EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2023
EMA/CHMP/402324/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inaqovi

International non-proprietary name: Decitabine / Cedazuridine

Procedure No. EMEA/H/C/005823/0000

Note

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

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Table of contents

List of abbreviations

AE	adverse event
AML	acute myeloid leukaemia
ANOVA	analysis of variance
AUC	area under the plasma concentration-time curve
AUC0-8 postdose	area under the plasma concentration-time curve from time 0 to 8 hours
AUC0-24 postdose	area under the plasma concentration-time curve from time 0 to 24 hours
AUC0-inf	area under the plasma concentration time curve from time 0 to infinity
AUC0-t	area under the plasma concentration time curve from time 0 to the time of last measurable concentration
AUEC	area under the effect curve
AUECD29	area under the effect curve for long interspersed nucleotide element-1 demethylation from Day 1 to Day 29
ASMF	active substance master file = drug master file
ASTX727	fixed dose combination of 35 mg decitabine and 100 mg cedazuridine, proposed product name "Inaqovi".
ASTX727-02 EU	study ASTX727-02 conducted in Canada and Europe in patients with AML (Clinical Study Report ASTX727-02-C)
ASTX727-02 NA	Study ASTX727-02 conducted in North America in patients with MDS and CMML (Clinical Study Report ASTX727-02-B)
BCS	biopharmaceutics classification system
BM	bone marrow
BQL	below quantifiable limit
BSA	body surface area
CDA	cytidine deaminase
CDAi	cytidine deaminase inhibitor
cedazuridine	international non-proprietary name for E7727
CFR	Code of Federal Regulations
CFU	colony forming units
CHMP	Committee for Human Medicinal Products
CI	confidence interval
CMML	chronic myelomonocytic leukaemia
CPMP	Committee for Proprietary Medicinal Products

CQA	critical quality attribute
CRh	complete response with partial hematologic recovery
CRi	complete response with incomplete blood count recovery
CRp	complete response with incomplete platelet recovery
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CV%	percent coefficient of variation
DSC	differential scanning calorimetry
E7727	code used for cedazuridine
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EFS	event-free survival
EMA	European Medicines Agency
EU	European Union
FAB	French-American-British
FDC	fixed-dose combination
GCP	good clinical practice
GI	gastrointestinal
HCT	haematopoietic (stem) cell transplant
HI	haematologic improvement
HI-E	HI-erythroid response
HI-N	HI-neutrophil response
HI-P	HI-platelet response
HMA	hypomethylating agent
HPLC	High performance liquid chromatography
HS-GC	headspace gas chromatography
ICH	International Conference on Harmonisation
INT-1/INT-2	intermediate-1, intermediate-2 risk levels in IPSS
IPSS	International Prognostic Scoring System
IQR	interquartile range
IRC	Independent Review Committee
IV	intravenous

IWG	International Working Group
K-M	Kaplan-Meier
LDPE	low density polyethylene
LFS	leukaemia-free survival
LINE-1	long interspersed nucleotide elements-1
LSM	least squares means
mCR	marrow complete response
MDS	myelodysplastic syndromes
MS	mass spectrometry
NA	North America
NE	not estimable, not evaluable
NMT	not more than
NR	non-responder
OR	overall response
OS	overall survival
PB	peripheral blood
PD	pharmacodynamic(s)
PFS	progression-free survival
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
PR	partial response
PS	performance score
Q	quartile
QbD	quality by design
QC	quality control
QTc: QTcB: QTcF	QT interval corrected; QTc using Bazett's correction formula; QTc using Fridericia's correction formula
QTPPq	Quality target product profile
RBC	red blood cell (count)
SAE	serious adverse event
SCE	summary of clinical efficacy
SD	standard deviation
SE	standard error

TAMC	total aerobic microbial count
TEAE	treatment-emergent adverse event
TI	transfusion independence
TYMC	total yeasts and moulds count
ULN	upper limit of normal
US	United States
USP-NF	United States Pharmacopoeia/National Formulary
WBC	white blood cell (count)
WHO	World Health Organisation
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Otsuka Pharmaceutical Netherlands B.V. submitted on 26 July 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Inaqovi, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 10 December 2020.

Inaqovi, was designated as an orphan medicinal product EU/3/21/2548 on 10 December 2021 in the following condition: Treatment of acute myeloid leukaemia.

On 5 July 2023, during the ongoing initial application procedure, the applicant withdrew the orphan designation.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was removed from the Union Register of designated orphan medicinal products on 5 July 2023. More information on the COMP's review can be found in the orphan withdrawal assessment report published under the 'Assessment history' tab on the Agency's website:

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

The applicant applied for the following indication:

Inaqovi is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0217/2022 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0217/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

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

1.6. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

The protocol assistance pertained to the following aspects:

Quality and Non-clinical:

- Orphan similarity.

Non-clinical:

- Overall non-clinical development.

Clinical:

- Acceptability of the, at the time, ongoing pivotal Phase 3 ASTX72702 study design for MAA for treatment of adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.
- Patient eligibility criteria.
- Agreement that the proposed clinical development program would provide adequate safety and exposure data for MAA.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Blanca Garcia Ochoa subsequently replaced by Carolina Prieto Fernandez

The application was received by the EMA on	26 July 2022
The procedure started on	18 August 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 November 2022

The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	25 November 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 November 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 December 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 March 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	2 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	5 July 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Inaqovi on	20 July 2023
The CHMP adopted a report on similarity of Inaqovi with Dacogen, Mylotarg, Xospata, Daurismo, Vyxeos liposomal, Rydapt and Tibsovo on (see Appendix on similarity)	20 July 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	20 July 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication for Inaqovi (ASTX727) is for the 'treatment of adult patients with newly diagnosed AML who are ineligible for standard induction chemotherapy.'

Acute myeloid leukaemia (AML) is a clonal disorder caused by malignant transformation of a bone marrow derived, myeloid stem cell or progenitor cell, that fail to undergo normal differentiation. AML is differentiated from other haematopoietic malignancies by the presence of greater than 20% myeloblasts in the bone marrow.

2.1.2. Epidemiology and risk factors, screening tools/prevention

AML is the most common form of acute leukaemia in adults, with incidence increasing with age and the shortest survival (5-year survival 24%) (Shallis et al 2019). The median age at diagnosis is 67 years (Fey and Buske 2013). The median age at diagnosis of AML is 67 years (Fey and Buske 2013). Based on the data from Globocan 2020 (Sung et al 2021), European Cancer Information System (ECIS) 2022 (ECIS 2022), and Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) in the United States (NCI SEER), supportive literature, and other community data, the estimated prevalence of AML in the European Union is below 5 per 10,000. In general, AML in elderly patients is more likely to be preceded by myelodysplastic syndrome, to have unfavourable cytogenetics, and to be refractory to chemotherapy (Appelbaum et al 2006).

2.1.3. Clinical presentation, diagnosis and prognosis

The clinical presentation of AML is directly related to ineffective haematopoiesis; patients typically present with signs and symptoms of fatigue, haemorrhage, as well as infections and fever (Löwenberg 1999). The effects of uncontrolled, exaggerated growth and accumulation of blasts that fail to function as normal blood cells, and the resultant reduction of normal marrow cells, are anaemia, thrombocytopenia, and neutropenia. Untreated, AML is a rapidly progressing and fatal disease that requires prompt attention (Gilliland 2008). Only 20% of AML patients >70 years are alive 1 year after the diagnosis (Naur et al 2021).

In addition to age, other adverse prognostic indicators in AML include adverse cytogenetic or molecular genetic abnormalities, past exposure to chemicals, radiation, or chemotherapy, or history of another haematological disorder (Schiffer 2021). There are correlations between age at diagnosis of AML, medical comorbidities, and underlying cytogenetic and molecular aberrations (DiNardo and Cortes 2016); furthermore, cytogenetics and genetic mutations are the most accurate predictors of treatment resistance (Estey 2018).

2.1.4. Management

Curative therapies, including intensive chemotherapy and allogeneic stem cell transplantation, are generally applicable to the minority of patients who are younger. Patients not suitable for induction therapy (generally >65 years old and/or with significant co-morbidities) are often treated with

hypomethylating agents (HMAs) administered parenterally which imposes a significant treatment burden. The HMAs decitabine (Dacogen®) and azacitidine (Vidaza®) are approved by the EMA for adult patients with AML who are not candidates for standard induction chemotherapy. Administration of these products requires hospital visits for the patient.

2.2. About the product

Inaqovi (ASTX727) is a fixed-dose combination tablet for oral administration, containing 35 mg decitabine and 100 mg cedazuridine. It is intended to provide decitabine exposures equivalent to intravenous (IV) decitabine at the European Union (EU)-approved dose.

Cedazuridine (E7727), is a novel cytidine deaminase (CDA) inhibitor. It is a new chemical entity. Administration of cedazuridine with oral decitabine reduces first pass metabolism of decitabine upon absorption, thus enhancing the oral bioavailability of decitabine so that oral administration is feasible.

Decitabine is a known substance, previously approved for intravenous administration at a dose of 20 mg/m^2 by intravenous infusion over 1 hour repeated daily for 5 consecutive days (i.e., a total of 5 doses per treatment cycle).

The proposed indication for Inaqovi is:

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

This is essentially the same indication as that approved for Dacogen ("*Dacogen is indicated for the treatment of adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy*").

The proposed dosage for Inaqovi is:

The recommended dose of Inaqovi is 1 tablet once daily on Days 1 through 5 of each 28-day cycle. Repeat cycles every 28 days. Treatment with Inaqovi should continue for a minimum of 4 cycles until disease progression or unacceptable toxicity.

Blood cell counts should be obtained prior to initiating Inaqovi and before each cycle. Dose adjustments can be made by reducing the number of treatment days in a cycle or by delaying the next cycle, based on toxicity (haematological and non-haematological).

Inaqovi is intended for self-administration at home.

The application involves a new route of administration for decitabine.

2.3. Type of application and aspects on development

This application is based on a PK bridge, assuming that previous efficacy and safety data for IV decitabine can be extrapolated to Inaqovi if the decitabine plasma exposure (total AUC over the 5-day treatment cycle) is similar.

This is in accordance with the CHMP Scientific advice (EMA/CHMP/SAWP/485806/2018), provided on 26 July 2018, where the CHMP considered that the ongoing pivotal phase 3 randomised, crossover study design (ASTX727-02) with AUC equivalence to decitabine IV as the primary endpoint, and clinical efficacy/safety and biological activity as secondary endpoints, should provide sufficient information to support bridging to the clinical data that supported the approval of Dacogen® (decitabine). If the data demonstrates similarity between ASTX727 and IV decitabine, in terms of the clinically relevant

pharmacokinetics, efficacy and safety, then this would support inclusion of the indication as current registered by Dacogen in the EU. The CHMP advice included recommendations to include AML subjects in the Phase 3 study as well as adding justification for absence of specific nonclinical studies. Study ASTX727-02 was amended to incorporate CHMP's recommendation, including the addition of AML subjects.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film coated tablets containing 35 mg decitabine and 100 mg cedazuridine as active substances.

Other ingredients are:

Tablet core - Lactose monohydrate, hypromellose (E464), croscarmellose sodium (E466), colloidal anhydrous silica, magnesium stearate (E572)

Film-coating - Polyvinyl alcohol (E1203), titanium dioxide (E171), polyethylene glycol (E1521), talc (E553b), iron oxide red (E172).

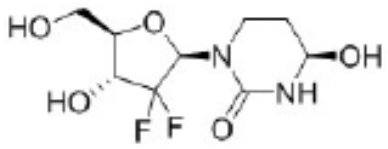
The product is available in PVC/Aluminum blisters with laminated desiccant (3-ply cold formable aluminum-plastic).

2.4.2. Active substance: Cedazuridine

General information

The chemical name of cedazuridine is (4*R*)-1-[(2*R*,4*R*,5*R*)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-4- hydroxy-1,3-diazinan-2-one corresponding to the molecular formula $C_9H_{14}F_2N_2O_5$. It has a relative molecular mass of 268.21 g/mol and the following structure:

Figure 1: Cedazuridine structure



The chemical structure of cedazuridine was elucidated by a combination of ^{1}H-, ^{13}C and ^{19}F spectroscopy, mass spectrometry, infrared spectroscopy, elemental analysis. The solid state properties of the active substance were measured by XRPD and DSC.

Cedazuridine is a white to off-white solid, not hygroscopic, soluble in water and freely soluble in apolar solvents.
Cedazuridine is a chiral molecule with four stereocentres. Cedazuridine has one anomeric stereocentre, which is potentially prone to epimerisation and has β stereochemistry; the required configuration is ensured during the synthesis via a resolution step. All other stereocentres cannot be epimerise. The chirality in regulatory starting material T6 is introduced *via* naturally occurring D-mannitol.
Enantiomeric purity is controlled routinely by chiral HPLC (related substances) and specific optical rotation.

Polymorphism has not been observed for cedazuridine. Only one form was identified, and this was designated as Form A.

Manufacture, characterisation and process controls

A schematic representation of the synthesis of cedazuridine is provided. The specifications and control methods for intermediate products, starting materials and reagents have been presented and updated during the procedure; they are now considered acceptable.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program.

Changes introduced have been presented in sufficient detail and have been justified.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in low density polyethylene (LDPE) bags which complies with EU Commission Regulation No. 10/2011, as amended.

Specification

The active substance specification includes tests for appearance (visual), identification by infrared spectrum (Ph. Eur.), identification by chromatographic retention time (HPLC), assay (HPLC), related substances (HPLC), residual solvents (HS-GC), palladium content (Ph. Eur.), particle size (Ph. Eur.), water (Ph. Eur.), specific rotation (Ph. Eur.), residue on ignition (Ph. Eur.) and microbial examination (Ph. Eur.).

The specification tests and limits are in accordance with ICH and EU guidance documents. The limit for ER-849726 (epimer) has been tightened in line with batch data. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specification limits have been set.

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

Batch analysis data, for three full scale commercial scale batches of the active substance, manufactured by the two proposed manufacturing sites for step 5-8, are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from commercial scale batches of the active substance as manufactured by the proposed manufacturing sites, stored in the intended commercial package for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. All tested parameters were within the specification limits.

Photostability testing following the ICH guideline Q1B was performed on samples of the active substance. Samples were tested forassay and related substances. All tested parameters were within the specification limits.

Results on stress conditions were also provided on samples of the active substance in the solid form and in solution. All tested parameters were within the specification limits in the solid samples. The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period, when stored in the proposed container.

2.4.3. Active substance: Decitabine

General information

The chemical name of decitabine *is* 4-amino-1-[(2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-1,3,5-triazin- 2(1*H*)-one corresponding to the molecular formula $C_8H_{12}N_4O_4$*.* It has a molecular mass of 228.21 g/mol and the following structure:

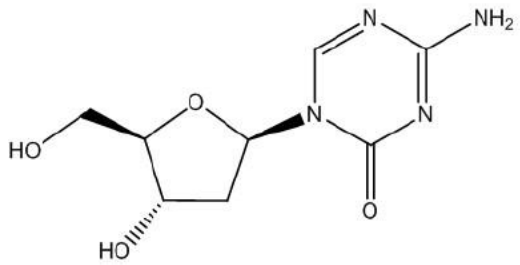


Figure 2: Decitabine structure

The chemical structure of decitabine was elucidated by a combination of IR, GC, MS, elemental analysis, ^{13}C-NMR and ^{1}H-NMR. The solid state properties of the active substance were measured by XPRD.

