 ml/min/1.73 m^2) and these patients should be monitored closely. There is an ongoing clinical pharmacokinetic trial in severe renal impairment and/or end stage renal disease subjects as a condition of marketing approval in the United States. The trial name is Study ASTX727-17: Clinical pharmacokinetic trial in severe renal impairment and/or end stage renal disease subjects.

Table 2.7.3.2-2	**SVII.3.2-2: Details of Missing Information: Use in Moderate and Severe Hepatic Impairment**
MedDRA Terms	N/A. Verbatim: Use in moderate and severe hepatic impairment
Evidence Source(s)	Patients with moderate and severe hepatic impairment were excluded from clinical trials. Therefore, use in patients with moderate and severe hepatic impairment has not been established. Caution should be exercised in the administration of INAQOVI to patients with moderate and severe hepatic impairment and patients should be monitored closely. There is an ongoing clinical pharmacokinetic trial in moderate and severe hepatic impairment subjects as a condition of marketing approval in the United States. The trial name is Study ASTX727-18: Clinical pharmacokinetic trial in moderate and severe hepatic impairment subjects.

Table 2.7.3.2-3	**SVII.3.2-3: Details of Missing Information: Use in Severe Cardiac Disease (eg, uncontrolled angina or severe congestive heart failure [NYHA III-IV])**
MedDRA Terms	N/A. Verbatim: Use in severe cardiac disease
Evidence Source(s)	Patients with a history of severe cardiac disease were excluded from clinical studies and therefore the safety and efficacy of INAQOVI in these patients has not been established. Caution should be exercised in the administration of INAQOVI to patients with severe cardiac disease and patients should be monitored closely.

2.8 Module SVIII: Summary of the Safety Concerns

The Important Identified Risks, Important Potential Risks, and Missing Information with INAQOVI are based on the nonclinical, clinical trial, and post-marketing experience and are summarised in Table 2.8-1.

Table 2.8-1	**SVIII-1: Summary of Ongoing Safety Concerns**
Important Identified Risks	• None
Important Potential Risks	• None
Missing Information	• Use in severe renal impairment • Use in moderate and severe hepatic impairment • Use in severe cardiac disease (e.g., uncontrolled angina or severe congestive heart failure [New York Heart Association [NYHA] IIIIV])

3 PART III: PHARMACOVIGILANCE PLAN (Including Postauthorisation Safety Studies)

3.1 III.1: Routine Pharmacovigilance Activities

3.1.1 Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific adverse reactions follow-up questionnaires: No specific adverse reactions follow-up questionnaire is planned for INAQOVI.

Other forms of routine pharmacovigilance activities: No other forms of routine pharmacovigilance activities are planned.

3.2 III.2: Additional Pharmacovigilance Activities

Not applicable.

3.3 III.3: Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1 III.3-1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
None	None	None	None	None

4 PART IV: PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

No such study required.

5 PART V: RISK MINIMISATION MEASURES (including evaluation of the effectiveness of risk minimisation activities)

5.1 V.1: Routine Risk Minimisation Measures

A description of routine risk minimisation measures by safety concern is provided in Table 5.1-1.

Table 5.1-1 V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risk	
None	
Important Potential Risk	
None	
Missing Information	
Use in severe renal impairment	Routine risk communication: • SmPC: o Section 4.2 Posology and method of administration: Special Populations o Section 4.4 Special warnings and precautions for use: Renal impairment o Section 5.2 Pharmacokinetic properties: Special populations • PL Section 2, where patients are advised to notify their healthcare provider before using Inaqovi in case of serious kidney disorder Routine risk minimisation activities recommending specific clinical measures to address the risk: o Recommendation for serum creatinine monitoring are included in Section 4.2 Posology and method of administration: *Dose Adjustments* Other routine risk minimisation measures beyond the Product Information: • Medicinal product subject to restricted medical prescription

Table 5.1-1	**V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern**
Safety Concern	**Routine Risk Minimisation Activities**
Use in moderate and severe hepatic impairment	Routine risk communication: • SmPC: o Section 4.2 Posology and method of administration: Special populations o Section 4.4 Special warnings and precautions for use: Hepatic impairment o Section 5.2 Pharmacokinetic properties: Special populations • PL Section 2, where patients are advised to notify their healthcare provider before using Inaqovi in case of liver disorder Routine risk minimisation activities recommending specific clinical measures to address the risk: o Recommendation for liver chemistry monitoring are included in Section 4.2 Posology and method of administration: *Dose Adjustments* Other routine risk minimisation measures beyond the Product Information: • Medicinal product subject to restricted medical prescription
Use in severe cardiac disease (e.g., uncontrolled angina or severe congestive heart failure, [NYHA III-IV])	Routine risk communication: • SmPC: o Section 4.4 Special warnings and precautions for use: Cardiac disease • PL Section 2, where patients are advised to notify their healthcare provider before using Inaqovi in case of heart disorder Other routine risk minimisation measures beyond the Product Information: • Medicinal product subject to restricted medical prescription