Decitabine is a white to off-white solid, hygroscopic and slightly soluble in water.

Decitabine is a chiral compound with three stereogenic centres (2*R*, 4*S*, 5*R*). The configuration of decitabine active substance is given by the starting material used in its synthetic process, which is the natural monosaccharide 2-deoxy-D-ribose. The use of this starting material fixes the *S*, *R* configuration of the carbons C4 and C5, respectively. From the starting material, all the intermediates of the synthesis are obtained as a mixture of α and β anomers (C2), until the last manufacturing step where the β-anomer corresponding to decitabine active substance is isolated by crystallisation.

Enantiomeric purity is controlled routinely by optical rotation and as impurity (α-decitabine) in the active substance specifications.

Polymorphism has been observed for decitabine; two forms have been identified: one anhydrous crystalline polymorph (Form A) and a crystalline mono-hydrate (Form B). Form A is consistently produced by the proposed manufacturing process and is stable in long-term stability studies in the commercial packaging.

Manufacture, characterisation and process controls

Decitabine active substance is supported by an ASMF. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process. The manufacturing process of the active substance used in the clinical trial batches is the one proposed for commercial manufacture.

The active substance is packaged in in double LDPE bags which complies with Commission Regulation (EU) 10/2011, as amended.

Specification

The specification for decitabine includes tests for appearance (visual), identification by infrared spectroscopy (Ph. Eur.), identification by chromatographic retention time (HPLC), water content (Ph. Eur.), residue on ignition (Ph. Eur.), specific optical rotation (Ph. Eur.), particle size distribution (Ph. Eur.), assay (anhydrous basis, HPLC), organic impurities (5-azacytosine, α-decitabine, p-chlorobenzoyl decitabine, individual unspecified impurity, total impurities – by HPLC), residual solvent (methanol, GC) and microbial examination (Ph. Eur.).The specification tests and limits are in accordance with ICH and EU guidance. The limit for residue on ignition was tightened during the procedure. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data three commercial scale batches of the active substance are provided. The results are within the specification limits and consistent from batch to batch.

Stability

Stability data from commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. All tested parameters were within the specification limits.

Photostability testing following the ICH guideline Q1B was performed on samples of the active substance. Samples were tested forassay and related substances.

Results on stress conditions were also provided on samples of the active substance in the solid form and in solution. The analytical methods used were the same as for release and were stability indicating.
The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.4.4. Finished medicinal product - Inaqovi

Description of the product and pharmaceutical development

The finished product, Inaqovi, is an oral fixed-dose combination film-coated tablet containing 35 mg decitabine and 100 mg cedazuridine as active substances. The film-coated tablets are red, oval biconvex in shape, 15 mm x 8 mm, plain on one side and debossed with 'H35' on the other side.

No overages are proposed. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, with the exception of iron oxide red which complies with the NF, this is acceptable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

The purpose of the pharmaceutical development was to develop an oral dosage form as an alternative to the approved intravenous (IV) Dacogen, containing decitabine. Cedazuridine is a novel cytidine deaminase inhibitor. Administration of cedazuridine with oral decitabine reduces first pass metabolism of decitabine upon absorption, thus enhancing the oral bioavailability of decitabine so that oral administration is feasible.

Based on the results of a phase 1 clinical study, conducted using capsules containing different concomitant oral doses of cedazuridine and decitabine, a dosage of 100 mg cedazuridine and 35 mg decitabine was identified to provide decitabine exposure comparable to those of the therapeutic dose, 20 mg/m^2, of IV decitabine (Dacogen).

Pharmaceutical development of the finished product contains QbD elements.

The quality target product profile (QTPP) was defined as summarised in below.

Table 1: Quality Target Product Profile

Product Attributes	Quality Target Product Profile
Active pharmaceutical ingredient	For intended therapeutic effects
Dosage and dosing regimen	100 mg of cedazuridine and 35 mg of decitabine administered daily for 5 days in a 28-day treatment cycle.
Route of administration and release characteristics	Oral, immediate-release dissolution characteristics.
Dosage form	Film coated tablet
Container-closure systems	Blister pack with 1 tablet per cavity in a child-resistant design
Shelf life	At least 36 months stored at 20 – 25°C.

An excipient compatibility study was conducted to select appropriate excipients for the finished product formulation. The formulation development has been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes (CQAs) and critical process parameters.

The critical quality attributes identified were: aappearance (allow ease of visual product identification), identification (ascertain active identity), assay (confirm potency), related substances (ascertain product safety), dissolution (ascertain consistent absorption), uniformity of dosage units (ascertain consistent dosages), water content (ascertain product stability) and microbiological limits (ascertain microbial safety of the finished product).

Based on a risk analysis, the formulation ingredients which may have significant effects on the CQAs were identified. These ingredients were evaluated in a design of experiments study to confirm the robustness of the levels of these ingredients in the formulation.

Both cedazuridine and decitabine have high solubility, according to Biopharmaceutics Classification System (BCS). The particle size of these active substances is not expected to have significant impact on the dissolution performance. This has been confirmed by the dissolution of finished product batches manufactured up to date. It was concluded that particle size distribution is not a critical material attribute and micronisation of cedazuridine is not required from dissolution perspective.

Cedazuridine is a crystalline anhydrous free base and is not hygroscopic. It has only one crystalline form based on the results of a polymorph screening study (see active substance section). Form A was shown to be stable under mechanical stress. No significant change in the XRPD pattern was observed after compaction. Decitabine has two polymorphs. Form A, an anhydrate, and form B, a monohydrate. Decitabine Form A has been used in the development of the finished product; it is stable during storage and it was also shown to be stable under mechanical stress. No significant change was observed in the XRPD pattern after compaction. Decitabine is hygroscopic and should be protected from moisture.

The finished product has been formulated as an immediate release tablet, as the compounds have suitable physical, biopharmaceutical, chemical and pharmacokinetic characteristics. A direct compression manufacturing process was successfully developed for the manufacture of the finished product, consisting of sieving, blending, compression, and coating steps. Based on the results of the process development studies, proven acceptable ranges (PARs) have been accepted. During the procedure it has been confirmed that no more than one PAR is varied at a time in each unit operation, in line with guidance. The proposed control strategy and batch analysis data from commercial scale batches fully also support the proposed PARs.

The formulation and manufacturing process for the tablet used in the pivotal clinical study ASTX727-02 are identical to those proposed for the to-be-marketed tablet.

The primary packaging of the finished product is PVC/Aluminum blisters with laminated desiccant (3-ply cold formable aluminum-plastic). The material complies with EU Commission Regulation No. 10/2011, as amended. The suitability of the container closure system in terms of protection from light and moisture, safety of its materials, and compatibility between the materials and the finished product has been demonstrated. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process of the finished product, by direct compression, consists of 7 main steps: 1. pre-blending, 2. de-agglomeration, 3. main blending, 4. lubricant blending, 5. compression, 6 coating and 7. packaging. The process is considered to be a standard manufacturing process.

Satisfactory data on 3 consecutive validation batches has been provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a

reproducible manner. The in-process controls are adequate for this type of manufacturing process. During the procedure, stability data from 2 commercial scale batches has been provided, supporting the proposed bulk holding time of 12 months with no specific storage conditions.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), cedazuridine and decitabine identification (HPLC and MS), cedazuridine and decitabine assay (HPLC), cedazuridine and decitabine degradation products (HPLC), cedazuridine and decitabine dissolution (Ph. Eur.), content uniformity (Ph. Eur.), water (Ph. Eur.) and microbial examination (Ph. Eur.).

During the procedure the shelf-life limits for the assay of both active substances have been tightened. The proposed specifications are in line with guidance requirements and acceptable.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

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

Batch analysis results are provided for 6 commercial scale (process validation or clinical/stability) and 6 pilot scale (clinical and/or stability) batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on five different batches using a validated ICP-MS method were provided, and updated during the procedure, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed, and updated during the procedure, as requested by the CHMP, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020 Rev. 16) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Since the finished product falls under the scope of ICH S9, the point was raised as an "other concern". Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substances or the related finished product. Therefore, no specific control measures are deemed necessary.

Stability of the product

Stability data from three primary stability batches (half of the commercial scale) of finished product stored for up to 36 months under long term conditions (25ºC / 60% RH), for up to 12 months under intermediate conditions (30ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing

(PVC/alu blister). Cedazuridine batches from both of its manufacturers were used to manufacture the stability batches.

Samples were tested in line with the shelf-life specification. All the results were within the specification limits.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant differences were observed in the tested parameters (appearance, assay, degradation, dissolution and water content). The finished product is considered photostable.

Forced degradation studies were conducted on samples of the finished product by exposing them to thermal (70°C open dish) and thermal and humidity (60°C/35%RH open dish). An increase of decitabine degradation products was observed under the thermal with humidity (60°C/35% RH) stress condition. Little or no degradation was observed under the other conditions. Cedazuridine is stable and did not show increased trend of any impurity under the test conditions. The analytical procedures used were stability indicating. Due to the potential for moisture sensitivity of decitabine observed in the forced degradation study, it is recommended to maintain the tablets in the original container closure system.

Based on available stability data, the proposed shelf-life of 36 months, with the following storage conditions Store in the original package in order to protect from moisture. This medicinal product does not require any special temperature storage conditions, as stated in the SmPC (section 6.3), are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner. No major objections were raised during the procedure. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.7. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

2.5.2. Pharmacology

Mechanism of action

Decitabine is a nucleoside metabolic inhibitor that 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. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA.

Cytidine deaminase (CDA) is an enzyme that is responsible for the degradation of cytidine nucleosides, including the cytidine analog decitabine. High levels of CDA in the gastrointestinal tract and liver rapidly degrade these nucleosides and prohibit or limit their oral bioavailability. Cedazuridine inhibits CDA. Oral administration of cedazuridine with decitabine increases the systemic exposure of decitabine via inhibition of first pass metabolism of decitabine in the gut and liver by CDA.

2.5.2.1. Primary pharmacodynamic studies

Primary pharmacodynamics *in vitro*

The *in vitro* nonclinical primary pharmacodynamics (PD) studies have been focused on characterisation of the pharmacological profile of cedazuridine, the new chemical entity (NCE) in ASTX727. The other component, decitabine, is clinically well known as an intravenously administrated hypomethylating agent.

The inhibitory effect of cedazuridine on CDA was confirmed *in vitro*. Cedazuridine potency assays showed a Ki of 400 nM in a preliminary study, and EC50 of 281 ± 58 nM in a definitive study. Furthermore, the addition of cedazuridine to an incubation of gemcitabine and CDA (gemcitabine is a deoxycytidine, partly similar to decitabine, and both are CDA substrates), resulted in an increase in the half-life (t1/2) of gemcitabine from <36 minutes to >66 hours.

Measurement of anti-proliferative activity of cedazuridine in human cancer cell lines demonstrated that cedazuridine**,** as a single agent, do not have an anti-proliferative effect. Thus, the results are in agreement with cedazuridine being able to foster oral use of decitabine with its anti-proliferative effect and not being intended for administration as a single agent.

Primary pharmacodynamics *in vivo*

Administration of oral cedazuridine was demonstrated to enhance anti-tumour activity to oral decitabine, in similarity to anti-tumour activity of IV decitabine, without providing any anti-tumour activity in itself both in a syngeneic and a xenotransplant mouse leukaemia model. It is noted that in the groups receiving the highest dose of cedazuridine in combination with oral decitabine, the survival time was significantly longer as compared to the IV decitabine group. However, since no exposure values were provided, it is not possible to draw any conclusions from such a comparison of survival time.

Demethylating activity on long interspersed nucleotide element-1 (LINE-1) sequences was demonstrated in monkeys orally co-administered decitabine and cedazuridine. The decitabine dose level was kept the same in all groups while for the three groups administered cedazuridine the dose level of cedazuridine was increased stepwise between the groups. However, no control with only oral decitabine was included and no dose response to the various doses of cedazuridine could be observed, making it difficult to conclude on the contribution by the cedazuridine part in this particular study.

2.5.2.2. Secondary pharmacodynamic studies

The *in vitro* secondary pharmacology screen on cedazuridine do not indicate any cause for concern regarding off-target binding. Any off-target concerns for ASTX727 are anticipated to be the result of potential effects of decitabine which has been in clinical use for many years.

2.5.2.3. Safety pharmacology programme

The safety pharmacology studies on cedazuridine do not indicate any cause for concern. Regarding effects on the CV system, the conclusion is based on *in vitro* hERG and actional potential assay data and on *in vivo* evaluations on standard ECG parameters in monkeys (the latter with margins to the recommended clinical dose for AUC of >10-20-fold and for Cmax >10-30-fold). Furthermore, no cedazuridine-related effects were observed in the respiratory system (based on evaluations in conscious monkeys, with margins to the recommended clinical dose for AUC >20-fold and for Cmax >10-fold)) or in the CNS (based on observational battery study in mice after up to highest dose tested at 2000 mg/kg).

2.5.3. Pharmacokinetics

Nonclinical PK evaluations have been conducted to characterise the absorption profiles of cedazuridine, cedazuridine epimer (the main metabolite), decitabine and the combination of cedazuridine and decitabine (i.e., ASTX27). Nonclinical distribution, metabolism, and excretion profiling have been focused on cedazuridine, the NCE part of ASTX27. The single- and repeat-dose PK profiles were examined in mice, rats, and monkeys. Single-dose studies included comparative bioavailability and PK assessment studies with cedazuridine to evaluate potential differences in exposure in multiple species (mice, rats, and monkeys) and with decitabine to evaluate differences in exposure using multiple routes of administration (i.e., oral, IV, or intra-duodenal). The dose-response effects of cedazuridine in inhibiting CDA and increasing systemic decitabine exposure following oral administration, the key feature for the FDC approach, was evaluated in studies in mice and monkeys in which cedazuridine and decitabine were administered concomitantly or at staggered time points.

Distribution, metabolism, and excretion of cedazuridine have been examined in a quantitative whole-body autoradiography (QWBA) and mass balance study in mice following oral dosing and a mass balance study in monkeys following oral or IV dosing. In addition, distribution and metabolism of cedazuridine have been evaluated in *in vitro* studies including plasma protein binding and blood partitioning studies, metabolic stability studies in simulated gastric fluid and in hepatocytes, liver cytosol, and liver S9 fractions. Cytochrome P450 (CYP450) inhibition and induction assays, and human transporter studies are covered in the clinical pharmacokinetic assessment report.

Methods of analysis

Cedazuridine, cedazuridine epimer (the main metabolite), decitabine and cytidine were quantified by LC-MS/MS in samples of mouse, rat and monkey plasma. Parent compound and metabolite concentrations in plasma, urine, faeces, cage rinse and cage debris were obtained by HPLC. Metabolite structural elucidation was performed by the use of LC MS/MS. The bioanalytical methods are considered adequate.

Absorption

A comparative PK study of cedazuridine alone was conducted in mouse, rat and monkey. The results indicate that the oral absorption is fast to moderate in mouse, and moderate in rat and monkey. Furthermore, the PK of cedazuridine in all three species was characterised by a moderate volume of distribution, slow clearance, and moderate t1/2 following IV administration. The oral bioavailability of cedazuridine ranged from 8.9% to 22.9% in mice and indicates possible saturation of absorption and a less than dose-proportional PK. In rats and fasted monkeys, the oral bioavailability of cedazuridine ranged from 10.6% to 15.3% and exposures to cedazuridine were generally dose-proportional over the dose ranges tested. In monkeys, food decreased the absorption of cedazuridine by approximately 50% and the Cmax and AUCinf values in fed animals were approximately 25% and 50%, respectively, of those observed in fasted animals.

In the comparative PK study, an evaluation the cedazuridine epimer was also included. The exposure (AUCinf) to the epimer following oral administration of cedazuridine was noted to be approximately 30% of the exposure of the parent compound in mice while in rats and monkeys, the exposure to the epimer ranged from 51.5% to 62.7% and 28.3% to 38.7% of the parent compound exposure, respectively. The corresponding exposure to the epimer in human plasma following administration of RHD was 43.1 to 46.9% of total radioactivity. In the animal species, a larger formation of the epimer was observed following oral administration than IV administration.

The single-dose PK of decitabine administered alone was evaluated in a single non-GLP study examining the comparative PK of decitabine via multiple routes of administration (IV, oral, and intra-duodenal (ID)) in male rhesus monkeys. When decitabine was administered alone without coadministration with cedazuridine, the plasma concentration declined rapidly with mean terminal t1/2 of 0.17, 0.44 and 0.16 hours, following IV, PO or ID administration, respectively. The results from this study suggest that absorption and bioavailability of decitabine appear to be greater in the stomach than in the duodenum and the small intestine, resulting in higher exposures after oral dosing than after intra-duodenal dosing.

For the PK evaluation of the combination of cedazuridine and decitabine (ASTX727), the dose-response effect of cedazuridine pre-treatment on decitabine systemic exposure was investigated in mice and monkeys.

In the mouse study, following administration of 1 mg/kg of decitabine alone by IV or oral administration, the decitabine plasma concentration declined rapidly with short terminal phase t1/2 values (0.57 and 0.45 hours, respectively). Pretreatment with oral cedazuridine (at 0.1, 1 or 10 mg/kg) 30 min before oral decitabine (0.1 mg/kg) resulted in a decitabine dose-related increase in Cmax (47.4, 63.4 and 71.6 ng/mL) and AUC0-t (45.2, 56.1 and 126 ng*h/mL) as compared to treatment with oral decitabine (0.1 mg/kg) only (Cmax: 23.8 ng/mL, AUC0-t: 22.7 ng*h/mL). As expected, IV administered cedazuridine (1 mg/kg) led to higher cedazuridine exposure than oral cedazuridine (1 mg/kg) but was shown to have a similar level of boosting effect on decitabine plasma exposure as following the orally administered cedazuridine.

In the monkey study, increasing pre-treatment doses of cedazuridine (0.1, 1, and 10 mg/kg) combined with a single oral fixed dose of 10 mg/kg decitabine, administered 2 hours after cedazuridine, resulted in increased systemic exposures to decitabine (AUC 0-t: 138, 1030 and 1130 ng*h/ml; Cmax: 110, 647 and 725 ng/ml, respectively). However, the maximum increase in decitabine exposure was achieved with cedazuridine pre-treatment at 1 mg/kg, and no further increase occurred at 10 mg/kg cedazuridine, although a dose-related 4- to 5-fold increase in cedazuridine AUC and Cmax occurred. Thus, increasing the dose of cedazuridine from 1 to 10 mg/kg resulted in a less than dose proportional increase in oral decitabine exposure. No control with only oral decitabine was included. The decitabine half-life for the cedazuridine 1 and 10 mg/kg treated groups was 1.45 and 1.05 hours, respectively. For the cedazuridine 0.1 mg/kg treated group the decitabine half-life were not determined due to insufficient data.

Pre-administration of the cedazuridine epimer (1 mg/kg) to mice prior to oral administration of decitabine (0.1 mg/kg) resulted in plasma exposures of decitabine that was approximately 25% of those observed following cedazuridine pre-treatment. As also observed in monkey, the epimer plasma concentrations were higher following an oral dose of cedazuridine (1 mg/kg) in comparison to an equivalent IV dose of cedazuridine, possibly due to higher inter-conversion of the epimer in the GI tract prior to or during absorption.

To evaluate a more clinically relevant dose of decitabine, an additional study in monkeys was conducted. In this study, increasing doses of oral cedazuridine followed 1 hour later by a fixed oral dose of decitabine (3 mg/kg) resulted in a dose-dependent increase in decitabine exposure (table 1). However, the decitabine t1/2 did not show any clear dose-dependent pattern.

Table 7. PK of decitabine in monkeys after oral decitabine and increasing doses of oral Cedazuridine

Dose (mg/kg)		AUC0-t (ng*h/mL)	AUC0-t Fold Increase	Cmax (ng/mL)	Cmax Fold Increase	tmax (h)	t1/2 (h)
Decitabine	Cedazuridine						
3	0	21.7	1.0	24.4	1.0	1.7	0.3
3	0.1	138.4	6.4	140.2	5.7	1.4	0.4
3	0.3	164	7.6	128.9	5.3	1.8	0.7
3	1	300.6	13.9	281.1	11.4	1.8	0.5
3	3	582.2	26.8	425	17.4	2	0.5
3	10	1494.3	68.9	622	25.5	2.3	0.7

Circulating cedazuridine epimer exposures, although varied across individual animals and groups, appeared on average to be at near-equivalent levels compared to cedazuridine. Based on formulation analysis and observed epimer exposures, it can be concluded that it is apparent that most of the cedazuridine conversion to its epimer takes place following dosing by the oral route and this is accepted.

The plasma cytidine levels appeared to increase transiently after treatment with cedazuridine in a dose-dependent manner and it is consistent with cedazuridine acting as an inhibitor of CDA. The plasma cytidine levels reverted to or trended towards baseline by 8 hours post-dose. it is suggested that this change in plasma cytidine can be a surrogate measure of the CDA inhibitory effect of cedazuridine.

Distribution

Tissue distribution was evaluated after oral dosing of [14C]-cedazuridine in non-pigmented (CD-1) and pigmented (C57BL/6) mice by quantitative whole-body autoradiography (QWBA). Cedazuridine was rapidly absorbed and distributed to tissues but [14C]-cedazuridine did not overall show a strong tendency to distribute into tissues. In both C57BL/6 and CD-1 mice, the metabolic/excretory tissues as well as the tissues of the GI tract contained the highest distribution of [14C]-cedazuridine derived radioactivity. The tissues with higher relative distribution in both strains were large intestine wall, cecum mucosa, and entire kidney. In addition, urinary bladder wall and stomach wall glandular in C57BL/6, and small intestine wall and kidney medulla in CD-1 mice, had higher relative tissue distribution. The tissues with lowest relative levels of distribution found in both C57BL/6 and CD-1 mice were brain, spinal cord, eye lens, and white fat, which were all below quantifiable limit (BQL) at all sampled time points. Furthermore, no enhanced binding of cedazuridine to melanin containing tissues was observed in the skin or uveal tract in the pigmented as compared to the non-pigmented mice.

The tissue:plasma AUC0-t ratios were <1.0 for liver (0.97) and bile (0.89) in comparison to the corresponding ratios in kidney (1.85) and urinary bladder wall (25.04), suggesting that a significant portion of the circulating radioactivity was likely excreted renally.

The plasma protein binding of cedazuridine was low, 30-38%, across mouse, monkey and human. The plasma protein binding of decitabine was very low, 0-12% across mouse, rat, monkey, rabbit, and human. The similar level of plasma protein binding across the species tested facilitates interpretations of interspecies PK/PD and TK/toxicological comparisons. The *in vitro* blood-to-plasma partitioning ratio for cedazuridine, as measured by LC-MS/MS, was ranging from 0.87 to 0.91 in mouse, 0.69 to 0.91 in monkey, and 0.72 to 0.80 in human. These data suggest no concentration or species differences and that cedazuridine does not preferentially partition into blood cells. *In vivo* distribution studies with [14C]-cedazuridine detected by LSC confirmed the *in vitro* results.

Metabolism

Metabolic profiling *in vivo* showed that unchanged cedazuridine was the most abundant circulating entity followed by its epimer which was the most prominent circulating metabolite. All other metabolites were minor both in humans and animal models. Following oral administration of [14C]-cedazuridine, the epimer was quantified to 37% of total radioactivity in female mice, and 33 and 29.5% in male and female monkeys, respectively, as compared to 43.1% to 46.9% of the total drug-related components in humans after receiving a RHD. No species-specific metabolites at a significant concentration were identified. Thus, toxicological coverage for metabolites is available as all metabolites detected *in vivo* in humans were also present in mouse and monkey plasma.

Attempts with metabolic profiling *in vitro* revealed that [14C]-cedazuridine appeared to be metabolically stable in the liver S9 fractions and liver cytosols from mice, monkeys, and humans. The similar disappearance of cedazuridine in *ex vivo* incubations with or without the presence of hepatocytes, suggests a very low contribution of hepatic metabolism to cedazuridine clearance.

Cytochrome P450 (CYP450) inhibition and induction assays, and human transporter studies are presented in the clinical pharmacokinetic section.

Excretion

The urinary excretion of cedazuridine was evaluated in rats and monkeys after oral or intravenous administration of cedazuridine. In addition, the excretion profile of [14C]-cedazuridine was evaluated in single-dose mass balance studies in mice following oral dosing and in monkeys following oral and IV dosing. The levels of cedazuridine and cedazuridine epimer in the urine were quantified by LC-MS/MS

methods. The concentrations of the epimer were estimated against the cedazuridine calibration curve as an epimer standard reference was not available.

Following single IV administration of cedazuridine to rats at 3, 10, and 30 mg/kg, the mean percent of dose recovered as unchanged cedazuridine in urine was 57.6%, 67.5%, and 50.3%, respectively, with corresponding CLren of 403.03, 420.65, and 390.92 mL/h/kg. This is higher than the reported value for the glomerular filtration rate (GFR) in rats suggesting the involvement of active tubular transport. The percent of dose excreted in urine as the epimer averaged 25.9%, 6.7%, and 9.5%, while the respective CLren averaged 2196.03, 579.96, and 1154.33 mL/h/kg, which also suggests the involvement of active tubular secretion in the renal elimination of epimer. Following single oral administration of cedazuridine at 10, 30, and 100 mg/kg, the mean percent of dose recovered as unchanged cedazuridine in urine was 20.3%, 6.7%, and 5.6%, respectively, with corresponding CLren of 562.63, 484.00, and 418.62 mL/h/kg. Adjusting for the oral bioavailability, these values were in general considered consistent with the values observed after IV doses of cedazuridine, however, the 10 mg/kg oral dose presented an approximate 3- to 4-fold increase in percent of cedazuridine dose excreted relative to the other dose groups, this was, largely due to high variability in one animal. The percent of dose excreted in urine as the epimer averaged 8.5%, 5.4%, and 4.1%, respectively, while the corresponding CLren averaged 740.36, 612.59, and 590.80 mL/h/kg.

In monkeys cedazuridine was administered via a cross-over design (with a 7 to 21-day washout period between single IV and oral doses). Cedazuridine was administered orally to fasted animals with the exception of the 10 mg/kg dose for which urine parameters were measured only in fed animals. Following IV administration of 3 mg/kg cedazuridine, the mean percent of dose recovered as unchanged cedazuridine in urine was 37.9% with a CLren of 95.39 mL/h/kg. This CLren is approximately 40% of the GFR reported in monkeys. The percent of dose excreted in urine as the epimer of cedazuridine averaged 1.9%. Following oral administration of 3, 10, and 30 mg/kg of cedazuridine, the mean percent of the dose recovered as unchanged cedazuridine in urine was 13.1%, 6.3% (fed monkeys), and 10.2%, respectively, with corresponding CLren of 217.36, 218.37, and 241.21 mL/h/kg, respectively. These values are approximately 2-fold higher than those observed following the 3 mg/kg IV dose of cedazuridine. The percentage of dose excreted as the epimer averaged 1.1%, 2.2%, and 2.9%, respectively, while the corresponding CLren at 10 and 30 mg/kg averaged 361.65 and 492.67 mL/h/kg, respectively (the CLren following 3 mg/kg IV or oral doses could not be calculated due to insufficient data).

Mass balance data was obtained from mice and monkeys. In mice, approximately 93% of the dosed radioactivity was excreted by 168 hours post-dose in males and females (with most of the excretion occurring in the first 24 hours). The main route of excretion was through the faeces in which approximately 70% of dosed radioactivity was recovered. Approximately 20% and 18% of the dosed radioactivity was found to be excreted in the urine in males and females, respectively. In monkeys, ≥ 64% of the administered dose was excreted in faeces over 7 days post-dose. The majority of radioactivity in urine, including cage rinse and faeces was recovered over the first 2 days post-dose (84.0% in males and 72.4% in females), with approximately 90.9% (males) and 89.8% (females) of the total administered dose recovered over 7 days post-dose. Approximately 2.2% and 3.4 % of the dosed radioactivity was found to be excreted in the faeces in males and females, respectively and approximately 48% and 47% in the urine in males and females, respectively.

Pharmacokinetic drug interactions

Pharmacokinetic drug interactions have been conducted in clinical study and can be found in the clinical pharmacokinetics section of this assessment report.

2.5.4. Toxicology

To support the marketing authorisation of ASTX727, a program of nonclinical toxicology studies was conducted including GLP-compliant oral toxicity studies for cedazuridine (in mice and monkeys) and decitabine (in mice and rats) and a non-GLP oral toxicity study for cedazuridine and decitabine administered together (in monkeys). Pivotal repeat-dose toxicity studies conducted with cedazuridine evaluated up to 4 dosing cycles that included 7 dosing days per 28-day cycle, thereby covering the planned clinical treatment cycle of 5 consecutive dosing days followed by 23 non-dosing days. Pivotal studies conducted with decitabine evaluated 1 dosing cycle in mice and 1 and 4 dosing cycles in rats, with a dosing regimen that mimicked the planned clinical treatment cycle. The study conducted in monkeys with ASTX727 (cedazuridine and decitabine administered concurrently) evaluated 1 cycle of dosing that mimicked the planned clinical dosing cycle. As relevant, these studies included TK evaluations for cedazuridine, its major metabolite (cedazuridine epimer), and/or decitabine. The genotoxic potential of cedazuridine was evaluated in GLP-compliant in vitro and in vivo studies. No carcinogenicity studies, stand-alone reproductive and developmental toxicity studies, or local tolerance studies have been conducted with ASTX727 or with its active components, cedazuridine and decitabine.

Mice and monkeys appear to have CDA tissue distribution and activity profiles that most closely resemble those of humans, making them appropriate species for the nonclinical evaluation of ASTX727 and its active components. Specifically, like humans, mice and monkeys have high CDA activity levels in the GI tract and liver, although differences may exist among different strains of mice. High activity levels also have been reported in mouse and monkey kidney, while monkeys and humans also have high activity in both spleen and lung. In contrast, little to no CDA activity has been reported in any tissues of rats. Thus, relatively high oral bioavailability of decitabine occurs in the rat which makes it an ideal species in which to evaluate systemic effects of decitabine following oral administration.

2.5.4.1. Single dose toxicity

Standard single-dose toxicity studies for ASTX727 or decitabine were not conducted.

A non-GLP study was conducted to evaluate the potential toxicity and TK profile of cedazuridine administered orally (by gavage) for 5 days to male and female CD1 (ICR) mice at dose levels of 0 [control; 0.5% methylcellulose (MC)], 500, or 1000 mg/kg/day (Study/Report No. S09032). There were no unscheduled deaths and no cedazuridine-related clinical signs after the first dose.