5.2 V.2: Additional Risk Minimisation Measures

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

5.3 V.3: Summary of Risk Minimisation Measures

Table 5.3-1 V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
None	Not applicable	Not applicable
Important Potential Risks		
None	Not applicable	Not applicable
Missing Information		
Use in severe renal impairment	Routine risk minimisation measures: • SmPC Section 4.2 Posology and method of administration, where serum creatinine monitoring is recommended, Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties • PL Section 2, where patients are advised to notify their healthcare provider before using Inaqovi in case of serious kidney disorder • Medicinal product subject to restricted medical prescription No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: • None

Table 5.3-1 V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Use in moderate and severe hepatic impairment	Routine risk minimisation measures: • SmPC Section 4.2 Posology and method of administration, where liver chemistry monitoring is recommended, Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties • PL Section 2, where patients are advised to notify their healthcare provider before using Inaqovi in case of liver disorder • Medicinal product subject to restricted medical prescription No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: • None
Use in severe cardiac disease (eg, uncontrolled angina or severe congestive heart failure [NYHA III-IV])	Routine risk minimisation measures: • Section 4.4 Special warnings and precautions for use • PL Section 2, where patients are advised to notify their healthcare provider before using Inaqovi in case of heart disorder • Medicinal product subject to restricted medical prescription No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: • None

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

6.1 VI.1: Summary of the Risk Management Plan for INAQOVI (Decitabine and Cedazuridine)

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

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

This summary of the RMP for INAQOVI 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 INAQOVI’s RMP.

6.1.1 I: The Medicine and What it is Used for

INAQOVI (decitabine and cedazuridine) is indicated as monotherapy for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy. INAQOVI is administered orally and contains decitabine and cedazuridine as the active ingredients. Additional information about the benefits of INAQOVI can be found in the Summary of Product Characteristics (SmPC).

Further information about the evaluation of INAQOVI’s benefits can be found in INAQOVI’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

6.1.2 II: Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of INAQOVI, together with measures to minimise such risks and the proposed studies for learning more about INAQOVI '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 Summary of Product Characteristics (SmPC) addressed to patients and healthcare professionals, respectively;
- 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, for example, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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

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

6.1.2.1 II.A: List of Important Risks and Missing Information

Important risks of INAQOVI 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 INAQOVI. 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).

Table 6.1.2.1-1 List of Important Risks and Missing Information

Important identified risks	None
Important potential risks	None
Missing information	Use in severe renal impairment Use in moderate and severe hepatic impairment Use in severe cardiac disease (eg, uncontrolled angina or severe congestive heart failure [NYHA III-IV])

6.1.2.2 II.B: Summary of Important Risks

Table 6.1.2.2-1 II.B-1: Missing Information: Use in severe renal impairment	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 4.2 Posology and method of administration, where serum creatinine monitoring is recommended, Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties • PL Section 2, where patients are advised to notify their healthcare provider before using Inaqovi in case of serious kidney disorder • Medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • No additional risk minimisation measures.

Table 6.1.2.2-2 II.B-2: Missing Information: Use in moderate and severe hepatic impairment	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 4.2 Posology and method of administration, where liver chemistry monitoring is recommended, Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties • PL Section 2, where patients are advised to notify their healthcare provider before using Inaqovi in case of liver disorder • Medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • No additional risk minimisation measures.

Table 6.1.2.2-3	**II.B-3 Missing Information: Use in severe cardiac disease (eg, uncontrolled angina or severe congestive heart failure [NYHA III-IV])**
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 4.4 Special warnings and precautions for use • PL Section 2, where patients are advised to notify their healthcare provider before using Inaqovi in case of heart disorder • Medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • No additional risk minimisation measures.

6.1.2.3 II.C: Post-authorisation Development Plan

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

N/A

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

N/A.

7 PART VII: ANNEXES TO THE RISK MANAGEMENT PLAN

7.4 Annex 4: Specific Adverse Drug Reaction Follow-up Forms

This annex is not applicable as there are no specific adverse drug reaction follow-up forms.

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

This annex is not applicable as there are no additional risk minimisation activities proposed.

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