A non-GLP study was conducted to investigate the potential toxicity and TK profile of cedazuridine following administration of single oral (gavage) escalating doses to male and female rhesus monkeys (Study/Report No. LFA00079). In this study, cedazuridine was administered on Day 1 at dose levels of 0 (control; 0.5% MC), 100, 300, or 1000 mg/kg (1/sex/group). No mortality was observed and there were no test article-related effects on body weight or food consumption. Soft faeces were noted in 1 female at the 1000 mg/kg dose level.

2.5.4.2. Repeat dose toxicity

Several pilot/non-pivotal studies exploring different doses and dosing regimens were investigated in the nonclinical program. Data from these studies were used to guide the design of the GLP and pivotal toxicology and TK studies.

Clinical trials with ASTX727 have been conducted using an oral dosing schedule involving once daily dosing on Days 1 to 5 of a 28-day cycle and marketing approval is currently being sought for this dosing schedule. As such, the repeat-dose toxicity studies considered to be pivotal to supporting

marketing approval of this dosing schedule are those in which the dosing schedule was the same or similar.

Cedazuridine

For cedazuridine, pivotal investigations evaluated the potential repeat-dose toxicity in 7-day studies in mice and monkeys and 13-week/4-cycle studies (with each cycle consisting of 7 consecutive dosing days and a 21-day treatment free period) in mice and monkeys.

Administration of cedazuridine was not associated with test article-related mortalities in either the non-pivotal or pivotal studies in mice or monkeys; however, severe bone marrow changes (i.e., severe leucopenia with neutropenia and lymphopenia and decreases in platelet counts) were noted in the non-pivotal study in which monkeys received 300 or 1000 mg/kg/day of cedazuridine for 5 days. These bone marrow changes resulted in secondary infections, poor physical condition, and moribundity in monkeys at these dose levels.

In the pivotal, GLP-compliant, 4-cycle oral toxicity studies in mice and monkeys (dosing on Days 1 to 7 of each 28-day cycle for a total of 4 cycles), administration of cedazuridine was associated with bone marrow cytology changes as follows:

- In mice, dose levels of 1000 mg/kg/dose were associated with "mildly higher" myeloid:erythroid (M:E) ratios in females and "minimally lower" M:E ratios in males. Mild to marked decreases in lymphocyte percentages and mild decreases in mean peripheral lymphocyte counts also were noted in both sexes.
- In monkeys, dose levels of 20 and 60 mg/kg/day were associated with mild morphologic changes in the erythroid lineage and a dose level of 200 mg/kg/day was associated with marked morphologic changes in the myeloid and erythroid lineages.

The bone marrow cytology changes were associated with correlating histopathology in mice and monkeys. Reversibility of the bone marrow changes and histopathology findings were noted in both species following completion of the treatment-free recovery period.

In addition to the bone marrow changes (and associated histopathology), the main toxicological findings associated with cedazuridine in the pivotal repeat-dose toxicity studies conducted in mice and monkeys were adverse histopathology findings in the male and female reproductive tracts in mice and haematological effects and GI tract histopathology findings in monkeys.

Decitabine

For decitabine, pivotal investigations evaluated the potential repeat-dose toxicity in a 5-day study in mice, a 5-day study in rats, a 14-day study in rats, a 13-week/4-cycle study in rats and a 98-day/4-cycle study in rats.

In the repeat-dose toxicity studies conducted in rats, the key findings that were consistently associated with decitabine administration included thrombocytopenic changes (consisting of decreases in platelet counts), anaemic changes (consisting of decreases in RBCs, HCT, haemoglobin, and reticulocytes), and leucopenic changes [consisting of decreases in white blood cells (WBCs), lymphocytes, neutrophils, monocytes, eosinophils, and basophils]. In the pivotal, GLP-compliant 5-day (one-cycle) repeat-dose toxicity study, myelosuppression was noted at dose levels as low as 1 mg/kg/day while, in the pivotal, GLP-compliant 13-week/4-cycle repeat-dose toxicity study, this effect was noted at dose levels as low as 0.75 mg/kg/day, with the effects appearing to be more pronounced in males compared to females.

ASTX727 (cedazuridine and decitabine)

Oral administration to monkeys resulted in increased systemic exposure to decitabine with increasing doses of cedazuridine, consistent with the intended inhibition of CDA by cedazuridine. In this non-GLP study, cedazuridine was administered at dose levels of 1, 3, or 6 mg/kg/day followed immediately by decitabine at a fixed dose level of 2 mg/kg/day for 5 consecutive days, both via oral gelatin capsules. The main toxicological findings noted in male and female monkeys included anaemia (decreases in RBC and WBC counts, haemoglobin, and HCT levels) and leucopenia (decreases in the levels of reticulocytes, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) in treated animals and higher M:E ratios among the different groups of treated males (based on higher mean total myeloid cell counts and lower mean total erythroid cell counts). The changes in the haematology parameters were noted to be reversible following a 23-day treatment-free recovery period (i.e., at the end of the 28-day cycle).

Gastrointestinal toxicity was also observed and in males, testicular atrophy that did not reverse over the scheduled recovery periods.

2.5.4.3. Genotoxicity

Standard genotoxicity studies for ASTX727 or decitabine were not conducted. Nevertheless, the genotoxicity of decitabine is well known; Decitabine was mutagenic in in vitro and in vivo studies as per public available information. Decitabine increased mutation frequency in L5178Y mouse lymphoma cells and mutations were produced in an Escherichia coli lac-I transgene in colonic DNA of decitabine-treated mice. Decitabine caused chromosomal rearrangements in larvae of fruit flies.

The potential genotoxicity of cedazuridine was investigated in a reverse mutation assay in bacteria, an in vitro chromosome aberration assay in human lymphocytes, an in vivo mouse micronucleus assay, an in vivo comet assay in mice, and an in vivo phosphatidyl inositolglycan class A gene (pig-a) mutation assay in rats.

- Cedazuridine was mutagenic in S. typhimurium strain TA1535 both in the presence and absence of external metabolic activation, but only at the highest tested concentration of 5000 µg/plate, and was non-mutagenic in S. typhimurium strains TA98, TA100, and TA1535 and in E. coli strain WP2 *uvrA* (pKM101) both in the presence and absence of external metabolic activation;
- Cedazuridine was genotoxic in a chromosome aberration assay in human lymphocytes both in the presence and absence of external metabolic activation;
- Cedazuridine was non-genotoxic in an in vivo mouse bone marrow micronucleus assay;
- Cedazuridine was non-genotoxic in an in vivo mouse liver comet assay; and
- Cedazuridine did not induce mutagenic effects in circulating RBCs or reticulocytes in an in vivo pig-a mutation assay in rats.

The positive genotoxicity findings noted in the human lymphocytes were generally only observed in the presence of significant cell toxicity (as indicated by a decrease in the relative mitotic index compared to concurrent controls).

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been conducted with ASTX727 or with its active components, cedazuridine and decitabine.

2.5.4.5. Reproductive and developmental toxicity

In male mice given intraperitoneal injections of 0.15, 0.3, or 0.45 mg/m2 decitabine (approximately 0.3% to 1% the recommended clinical dose) 3 times a week for 7 weeks, testes weights were reduced, abnormal histology was observed, and significant decreases in sperm number were found at doses ≥ 0.3 mg/m2. In females mated to males dosed with ≥ 0.3 mg/m2 decitabine, pregnancy rate was reduced, and preimplantation loss was significantly increased. Decitabine was administered orally to male rats at 0.75, 2.5, or 7.5 mg/kg/day in cycles of 5- days- on/23- days- off for a total of 90 days. Low testes and epididymis weights, abnormal histology, and reduced sperm number were observed at doses ≥ 0.75 mg/kg (approximately ≥ 3 times the exposure in patients at the recommended clinical dose based on AUC).

Cedazuridine was administered orally to male and female mice at 100, 300, or 1,000 mg/kg/day in cycles of 7- days- on/21- days- off for a total of 91 days. Adverse reactions including abnormal histology in the testes, epididymis, and ovaries, as well as reduced sperm numbers were observed at the 1,000 mg/kg dose (approximately 108 times the exposure in patients at the recommended clinical dose). These findings showed evidence of reversibility following 3 weeks off- dose.

Teratogenic effects

No stand-alone study on early embryonic development was performed with ASTX727 or with its components, decitabine and cedazuridine. This is line with IHC S9.
Data from the literature also indicate that decitabine has adverse effects on all aspects of the reproductive cycle, including fertility, embryo-foetal development and post-natal development.

Decitabine administration to neonatal/juvenile rats showed a comparable general toxicity profile as in older rats. Neurobehavioural development and reproductive capacity were unaffected when neonatal/juvenile rats were treated at dose levels inducing myelosuppression.

2.5.4.1. Phototoxicity

Studies were performed to determine the ultraviolet absorption data for cedazuridine and decitabine, between 290 and 700 nm. In these studies, minimal absorption was observed within this range and the calculated molar extinction coefficient for any wavelength within this range was less than 1000 L mol^{-1} cm^{-1}. Based on these results, cedazuridine and decitabine are not expected to be phototoxic.

2.5.4.2. Toxicokinetic data

Table 8. Margins of exposure in nonclinical toxicology studies

Species	Study	Effect Level	AUC (ng*h/ml)			Cmax (ng/mL)			Cedazuridine - Margin of Exposure		Cedazuridine Epimer - Margin of Exposure		Decitabine - Margin of Exposure	
			Cedazuridine	Cedazuridine epimer	Decitabine	Cedazuridine	Cedazuridine epimer	Decitabine	Relative to AUC	Relative to Cmax	Relative to AUC	Relative to Cmax	Relative to AUC	Relative to Cmax
Mouse	13-Week/4-cycle oral toxicity study with cedazuridine	NOAEL = 300 mg/kg/day (M)	165,000 (M) 46,600 (F)	112,000 (M) 31,000 (F)	NA	21,300 (M) 9280 (F)	15,000 (M) 6390 (F)	NA	50.2 (M) 14.2 (F)	57.6 (M) 25.0 (F)	77.8 (M) 21.5 (F)	88.8 (M) 37.8 (F)	NA	NA

	(Study/Report No. 0862-16193)[b]	and 100 mg/kg/day (F)												
Monkey	92-Day/4-cycle oral toxicity study with cedazuridine (Study/Report No. 20124863)[b]	NOAEL = 60 mg/kg/day	28,800 (M) 27,500 (F)	8790 (M) 13,900 (F)	NA	5050 (M) 4150 (F)	1400 (M) 2650 (F)	NA	8.75 (M) 8.36 (F)	13.6 (M) 11.2 (F)	6.10 (M) 9.65 (F)	8.28 (M) 15.7 (F)	NA	NA
Rat	13-Week/4-cycle oral toxicity study with decitabine (Study/Report No. T73417002-GN)[b]	STD_{10} = >7.5 mg/kg/day	NA	NA	17,100 (M) 18,000 (F)	NA	NA	2220 (M) 2350 (F)	NA	NA	NA	NA	93.2 (M) 98.1 (F)	15.3 (M) 16.2 (F)
Monkey	5-Day oral toxicity study with ASTX727 (cedazuridine + decitabine) (Study/Report No. 031554)[c]	Not reported (well tolerated at 6/2 mg/kg/day for cedazuridine / decitabine	5470 (M) 4230 (F)	3870 (M) 3770 (F)	567 (M) 540 (F)	1770 (M) 1270 (F)	1150 (M) 1070 (F)	398 (M) 337 (F)	1.66 (M) 1.28 (F)	4.8 (M) 3.4 (F)	2.7 (M) 2.6 (F)	6.8 (M) 6.3 (F)	3.1 (M) 2.9 (F)	2.7 (M) 2.3 (F)
Human	Phase 3 study of oral ASTX727 in adult patients with MDS or CMML (Study No. ASTX727-02)	NA	3290[d]	1440[d]	183.5	371[c]	169[c]	145	NA	NA	NA	NA	NA	NA

2.5.5. Ecotoxicity/environmental risk assessment

Inaqovi (ASTX727) consists of two active substances; cedazuridine, a cytidine deaminase inhibitor, and decitabine, a nucleoside metabolic inhibitor. An environmental risk assessment (ERA), phase I, was prepared for both substances.

Inaqovi is indicated for treatment of acute myeloid leukaemia (AML) which is a rare condition in the EU. AML is estimated to affect approximately 1.7 in 10,000 persons in the EU.

Cedazuridine has a molecular weight of 268.21 g/mol and a log K_{OW} of -0.55 at pH 6.8. The Phase I surface water PEC (PEC_{SW}) for cedazuridine was estimated using the maximum dose for cedazuridine of 17.8 mg/day, to 0.0094 µg/L using a refined Fpen based on incidence (according to COMP). This is just below the 0.01 ug/L cut-off value.

Decitabine has the molecular weight of 228.21 g/mol and a log K_{OW} of -1.50 at pH 6.8. The Phase I PEC_{SW} for decitabine was calculated using the maximum dose of 6.23 mg/day to 0.19 µg/L using a refined Fpen based on incidence (according to COMP) to 0.00053 µg/L.

Table 9. Summary of main study results for cedazuridine

Substance (INN/Invented Name): Cedazuridine			
CAS-number (if available): 1141397-80-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Shake-flask method	log K_{OW} = -0.99, -0.55 and -0.58 at pH 5, 6.8 and 9	Potential PBT N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ refined (e.g. prevalence, literature)	0.0094	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

Table 10. Summary of main study results for decitabine

Substance (INN/Invented Name): Decitabine			
CAS-number (if available): 2353 -33-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Shake-flask method	log K_{OW} = -1.87, -1.50 and -0.54 at pH 5, 6.8 and 9.	Potential PBT N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ refined (e.g. prevalence, literature)	0.00053	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

2.5.6. Discussion on non-clinical aspects

Pharmacology

In vivo administration of oral cedazuridine was demonstrated to enhance anti-tumour activity to oral decitabine, without providing any anti-tumour activity in itself both in a syngeneic and a xenotransplant mouse leukaemia model by increasing life span ranged from 41% to 88%. This provides preclinical support of the FDC treatment concept.

Based on the results from the studies conducted with cedazuridine, any safety pharmacology concerns for ASTX727 are anticipated to be the result of potential effects of decitabine which has been in clinical use for many years. To conduct safety pharmacology studies with the combination, cedazuridine and decitabine co-administered, would not be meaningful since the boosting effect of cedazuridine on the known cytotoxic effects of decitabine occur at a much lower cedazuridine concentration than cedazuridine would cause acute toxic effect in itself. In addition, no overlapping toxicological findings from the two drug substances have been observed, and the adverse event profile of the combination is similar to decitabine monotherapy. This reasoning is agreed.

The nonclinical pharmacology data package appears to support the rationale to us the oral FDC of cedazuridine and decitabine in the suggested disease indication.

Pharmacokinetics

Of central importance for the ASTX727 fixed dose combination is that oral cedazuridine prevent the first-pass breakdown of the orally co-administered decitabine, significantly increase absorption and increase the plasma exposure levels as compared to oral decitabine alone and reach a similar exposure as following IV decitabine. This has been shown to occur in several preclinical studies. It appears also clear that oral cedazuridine pretreatment (30 min in mice, 1 or 2 hours in monkey), before oral administration of decitabine enhance the Cmax and AUC but have no major influence on t½ of decitabine in plasma in mice and monkeys. In terms of decitabine exposure, higher levels of decitabine were observed with increasing doses of cedazuridine.

Some minor notes on Absorption:

The exposure (AUCinf) to the epimer following oral administration of cedazuridine was noted to be approximately 30% of the exposure of the parent compound in mice while in rats and monkeys, the exposure to the epimer ranged from 51.5% to 62.7% and 28.3% to 38.7% of the parent compound exposure, respectively. The corresponding exposure to the epimer in human plasma following administration of RHD was 43.1 to 46.9% of total radioactivity. This indicates that the epimer was qualified for toxicological studies in all three tested species, mice, rats, and monkeys (further substantiated in the preclinical toxicology section).

In *the animal* species, a larger formation of the epimer was observed following oral administration than IV administration which likely indicates that the formation of the epimer occurs prior to systemic absorption. This appears as a plausible explanation.

The reduction in the exposures to cedazuridine in fed monkeys were likely a consequence of its decreased absorption from the GI tract, and not due to an increase in the formation of the epimer in the presence of food, as indicated by the similar AUCinf ratio of the cedazuridine epimer to the parent compound between fasted and fed animals (0.288 vs 0.221, respectively). This suggestion appears reasonable and is accepted.

Since the level of distribution found in brain and spinal cord in both C57BL/6 and CD-1 mice were BQL at all sampled time points, there was less need for a brain penetration study.

No enhanced binding of cedazuridine to melanin containing tissues was observed in the skin or uveal tract in the pigmented as compared to the non-pigmented mice. Thus, phototoxicity risk was not indicated (however, further discussed in the preclinical toxicology section).

The mass balance studies indicates that the majority of oral cedazuridine is excreted unabsorbed in the faeces and the absorbed dose is primarily excreted renally. No studies examining excretion into bile have been conducted with cedazuridine, decitabine, or ASTX727, which is accepted.

To summarise, the nonclinical pharmacokinetic profile of cedazuridine alone and in combination with decitabine is considered to have been adequately characterised. Mice and monkeys were used in the pivotal toxicological studies for cedazuridine. These species showed several qualitative similarities in metabolic profile with humans and are thus considered suitable for the evaluation of the toxicity of cedazuridine as NCE in the actual FDC.

Toxicology

The extent of the nonclinical toxicology program was agreed in the CHMP Scientific Advice EMA/CHMP/SAWP/485806/2018

A large number of non-pivotal toxicity studies were performed with cedazuridine and decitabine, in order to establish dose ranges for pivotal studies and to explore different treatment schedules. Toxicity findings in these studies were in line with what is seen in the pivotal studies.

Administration of cedazuridine was not associated with test article-related mortalities in mice or monkeys. Overall, administration of cedazuridine to male and female mice and monkeys on a dosing schedule that was the same or similar to that which is proposed for clinical use of ASTX727 appears to be well-tolerated at dose levels of 100 mg/kg/dose in female mice, 300 mg/kg/dose in male mice, and 60 mg/kg/dose in male and female monkeys. The main toxicological findings in both species were bone marrow cytology changes with correlating histopathology, adverse histopathology changes in the male and female reproductive tracts, and haematology changes (in monkeys). Most of these findings were at least partially reversed following a treatment-free recovery period.

For decitabine, compound class-specific findings including thrombocytopenic changes, anaemic changes, and leucopenic changes as well as testicular toxicity were observed in rats following repeated oral dosing and were consistent with the lack or low level of CDA in this species. When cedazuridine and decitabine were administered together in a repeat-dose oral study in monkeys, increased decitabine exposure was observed and was associated with anaemia, leucopenia, and higher M:E ratios. These effects were reversible after a 23-day treatment-free recovery period.

Toxicity findings with cedazuridine were observed only at exposures substantially above clinical exposure. It is likely that safety for this combination is driven mainly by the decitabine component with the cedazuridine only contributing by its ability to increase bioavailability for decitabine. The fact that the exposure to cedazuridine with the FDC is far below exposures where cedazuridine toxicity has been observed also serves to justify the absence of a formal combination toxicity study.

A comprehensive evaluation of the genotoxicity of cedazuridine was performed to support clinical studies in healthy volunteers. While equivocal results were reported both in the Ames assay and in the chromosome aberration study, it is agreed that the in vivo studies performed supported that a genotoxic potential in patients is unlikely. Since decitabine is genotoxic, the importance of this conclusion is limited for this fixed dose combination.

No carcinogenicity studies have been conducted with ASTX727 or with its components, cedazuridine and decitabine. Decitabine is genotoxic and a likely carcinogen and based on its positive genotoxicity, decitabine may be expected to have carcinogenic potential. As such, there is a carcinogenic risk associated with exposure to ASTX727. Also, in line with ICH S9 carcinogenicity studies are not required for products indicated for the treatment of advanced cancer.

No stand-alone reproductive and developmental toxicity studies have been conducted with ASTX727 or with its components, decitabine and cedazuridine. Based on its mechanism of action, decitabine is expected to result in adverse reproductive effects. Studies with decitabine in rats showed testicular toxicity likely to indicate clinically relevant impairment of fertility. Studies with cedazuridine showed toxicity to both male and female reproductive tracts, but only at high exposure multiples. Therefore, decitabine is considered most important for fertility assessment and a text om SmPC 4.6 in line with the text for Dacogen is appropriate. For embryo-fetal development, reference is made to literature data supporting the Dacogen approval showing embryofetal toxicity in mice. Also for the SmPC text concerning pregnancy, a text in line with the text for Dacogen is considered appropriate.

Both cedazuridine and decitabine showed minimal light absorption at wavelengths between 290 and 700 nm: Based on these results, cedazuridine and decitabine are not expected to be phototoxic.

Environmental risk assessment

Cedazuridine PEC surfacewater value is just below the action limit of 0.01 µg/L and it is not a PBT substance as log Kow does not exceed 4.5. Therefore, cedazuridine is not expected to pose a risk to the environment.

Decitabine PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore, decitabine is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

There are no objections to a marketing approval from a nonclinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 11: Tabular overview of main clinical studies

Type of Study	Study Identifier and Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen[a] Route of Administration	Number of Subjects Treated	Healthy Subjects or Diagnosis of Patients	Duration of Treatment[b]	Study Status; Type of Report
PK	ASTX727-04 5.3.1.1	Safety, tolerability, PK, food effect	Phase 1b, open-label, randomised, 2-sequence	ASTX727 FDC tablet PO (35 mg decitabine and 100 mg cedazuridine) (Randomisation to high calorie, high fat breakfast administered on either Day 2 or Day 4 of Cycle 1)	17	Adults (≥18 yrs) MDS, CMML, or AML No subjects with AML enrolled	Continuous (median 5 cycles; max 9 cycles)	Complete Full CSR
PK	E7727-01 5.3.3.1	Mass balance, ADME, safety, tolerability	Phase 1, open-label, 2-treatment period, fixed sequence	Period 1: • Single dose of cedazuridine 100 mg capsule PO followed 3 hours later by microtracer dose (100 µg) of ^{14}C-cedazuridine IV Period 2: • Single dose of ^{14}C-cedazuridine 100 mg capsule PO	8	Adults (≥65 yrs) Healthy Subjects	2 single doses separated by a washout	Complete Full CSR
PK/Safety	ASTX727-01-A[c] 5.3.3.2	Safety, tolerability, PK, PD, preliminary efficacy	Phase 1, first-in-human, open-label, dose-escalation	Cycle 1 Day -3: single dose decitabine (capsule) PO Cycle 1 Day 1: 20 mg/m^2 IV decitabine Cycle 1 Days 2-5, and Days 1-5 of subsequent cycles: concomitant administration of decitabine and cedazuridine capsules PO: Cohort 1: 20mg / 40 mg Cohort 2: 20 mg / 60 mg Cohort 3: 20 mg / 100 mg Cohort 4: 40 mg / 100 mg Cohort 5: 30 mg / 100 mg Cycle 2 Day -3: single dose oral cedazuridine (capsule) PO	44 total Cohort 1: 7 Cohort 2: 6 Cohort 3: 6 Cohort 4: 6 Cohort 5: 19	Adults (≥18 yrs) MDS including IPSS Int-1, Int-2, or high risk; CMML	Single dose (for PK analysis) or continuous (median 5 cycles; max 49 cycles)	Complete Full CSR
Safety/ QTc	E7727-02 5.3.4.1	PK, safety, effect on QTc	Phase 1, randomised, double-blind, placebo-controlled, 4-period crossover,	100 mg cedazuridine encapsulated tablet PO 400 mg cedazuridine encapsulated tablet PO 400 mg moxifloxacin encapsulated tablet PO Placebo capsule PO	32	Adults (18-55 yrs) Healthy Subjects	Four single doses separated by a 5-day washout	Complete Full CSR

Type of Study	Study Identifier and Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen[a] Route of Administration	Number of Subjects Treated	Healthy Subjects or Diagnosis of Patients	Duration of Treatment[b]	Study Status; Type of Report
			single dose study					
Efficacy/ Safety	ASTX727-01-B[c] 5.3.5.1	PK, PD, efficacy, safety	Phase 2, open-label, randomised, crossover	Decitabine/cedazuridine 35 mg /100 mg PO **Dose Confirmation:** Cycles 1 and 2 (2-way crossover): Decitabine/cedazuridine Daily×5 (administered concomitantly as separate capsules), 1 cycle IV decitabine 20 mg/m^2 Daily×5, 1 cycle Cycles ≥3: Decitabine/cedazuridine Daily×5 **Fixed-dose Combination:** Same as above, except with ASTX727 FDC tablet	80 total 50 30	Adults (≥18 yrs) MDS and CMML	Continuous (median 7 cycles; max 44 cycles)	Complete Full CSR
Efficacy/ Safety	ASTX727-02 EU[d] 5.3.5.1	PK, safety, PD, efficacy	Phase 3, open-label, randomised, crossover	ASTX727 FDC tablet (35 mg decitabine/100 mg cedazuridine) PO Cycles 1 and 2 (2-way crossover): ASTX727 Daily×5, 1 cycle IV decitabine 20 mg/m^2 Daily×5, 1 cycle Cycles ≥3: ASTX727 Daily×5	87	Adults (≥18 yrs) AML	Continuous (median 5 cycles; max 20 cycles)	Ongoing Full CSR (data cut 10 Sep 2021) 30 subjects ongoing treatment as of CSR data cutoff
Efficacy/ Safety	ASTX727-02 NA[d] 5.3.5.1	PK, safety, PD, efficacy	Phase 3, open-label, randomised, crossover	ASTX727 FDC tablet (35 mg decitabine/100 mg cedazuridine) PO Cycles 1 and 2 (2-way crossover): ASTX727 Daily×5, 1 cycle IV decitabine 20 mg/m^2 Daily×5, 1 cycle Cycles ≥3: ASTX727 Daily×5	133	Adults (≥18 yrs) MDS and CMML	Continuous (median 9 cycles; max 28 cycles)	Complete Full CSR

ADME=absorption, distribution, metabolism, excretion; AML=acute myeloid leukemia; CMML=chronic myelomonocytic leukemia; CSR=clinical study report; DDI=drug-drug interaction; EU=Europe; FDC=fixed dose combination; IPSS=International Prognostic Scoring System; Int-1=IPSS Intermediate-1 risk category; Int-2=IPSS Intermediate-1 risk category IV=intravenous; MDS=myelodysplastic syndrome; NA=North America; PD=pharmacodynamic(s); PK=pharmacokinetic(s); PO=by mouth; QT=QT interval of electrocardiogram; QTc=corrected QT interval; QTcF=corrected QT interval using Fridericia's formula

Note: All studies were conducted in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, principles enunciated in the Declaration of Helsinki, and all human clinical research regulations in countries where the study is conducted such as the European Union Clinical Trials Directive 2001/20/EC (EUCTD).

[a] All studies had 28-day treatment cycles unless otherwise specified.

[b] Duration of Treatment: Unless otherwise specified, subjects were treated as long as, in the judgment of the investigator, the subject was still benefitting from treatment with manageable side effects.

[c] Study ASTX727-01 was a two-part Phase 1-2 study conducted under a single protocol. The results of this study have been reported in 2 separate CSRs (ASTX727-01-A and ASTX727-01-B).

[d] Study ASTX727-02 was a study that included two arms (subjects with MDS/CMML and subjects with AML) conducted under a single protocol. The study designation ASTX727-02 NA refers to the arm of the study in subjects with MDS/CMML, and the study designation ASTX727-02 EU refers to the arm of the study in subjects with AML. The results of this study have been reported in 2 separate CSRs (ASTX727-02-B [in subjects with MDS/CMML] and ASTX727-02-C [in subjects with AML]).

Relevant ongoing studies include ASTX727-06 (long-term safety with food effect substudy), ASTX727-18 (HI study) and ASTX727-17 (RI study).

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Inaqovi (ASTX727) is a fixed-dose combination tablet containing 35 mg decitabine and 100 mg cedazuridine that is intended to provide decitabine exposures equivalent to intravenous (IV) decitabine at the European Union (EU)-approved dose.

Cedazuridine (E7727), is a novel cytidine deaminase [CDA] inhibitor). It is a new chemical entity and the pharmacokinetic studies should thus aim at describing the disposition and also to identify subgroups where an increased or decreased exposure can be expected based on the pharmacokinetic properties. Potential interactions based on the pharmacokinetic properties should also be evaluated. Administration of cedazuridine with oral decitabine reduces first pass metabolism of decitabine upon absorption, thus enhancing the oral bioavailability of decitabine so that oral administration is feasible.

Decitabine is a known substance, previously approved for intravenous administration at a dose of 20 mg/m^2 by intravenous infusion over 1 hour repeated daily for 5 consecutive days (i.e., a total of 5 doses per treatment cycle). This application is based on a PK bridge, assuming that previous efficacy

and safety data for IV decitabine can be extrapolated to Inaqovi if the decitabine plasma exposure (total AUC over the 5-day cycle) is similar.

Cedazuridine has one major metabolite, its epimer. The epimer has been reported to be 1/10th as active as cedazuridine in CDA inhibition and has similar or lower exposure than cedazuridine. It is thus not expected to significantly contribute to the effect of cedazuridine. Rather, conversion to the epimer will lead to lower effect.

Methods

Bioanalytical methods

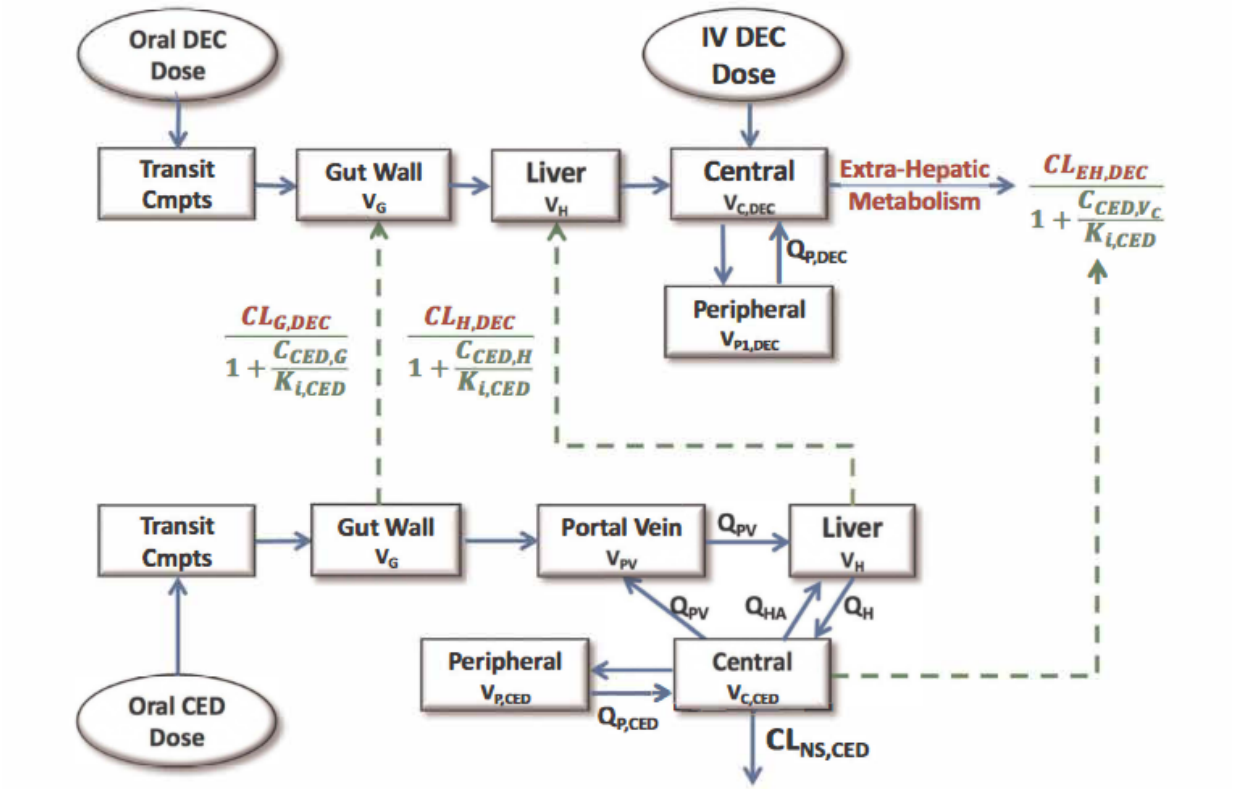
Validated methods were used for determination of decitabine, cedazuridine and cedazuridine-epimer in plasma and for determination of cedazuridine and cedazuridine-epimer in urine.

Population PK

The population PK analysis is mainly used to inform on the impact of covariates on the exposure of decitabine and cedazuridine.

Previously developed population PK models (IV decitabine, oral decitabine and oral cedazuridine; Figure 1) were combined to describe the PK of decitabine and cedazuridine given alone and in combination, and for the IV and oral formulation of decitabine. The semi-mechanistic model was initially developed on data from patients with myelodysplastic syndrome (MDS). This modelling analysis focused on re-estimating model parameters using the available AML data, evaluating the influence of covariates, and subsequently comparing disease population-specific model parameterisations.

Figure 3. Semi-Mechanistic Population PK Model development Schematic



Schematic pharmacokinetic interaction model of DEC (top) and CED (bottom). $V_{C,DAC}$ and $V_{C,CED}$ are DEC and CED central compartment volumes, $V_{P,DCA}$ and $V_{P,CED}$ are DEC and CED peripheral compartment volumes, V_H and V_{PV} are liver and portal vein volumes, respectively. $Q_{P,DEC}$, $Q_{P,CED}$, Q_H, Q_{HA}, and Q_{PV} are DEC and CED peripheral compartment, and liver, hepatic artery, and portal vein flow rates, respectively. $CL_{NS,CED}$, $CL_{H,DEC}$, $CL_{EH,DEC}$ and $CL_{G,DEC}$ are CED clearance, DEC hepatic, extra-hepatic, and gut clearance due to CDA (cytidine deaminase) metabolism, respectively. $C_{CED,VC}$, $C_{CED,H}$, and $C_{CED,G}$ are CED concentrations in the central, liver, and gut compartments, respectively. $K_{I,CED}$ is the inhibition constant of CED for CDA inhibition. Fraction unbound and blood to plasma ratio were fixed based on studies to 0.99/0.65 and 1/1 DCA/CED, respectively.

The dataset included data from AML (N=87) and MDS (N=243) patients from the phase 1, 2, and 3 studies Missing PK observations, PK observations with missing preceding dose information, and PK observation values below the quantifiable limit (BQL) were excluded from the analysis. The covariates of interest included sex (221 males, 109 females), age (32-92 years), baseline body weight (41-158 kg), and use of PPI at any time during the study (235 No, 95 Yes). In addition, renal function based on normalised CrCL, and hepatic function based on bilirubin values followed the NCI guidance, were investigated. Although the dataset (and all provided summaries of the data) included data from both AML and MDS patients, during this analysis the model was only fitted to data from AML patients.

The final models (decitabine and cedazuridine) included covariate effects of height, with a fixed exponent (0.75), on the liver blood flow and volumes. In addition, in the cedazuridine model, covariate effects of sex and CrCL were estimated on k_{tr} and CL, respectively (Table 12), and in the decitabine model, covariate effects of body weight and sex were estimated on CL_H and Q (simultaneously estimated), as well as V_c and k_a (only effect of sex; Table 13 and Table 14).

Table 12. ASTX727-02 oral cedazuridine (AML+MDS) PK model parameter estimates

Parameter	Estimate	Mean	Median	CI (95%)
Fixed-effects				
$CL_{NS,CED}$ (L/h)	37.5	36.5	36.7	(32.0, 39.4)
Q_{CED} (L/h)	18.3	18.3	18.3	(15.9, 20.5)
$V_{c,CED}$ (L)	32.0	31.2	31.0	(25.3, 38.5)
$V_{p,CED}$ (L)	247	246	245	(211, 292)
$k_{tr,CED}$ (/h)	0.414	0.412	0.413	(0.380, 0.445)
$Sex-k_{tr,CED}$	1.11	1.10	1.10	(1.01, 1.17)
$CrCL-CL_{NS,CED}$	0.902	0.856	0.861	(0.641, 1.03)
Inter-individual variability				
$\omega_{CL_{NS,CED}}$ (CV%)	52.7	51.2	51.1	(45.8, 56.3)
$\omega_{CL_{NS,CED}-Q_{CED}}$ (r)	0.256	0.236	0.235	(0.182, 0.289)
$\omega_{Q_{CED}}$ (CV%)	74.6	73.2	72.7	(61.6, 84.8)
$\omega_{V_{c,CED}}$ (CV%)	90.3	101	99.5	(76.5, 138)
$\omega_{k_{tr,CED}}$ (CV%)	17.6	20.5	20.0	(15.0, 28.3)
Residual error				
σ_{prop} (CV%)	26.4	27.1	26.9	(24.4, 29.8)
σ_{add} (SD)	19.5	18.0	18.9	(8.15, 27.8)

Source code: 06_BOOT_joint.Rmd
Source file: partabBoot_102.tex

Table 13. ASTX727-02 IV decitabine PK model (AML+MDS) parameter estimates

Table 2: IV decitabine PK model parameter estimates (AML + MDS)

Parameter	Estimate	Mean	Median	CI (95%)
Fixed-effects				
$CL_{H,DAC}$ (L/h)	60.2	60.0	60.1	(55.9, 64.3)
$V_{c,DAC}$ (L)	57.6	57.9	58.1	(53.3, 62.9)
Q_{DAC} (L/h)	13.8	13.6	13.6	(11.9, 15.4)
$V_{p,DAC}$ (L)	26.1	26.8	26.6	(24.1, 30.8)
$WT-CL_{H,DAC}$	0.245	0.263	0.252	(0.0961, 0.467)
$WT-Q_{DAC}$	0.317	0.336	0.307	(0.0398, 0.746)
$Sex-CL_{H,DAC}$	0.777	0.784	0.788	(0.688, 0.879)
$Sex-Q_{DAC}$	0.766	0.776	0.773	(0.633, 0.909)
$Sex-V_{c,DAC}$	0.767	0.776	0.774	(0.685, 0.884)
Inter-individual variability				
$\omega_{CL_{H,DAC}}$ (CV%)	53.8	53.4	53.0	(45.6, 61.1)
$\omega_{CLHD-VCD}$ (r)	0.200	0.198	0.197	(0.131, 0.277)
$\omega_{V_{c,DAC}}$ (CV%)	57.5	57.1	56.6	(47.1, 67.1)
$\omega_{CLHD-QP1D}$ (r)	0.318	0.308	0.306	(0.239, 0.381)
$\omega_{VCD-QP1D}$ (r)	0.213	0.208	0.205	(0.137, 0.282)
$\omega_{Q_{DAC}}$ (CV%)	73.8	71.7	71.4	(62.3, 81.8)
Residual error				
σ_{prop} (CV%)	39.1	39.0	39.1	(36.8, 41.1)
σ_{add} (SD)	0.888	0.818	0.833	(0.384, 1.14)

Table 14. ASTX727-02 oral decitabine PK model (AML+MDS) parameter estimates

Parameter	Estimate	Mean	Median	CI (95%)
Fixed-effects				
$N_{tr,DAC}$	2.76	2.82	2.78	(2.43, 3.44)
MTT_{DAC} (h)	0.398	0.397	0.397	(0.366, 0.425)
$k_{a,DAC}$ (/h)	2.52	2.55	2.55	(2.34, 2.79)
$Sex - k_{a,DAC}$	1.00	0.981	0.977	(0.862, 1.13)
Inter-individual variability				
$\omega_{N_{tr,DAC}}$ (CV%)	72.5	72.8	71.9	(42.4, 100)
$\omega_{MTT_{DAC}}$ (CV%)	49.6	49.5	49.7	(42.9, 55.1)
$\omega_{k_{a,DAC}}$ (CV%)	46.8	47.2	47.4	(40.0, 54.7)
Residual error				
σ_{prop} (CV%)	49.2	49.2	49.1	(47.2, 51.0)
σ_{add} (SD)	1.49	1.47	1.45	(0.585, 2.02)

Source code: 06_BOOT_joint.Rmd
Source file: partabBoot_304M6j0.tex
DEC=decitabine; V_c=central volume; CL_H=hepatic clearance;
Q=inter-compartmental clearance; V_p=peripheral volume;
$\omega_{parameter}$=variability of the given parameter;
$\omega_{parameter1-parameter2}$=correlation between parameter 1 and parameter 2;
σ_{prop}=proportional error; σ_{add}=additive error; CV=coefficient of variation;
SD=standard deviation; CI=confidence interval. Mean, Median, and CI are

Absorption

Both cedazuridine and decitabine can be classified as highly soluble substances according to the BCS classification.

After oral administration of Inaqovi in the Phase 3 Study ASTX727-02 NA MDS/CMML, the median t_{max} was 1 hour (range, 0.3 to 3 hours) for decitabine and 3 hours (range, 0.52 to 7.9 hours) for cedazuridine.

In vitro permeability for decitabine or cedazuridine was not specifically discussed by the applicant, but in the Caco-2 cell study P_{app} values for cedazuridine were much lower than those of the high-permeability control antipyrine. Cedazuridine is not a P-gp substrate.

Study ASTX727-01-A (dose escalation and absolute bioavailability of decitabine)

This was a single-arm, dose escalation study to assess the safety, tolerability, and PK of concomitant orally administered cedazuridine plus decitabine in adult subjects with MDS or CMML. Treatment was given in 28-day cycles and included single-dose oral decitabine (on Day −3 of Cycle 1), decitabine by 1-hour IV infusion administered at 20 mg/m2 (Cycle 1 Day 1), single dose of oral cedazuridine (on Day −3 of Cycle 2), and cedazuridine plus decitabine administered concomitantly as separate oral capsules (on Days 2 to 5 of Cycle 1 and Days 1 to 5 of Cycle 2 and subsequent cycles). Doses of cedazuridine/decitabine (in mg) were 40/20, 60/20, 100/20, 100/40, and 100/30 for Cohorts 1, 2, 3, 4, and 5, respectively.

In total 44 subjects with MDS or CMML were randomised and treated in the study. The median age was 71.5 years (range 59-86 years), most subjects were male (68%) and median body weight was 83.7 kg (range 51.1-145.6 kg).

Results

Results regarding decitabine AUC and increases in bioavailability are presented in Table 1515 and Table 16.

Table 15: 5-day Decitabine Plasma AUC_{0-t}

Subjects Who Completed Cycle 1 (N=43); Data are Geometric Mean (gCV%)										
	Oral Dose[a] (mg)			AUC_{0-t} by Day (ng*h/mL) Geometric Mean (g				5-Days Total AUC_{0-t}		
Cohort	DAC	CED	N	D −3	D2	D5	IV D1	Oral	IV (N=41)	% of AUC (Oral/IV)
1	20	40	6	10.7 (108)	42.8 (136)	70.3 (86)	159 (53)	324		40
			5[b]	7.90 (58)	29.0 (45)	53.6 (40)	138 (41)	243		30
2	20	60	6	7.49 (52)	30.5 (62)	68.9 (44)	170 (39)	306	821[d]	37
3	20	100	6	7.90 (147)	53.5 (44)	94.8 (46)	192 (47)	433		53
4	40	100	6	29.8 (100)	167 (45)	221 (74)	153 (50)	1050		128
5	30	100	19[c]	15.3 (92)	81.7 (59)	146 (50)	166 (41)	667		81

AUC=area under the concentration versus time curve; AUC_{0-t}=area under the curve during the dosing interval; CED=cedazuridine (E7727); D=day; DAC=decitabine; gCV%=geometric coefficient of variation; IV=intravenous

[a] Oral dosing was not body weight or body surface area adjusted. IV dose was 20 mg/m^2 in all cohorts.

[b] One subject in Cohort 1 was excluded as an extreme outlier.

[c] IV used n=18 as one subject was excluded as an extreme outlier.

[d] Geometric mean for total 5-day IV AUC_{0-t} calculated for the total IV population (N=41).

Table 16: Mean Oral Bioavailability and Increase in Decitabine AUC_{0-t} Compared with Day −3

	Oral Dose[a] (mg)			Geometric Mean (gCV%)					
Cohort	DAC	CED	N	F%		$R_{DDI}(AUC_{0-t})_{Day\ 2}$		$R_{DDI}(AUC_{0-t})_{Day\ 5}$	
1	20	40	6	12.9	(66)	4.01	(54)	6.60	(46)
			5[b]	11.3	(61)	3.68	(55)	6.79	(51)
2	20	60	6	9.16	(56)	4.07	(72)	9.21	(51)
3	20	100	6	7.81	(65)	6.77	(123)	12.0	(133)
4	40	100	6	18.8	(63)	5.60	(60)	7.42	(77)
5	30	100	19[c]	13.1	(77)	5.34	(94)	9.55	(77)

AUC_{0-t}=area under the curve during the dosing interval; BSA=body surface area; CED=cedazuridine (E7727); DAC=decitabine; F%=bioavailability (calculated as [(AUC_{0-t}ORAL*IV Dose) / (AUC_{0-t}IV*Oral Dose)]*100, where total dose in mg was used for both IV and oral administration; $R_{DDI}(AUC_{0-t})$=AUC_{0-t} Day 2 or 5 / AUC_{0-t} Day −3

[a] Oral dosing was not body weight or BSA adjusted. IV dose was 20 mg/m^2 in all cohorts.

[b] One subject in Cohort 1 was excluded as an extreme outlier.

[c] IV used n=18; one Subject was excluded as an extreme outlier.

A rapid oral absorption of decitabine was determined in MDS/CMML patients, followed by a rapid decline at 4-6 hours post dose across the dose levels tested. Total and peak exposure of oral decitabine were consistently lower on Day –3 when administered alone compared with Day 2 or Day 5 when administered in combination with cedazuridine. The lower increase in oral decitabine AUC0-t on Day 2 (the first combination dose with cedazuridine) compared to Day 5 is likely due to less cedazuridine present systemically.

The absolute bioavailability of oral decitabine dosed alone was low, ranging from 9%-19%. Coadministration of cedazuridine resulted in enhanced oral bioavailability of decitabine in every subject with an increase of AUC_{0-t} ranging from approximately 4-7 fold on day 2 and 7-12 fold on Day 5.

Correspondingly, the decitabine mean oral bioavailability (dose-normalised AUC-ratio compared to IV treatment) improved and was 111% for Day 2, and 146% for Day 5 in Cohort 4.

C_{max} values for oral decitabine when dosed alone were markedly lower than for IV decitabine. Decitabine C_{max} increased with coadministration of cedazuridine.

Geometric mean ratios of 81% and 128% for decitabine oral AUC/decitabine IV AUC were achieved with cedazuridine/decitabine doses of 100/30 and 100/40 mg, respectively. This supported the selection of an intermediate dose of decitabine between 30 and 40 mg (i.e., 35 mg) in combination with 100 mg cedazuridine for further testing. The dose of 35 mg decitabine corresponds to the IV dose of 20mg/m^2 (with a BSA of 1.73 m^2) recommended for Dacogen.

Co-administration of decitabine with cedazuridine did not appear to alter cedazuridine plasma PK at the relevant dose of 100 mg. No differences on absorption parameters (Cmax or tmax) were observed when cedazuridine was administered alone or in combination with decitabine.

Study ASTX727-01-B (dose confirmation study)

ASTX727-01-B was a Phase 2, open-label, randomised, 2-cycle, 2-sequence crossover study followed by a single-arm continuation of treatment conducted in 2 stages to assess the PK, safety, and efficacy of cedazuridine (100 mg) and decitabine (35 mg) administered concomitantly as separate capsules (in the Dose Confirmation Stage) and as the ASTX727 FDC tablet (in the FDC Stage). 86 Subjects with MDS or CMML were randomised to receive the investigational product Daily ×5 in Cycle 1 followed by IV decitabine Daily ×5 in Cycle 2 (Sequence A), or the same treatments in the reverse order (Sequence B). 80 subjects received treatment.

Results

Concomitant oral administration of cedazuridine (100 mg) with decitabine (35 mg) as separate capsules and as the Inaqovi FDC tablet showed similar exposure to that of IV decitabine (20 mg/m^2). The ratio (oral/IV) of geometric LSM (93.52 in Dose Confirmation Stage; 97.59 in FDC Stage) and its 80% CI (82.10, 106.5 in Dose Confirmation Stage; 80.48, 118.3 in FDC Stage) were fully contained within the prespecified CI limits for each stage. Steady state was reached with the second dose of the oral combination (Day 2), as decitabine exposures on Days 2 and 5 were comparable (ratio of 0.98 between days 2 and 5). The T1/2 was slightly higher (1.3-1.4 h) when co-administered with cedazuridine at day 2 and 5 compared to 1.08 h for decitabine IV.

Study E7727-01 (Period 1, Absolute bioavailability of cedazuridine)

Study E7727 (period 1) was a phase I, mass balance, absolute bioavailability study with 8 subjects (5 male and 3 female). Subjects were given a non-radiolabelled single oral 100 mg dose (capsule) of cedazuridine in the fasted state, followed by an intravenous microtracer dose of ^{14}C- cedazuridine. Plasma samples were taken up to 72 hours post oral dose and urine was collected up to 72 hours post dose for determination of cedazuridine and ^{14}C- cedazuridine.

Results

The mean (SD) absolute bioavailability of cedazuridine was 20.7% (4.3%), following an oral dose of 100 mg E7727 capsule formulation in the fasted state and intravenous administration of a microtracer dose of 100 µg [^{14}C]-E7727.

Relative bioavailability

The final commercial formulation was used in study ASTX727-02 EU and ASTX727-02 NA and also in study ASTX727-04 (food effect study). Separate cedazuridine and decitabine capsules were used in study ASTX727-01-A and an early formulation of the ASTX727 tablet (35 mg decitabine and 100 mg

cedazuridine) was manufactured for the Phase 2 FDC Stage of the ASTX727-01 study (ASTX727-01-B). It is concluded that the ASTX727 tablets used in the Phase 3 study (in subjects with MDS/CMML and AML) were not substantially different from the ASTX727 tablets used in the Phase 2 study and that no bioequivalence study was necessary between the 2 different formulations.

ASTX727-02 EU (AML) Pivotal Phase 3 study

ASTX727-02 EU was a Pivotal Phase 3 multicentre, randomised, open-label, 2-period, 2-sequence crossover study comparing decitabine AUC equivalence of ASTX727 and IV decitabine. Adult subjects with AML who were candidates to receive IV decitabine at 20 mg/m^2 were randomised in a 1:1 ratio to receive the ASTX727 FDC tablet Daily×5 in Cycle 1, followed by IV decitabine 20 mg/m2 Daily×5 in Cycle 2 (Sequence A), or the converse order (Sequence B). Adequate PK assessments from both cycles were required for subjects to be evaluable for analysis of the primary endpoint. After completion of the first 2 treatment cycles, subjects continued to receive treatment with Inaqovi in 28-day cycles until disease progression, unacceptable toxicity, or the subject decided to discontinue treatment or was withdrawn from the study. Subjects were permitted to have only clear liquids (no food or non-clear liquids) for 2 hours before and 2 hours after administration of ASTX727. Pharmacokinetics were evaluated on Days 1 through 5 during the cycle of ASTX727 administration (serial collections on Days 1, 2, and 5), and on Days 1, 3, and 5 during the cycle of IV decitabine administration (serial collections on Days 1 and 5). Blood-samples were collected pre-dose and until 24 h after ASTX727 treatment and until 8h after IV decitabine.

Total 5-day oral decitabine AUC_{0-24} exposures were calculated as follows using PK data from 3 days of serial PK sampling: Day 1 AUC_{0-24} (first ASTX727 dose) + (Day 2 AUC_{0-24} + Day 5 AUC_{0-24}) × 2.

Decitabine 5-day AUC_{0-24} exposures after IV decitabine was calculated as follows: (Day 1 AUC_{0-24} + Day 5AUC_{0-24}) / 2 x 5.

A total of 89 subjects were randomised in the study. Of the 87 subjects who received treatment the median age was 78 years (range 61-92 years), most subjects were male (60.9%) and median body weight was 73.7 kg (range 46-117 kg). There was a total of 69 subjects that completed the first 2 cycles with sufficient PK samples that were fully evaluable for the primary analysis of the primary study endpoint.

Results

ASTX727 given as an FDC of 35 mg decitabine and 100 mg cedazuridine achieved AUC exposures equivalent to IV infusion of decitabine at 20 mg/m^2. The 5-Day AUC_{0-24} percentage ratio (oral/IV) of geometric LSM was 99.64% (90% CI 91.23%, 108.8%); the 2 sided 90% CI was contained entirely within the prespecified range of 80% to 125%, see Table 17.

Table 17: Plasma Decitabine AUC Equivalence Assessment for the Primary Exposure Variable AUC_{0-24} (Primary Endpoint PK Analysis Set)

		AUC Parameter	IV Decitabine		Oral ASTX727		Ratio of Geo. LSM		Intra-Subject
		(ng*h/mL)	N	Geo. LSM	N	Geo. LSM	(%)	(90% CI)	(CV%)
Primary	**Paired**	5-day AUC_{0-24}	69	907.39	69	904.13	99.64	(91.23, 108.8)	31.55
Sensitivity	**Paired**	5-day AUC_{0-24}	71	908.77	71	893.00	98.26	(90.11, 107.2)	31.56
Sensitivity	**Unpaired**	5-day AUC_{0-24}	78	896.46	79	885.66	98.80	(90.81, 107.5)	31.31

AUC_{0-24}=area under the curve from time zero to 24 hours postdose; CI=confidence interval; CV=coefficient of variation; Geo. LSM=Geometric Least Squares Means. Reference treatment = IV decitabine 20 mg/m^2 IV 1-hour infusion. Test treatment = Oral ASTX727 (35 mg decitabine + 100 mg cedazuridine).

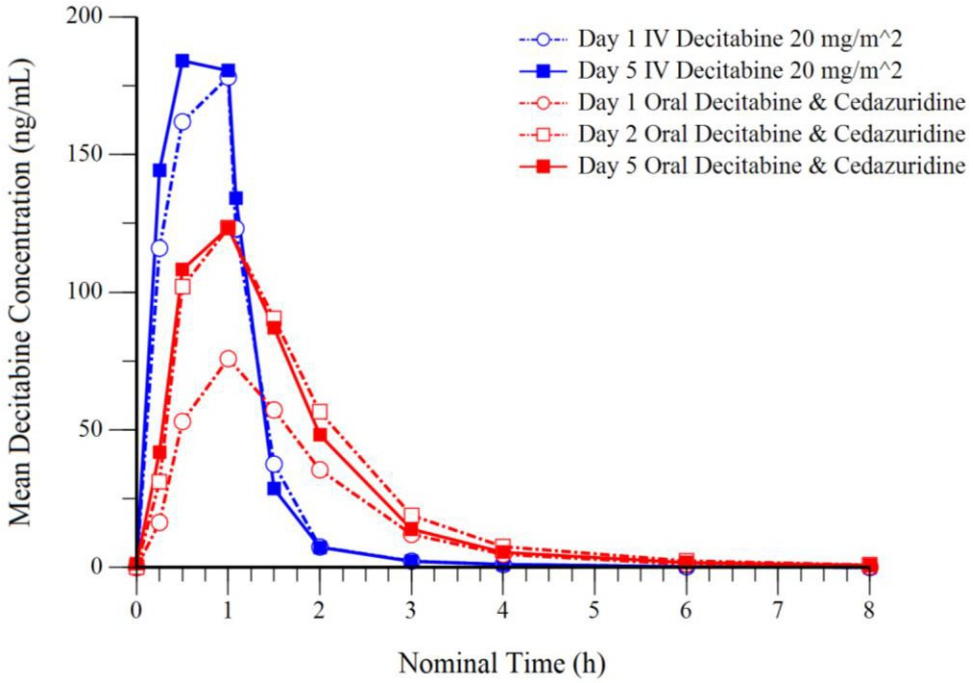
Results of the secondary analyses of AUC_{0-8}, AUC_{0-t}, and AUC_{0-inf} further supported the primary analysis of 5-Day AUC0 24.

Following multiple oral administrations of ASTX727 on Day 2 and Day 5, geoCV% plasma decitabine AUC_{0-24} values (194 ng*h/mL [59.6%] and 187 ng*h/mL [57.5%] at steady state for Day 2 and Day 5, respectively) were comparable to AUC_{0-24} values following IV decitabine (175 ng*h/mL [55.1%] and 180 ng*h/mL [58.2%] on Day 1 and Day 5, respectively.

C_{max} was consistently lower for ASTX727 compared to IV decitabine; on Day 1 the difference was 54% and on Day 5 28%. AUC_{0-24} day 1 was also lower for ASTX727 compared to IV decitabine.

Pharmacokinetic parameters of decitabine and cedazuridine are presented in Table 18 and Table 19 respectively.

Figure4: Mean Plasma Decitabine Concentration vs Time Profiles Following Single and Multiple Infusions of IV Decitabine 20 mg/m2 and Following Oral Administrations of ASTX727 on Days 1, 2, and 5 (Linear and Semi-Log Scales)



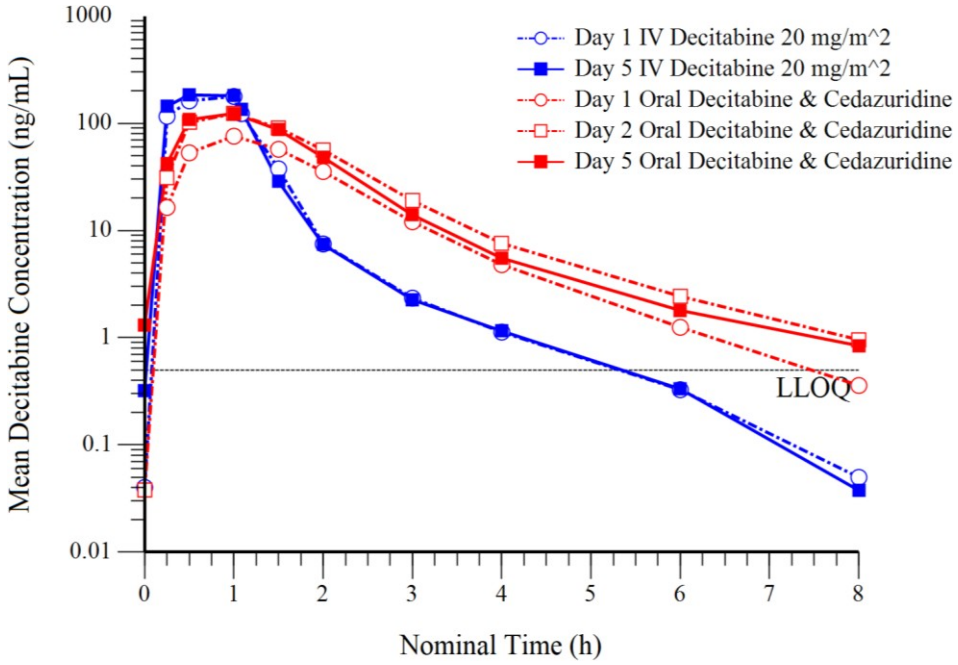


Table 28: Pharmacokinetic Parameters of Plasma Decitabine (ASTX727-02-EU, AML)

		IV Decitabine		ASTX727		
PK Parameters[a]	Units	Day 1	Day 5	Day 1	Day 2	Day 5
AUC_{0-8}	ng*h/mL	175 (54.6); 71	180 (58.6); 70	117 (54.4); 78	192 (59.4); 75	183 (58.1); 76
AUC_{0-24}	ng*h/mL	175 (55.1); 70	180 (58.2); 70	118 (54.6); 78	194 (59.6); 75	187 (57.5); 75
AUC_{0-last}	ng*h/mL	171 (57.2); 72	179 (59.1); 70	116 (55.1); 78	193 (59.6); 76	182 (58.4); 76
AUC_{0-inf}	ng*h/mL	175 (54.9); 70	181 (58.1); 70	118 (54.4); 78	193 (59.6); 74	187 (57.1); 75
5-DayAUC_{0-8}	ng*h/mL	—	898 (49.7); 79	—	—	883 (51.6); 79
5-DayAUC_{0-24}	ng*h/mL	—	898 (50.1); 78	—	—	893 (51.5); 79
5-DayAUC_{0-last}	ng*h/mL	—	891 (50.7); 79	—	—	881 (52.0); 79
5-DayAUC_{0-inf}	ng*h/mL	—	900 (50.0); 78	—	—	895 (51.3); 79
$AvgC_{max}$	ng/mL	—	194 (55.3); 79	—	—	161 (52.8); 80
C_{max}	ng/mL	187 (64.7); 72	192 (62.4); 70	85.9 (56.6); 78	139 (58.5); 76	139 (62.7); 76
T_{max}[b]	h	0.98 (0.25 – 2.00); 72	0.98 (0.00 - 1.17); 70	1.00 (0.25 - 2.02); 78	1.00 (0.25 – 3.00); 76	1.00 (0.47 – 3.00); 76
$t_{1/2}$	h	1.16 (56.7); 70	1.18 (49.0); 70	1.07 (31.6); 78	1.36 (35.0); 74	1.45 (34.0); 75
C_{avg}	ng/mL	7.28 (55.1); 70	7.51 (58.2); 70		8.09 (59.6); 75	7.77 (57.5); 75
C_{min}[c]	ng/mL	—	0.00 (NC); 70	—	0.00 (NC); 76	0.0180 (627.7); 76
T_{min}[b]	h	—	6.00 (0.23 - 8.47); 70	—	7.87 (0.22 - 8.17); 76	7.87 (0.22 - 8.17); 76
C_{trough}	ng/mL	0.823 (33.1); 72	0.801 (38.1); 70	4	1.14 (61.6); 76	1.07 (55.4); 76
CL;CL/F;CL_{ss};CL_{ss}/F	L/h	210 (56.2); 70	202 (61.4); 70	297 (54.4); 78	181 (59.8); 74	188 (57.5); 75
V_z;V_z/F;V_{ss}	L	309 (72.4); 70	78.6 (101.0); 70	434 (60.4); 78	337 (67.6); 74	373 (68.9); 75
R(AUC_{0-24})	—	—	1.02 (43.3); 62	—	—	1.60 (44.8); 74
R(C_{max})	—	—	1.01 (55.0); 63	—	—	1.61 (61.9); 75

For PK abbreviation definitions, please see Table 6.
NOTE: CL and V_z for IV Day 1, CL_{ss} and V_{ss} for IV Day 5, CL/F Oral Day 1, CL_{ss}/F Oral Days 2 and 5 and V_z/F for Oral Days 1, 2, and 5.
[a] Geometric Mean (Geometric CV%); N
[b] Median (Min - Max); N
[c] Mean (CV%)
Source: Appendix 16.1.13.4 PK Report Table 8

Table 39: Pharmacokinetic Parameters of Plasma Cedazuridine (ASTX727-02-EU, AML)

PK Parameters[a]	Units	ASTX727		
		Day 1	Day 2	Day 5
AUC_{0-8}	ng*h/mL	1690 (46.6); 78	1900 (43.0); 78	1930 (42.0); 76
AUC_{0-24}	ng*h/mL	3190 (49.2); 76	3600 (47.3); 78	1150 (NC); 1
AUC_{0-last}	ng*h/mL	3130 (49.8); 78	3600 (47.5); 78	1910 (42.0); 77
C_{max}	ng/mL	313 (47.7); 78	343 (43.4); 78	350 (42.7); 77
T_{max}[b]	h	3.98 (1.47 – 8.00); 78	4.00 (1.00 - 7.88); 78	3.98 (1.00 – 8.00); 77
$t_{1/2}$	h	6.68 (18.5); 52	7.05 (17.6); 56	2.41 (NC); 1
C_{avg}	ng/mL	—	150 (47.3); 78	48.0 (NC); 1
$C_{avg(0-8)}$	ng/mL	211 (46.6); 78	238 (43.0); 78	241 (42.0); 76
C_{min}[c]	ng/mL	—	41.6 (59.3); 78	54.5 (60.2); 77
T_{min}[b]	h	—	0.39 (0.22 - 24); 78	0.25 (0.22 - 8); 77
C_{trough}	ng/mL	—	44.6 (69.3); 78	208 (55.7); 77
CL/F	L/h	28.6 (55.5); 52	27.4 (45.4); 74	86.8 (NC); 1
V_Z/F	L	272 (59.9); 52	278 (49.8); 56	302 (NC); 1
$R(AUC_{0-24})$	—	—	—	0.375 (NC); 1
$R(AUC_{0-8})$	—	—	—	1.16 (40.8); 75
$R(C_{max})$	—	—	—	1.14 (43.5); 76

For PK abbreviation definitions, please see Table 6.
[a] Geometric Mean (Geometric CV%); N
[b] Median (Min - Max); N
[c] Mean (CV%); N
Source: Appendix 16.1.13.4 PK Report Table 12

ASTX727-02 NA (MDS and CMML) Supportive Phase 3 study

ASTX727-02 NA (MDS and CMML) was included in the application as a supportive study. The general study design was same as for ASTX727-2 EU (AML). However, Subjects were not permitted to take gastric pH altering drugs for 4 hours before and for 4 hours after ASTX727 dosing, due to the possible interference with decitabine absorption from ASTX727.

In total 138 subjects with MDS or CMML were randomised in the study. Of the 133 subjects who received treatment the median age was 71 years (range 44-88 years), most subjects were male (65.4%) and median body weight was 83.1 kg (range 45-158 kg). Of the 133 subjects treated, 123 completed the first 2 cycles with sufficient PK samples that were fully evaluable for the primary analysis of the primary study endpoint.

Results

The primary analysis showed that the 5-Day AUC0-24 percentage ratio of geometric LSM for ASTX727 relative to IV decitabine was 98.93% (90% CI 92.66%, 105.6%). The 2 sided 90% CI was contained entirely within the prespecified range of 80% to 125% for the primary analysis. All sensitivity and secondary analyses that included additional subjects (N between 124 and 131 subjects for paired and unpaired comparisons) confirmed that the 2-sided 90% CI of the geometric LSM ratio was contained entirely within 80% to 125%.

Results of the secondary analyses (area under the concentration time curve from time zero to 8 hours postdose [AUC_{0-8}], AUC_{0-t}, and AUC_{0-inf}) further supported the primary analysis of 5-Day AUC_{0-24}.

Pharmacokinetic parameters of decitabine and cedazuridine are presented in Table 20 and Table 21 respectively.

Table 20: Pharmacokinetic Parameters of Plasma Decitabine (ASTX727-02-NA, MDS/CMML)

		IV Decitabine		ASTX727		
PK Parameters[a]	Units	Day 1	Day 5	Day 1	Day 2	Day 5
AUC_{0-8}	ng*h/mL	172 (40.8);121	168 (42.1);121	101 (54.9);128	185 (55.2);127	175 (52.9);124
AUC_{0-24}	ng*h/mL	173 (40.9);119	169 (41.8);119	103 (55.4);127	189 (55.4);128	178 (52.8);123
AUC_{0-last}	ng*h/mL	170 (41.8);122	166 (42.5);122	100 (55.6);128	184 (55.6);128	175 (53.1);124
AUC_{0-inf}	ng*h/mL	174 (40.8);119	170 (41.7);119	102 (54.8);127	186 (55.3);126	178 (52.7);123
5-Day AUC_{0-8}	ng*h/mL	—	852 (40.6);127	—	—	835 (49.8);128
5-Day AUC_{0-24}	ng*h/mL	—	854 (40.4);127	—	—	851 (50.0);127
5-Day AUC_{0-last}	ng*h/mL	—	848 (40.7);127	—	—	833 (50.0);128
5-Day AUC_{inf}	ng*h/mL	—	856 (40.3);127	—	—	845 (49.8);127
Avg C_{max}	ng/mL	—	184 (47.2);127	—	—	146 (52.4);128
C_{max}	ng/mL	184 (48.1);122	180 (49.2);122	83.1 (66.1);128	145 (54.7);128	140 (62.8);124
T_{max}[b]	h	0.98 (0.23 - 1.27);122	0.97 (0.25 - 1.62);122	1.00 (0.48 – 3.00);128	1.00 (0.47 – 2.00);128	1.00 (0.25 – 3.00);124
$t_{1/2}$	h	0.967 (46.8);119	1.14 (44.9);119	1.18 (22.8);127	1.38 (24.7);126	1.47 (26.9);123
C_{avg}	ng/mL	—	7.06 (41.8);119	—	7.90 (55.5);128	7.40 (52.8);123
C_{min}[c]	ng/mL	—	0.0 (NC);122	—	0 (NC);128	0.0 (NC);124
T_{min}[b]	h	—	7.95 (6.02 - 8.62);122	—	23.90 (7.90 - 28.13);128	7.92 (0.22 - 8.33);124
C_{trough}	ng/mL	—	0.730 (27.5);122	—	0.903 (39.0);128	0.872 (38.0);124
CL;CL/F;CL_{ss}; CL_{ss}/F	L/h	226 (45.5);119	232 (46.1);119	342 (54.8);127	185 (55.5);127	197 (52.8);123
V_z;V_z/F;V_{ss}	L	315 (74.5);119	93.5 (79.0);119	585 (55.0);127	369 (59.0);126	417 (54.3);123
R(AUC_{0-24})	-	—	0.929 (67.3);113	—	—	1.72 (42.5);123
R(C_{max})	-	—	0.899 (78.5);122	—	—	1.69 (59.7);124

Note: CL and V_z for IV Day 1; CL_{ss} and V_{ss} for IV Day 1; CL/F Oral Day 1; CL_{ss}/F Oral Days 2 and 5; and V_z/F for ASTX727 Days 1, 2, and 5.
IV=intravenous; NC=not calculated; R=Accumulation ratio.
[a] Data are presented as Geometric Mean (Geometric CV%); N (number of subjects in the analysis).
[b] Median (Min - Max); N
[c] Mean (CV%); N
Source: Appendix 16.1.13.4 PK Report Table 6.5.3

Table 4. Pharmacokinetic Parameters of Plasma Cedazuridine (ASTX727-02-NA, MDS/CMML)

		ASTX727								
		Day 1			Day 2			Day 5		
PK Parameter	Units	Geo. Mean	Geo. CV%	N	Geo. Mean	Geo. CV%	N	Geo. Mean	Geo. CV%	N
AUC_{0-8}	ng*h/mL	1670	51.7	128	1860	46.1	127	2010	47.9	83
AUC_{0-24}	ng*h/mL	2950	49.2	120	3290	45.1	124	5120	28.5	3
AUC_{0-last}	ng*h/mL	2910	49.6	128	3270	45.6	128	1980	47.7	126
C_{max}	ng/mL	321	53.8	128	349	49.1	128	371	51.8	126
T_{max}[a]	h	3.00	(1.50-7.97)	128	3.01	(0.52-7.88)	128	3.00	(1.50-6.12)	126
$t_{1/2}$	h	6.33	18.1	109	6.70	18.9	115	2.59	5.43	2
C_{avg}	ng/mL	—	—	—	137	45.7	121	248	15.9	2
$C_{avg(0-8)}$	ng/mL	—	—	—	233	45.9	128	249	47.7	125
C_{min}[b]	ng/mL	—	--	—	36.0	61.4	128	46.9	57.5	126
T_{min}[a]	h	—	—	—	23.07	(0.17-28.13)	128	0.25	(0.2-8.0)	126
C_{trough}	ng/mL	—	—	—	36.6	61.1	128	192	52.6	126
CL/F	L/h	30.6	46.4	109	25.6	159	121	16.8	15.9	2
V_z/F	L	280	50.9	109	296	51.3	118	62.8	10.4	2
R(AUC_{0-24})	—	—	—	—	—	—	—	1.39	6.60	2
R(C_{max})	—	—	—	—	—	—	—	1.16	47.5	126

R=Accumulation ratio.
Geo. Mean=Geometric Mean; Geo. CV%=Geometric CV%; N=Number of subjects.
[a] Median (Min-Max); N
[b] Mean (%CV); N
Source: Appendix 16.1.13.4 PK Report Table 6.6.1

Study ASTX727-04 (food effect study)

ASTX727-04 was a Phase 1b, multicentre, open-label, randomised, study to evaluate the effect of food on the pharmacokinetics of ASTX727 in subjects with all subtypes of MDS, CMML and AML. Subjects

received one tablet of ASTX727 containing 100 mg cedazuridine and 35 mg decitabine once daily for 5 days in 28-day cycles starting from Cycle 1 Day 1.

18 subjects were randomised (17 treated, 16 included in PK population) in a 1:1 ratio to receive a high-calorie, high-fat breakfast meal pre-dose at steady state (which is achieved on Day 2) on either Day 2 or Day 4 of Cycle 1. Comparison of data for fed vs fasted was performed using equivalence analysis on the combined data from Days 2+4.

Results

Cedazuridine and cedazuridine-epimer exposure parameters were approximately 10% and 20% higher, respectively, following a high-fat meal compared to those following fasted conditions. T_{max} occurred slightly later (approximately 0.5 hour).

Decitabine exposure parameters were approximately 40% (AUC) to 53.5% (C_{max}) lower following a high-fat meal compared to those following fasted conditions. However, as data from this study were deemed to be too variable to conclude a definitive effect on decitabine, an additional study to evaluate the effect of food (high-calorie/high-fat meal, or low-calorie/light meal) is currently ongoing as a post-marketing commitment with FDA (a substudy of ASTX727-06) and is expected to be submitted to the EMA post approval when final and available.

It is currently recommended that ASTX727 should be administered in the fasted state, on an empty stomach with no food intake 2 hours before and following administration of the ASTX727 tablet.

Distribution

After oral administration of ASTX727 in the Phase 3 Studies ASTX727-02 EU (AML) and NA (MDS/CMML), the geometric mean (CV) V/F on Day 5 was 373L (68.9%) and 417 L (54%) for decitabine, respectively.

The volume of distribution (Vz/F) for cedazuridine was approximately 339 L after oral administration and after IV administration, the volume of distribution (V) was approximately 54 L (study E7727-01). In the phase III studies (ASTX727 02-B MDS/CMML NA and ASTX727-02-C AML EU) similar Vz/F of 296L and 278L, respectively, was shown.

Cedazuridine and decitabine were both observed to have low plasma protein binding in vitro (approximately 35% and 5% respectively). The major metabolite cedazuridine-epimer also had very low plasma protein binding in vitro (0%).

Based on in vitro-data, the mean blood/plasma ratio of cedazuridine in human blood was 0.76 and thus did not indicate preferential partition into blood cells. In the human mass-balance study, the blood/plasma ratio was 1.07 at 12 hours post-dose indicating some binding of cedazuridine to red blood cells.

Metabolism

No new in vitro metabolism data for decitabine has been submitted.

Five metabolites were identified in urine after SC administration of [^{14}C]-guadecitabine (pro-drug of decitabine). Three of these were also identified in plasma (study SGI-110-05).

In vitro metabolism of cedazuridine was investigated in hepatocytes and in liver S9 fractions and liver cytosols. As no in vitro metabolism was observed in these systems, the Applicant did not continue with

additional studies in order to determine which enzyme that was responsible for the metabolism. Results indicate that cedazuridine is not subject to hepatic metabolism.

In plasma, approximately 99% of all drug-related entities following oral administration of ^{14}C-cedazuridine consisted of three major products present; parent cedazuridine (58.7% of total drug-related material), the cedazuridine-epimer (30.9%) and metabolite M266/1 (9.7%) (study E7727-01). The cedazuridine-epimer is a major metabolite that needs further characterisation, no other metabolites need further investigations due to its low presence (below 10%).

The mean terminal $t_{1/2}$ of total radioactivity in plasma was 10.9 hours while the half-life for parent drug and epimer was about 8.4 hours, indicating presence of metabolites that have a longer half-life than parent drug.

Following IV administration, the exposure of parent drug cedazuridine in plasma was about 3-fold that of the epimer.

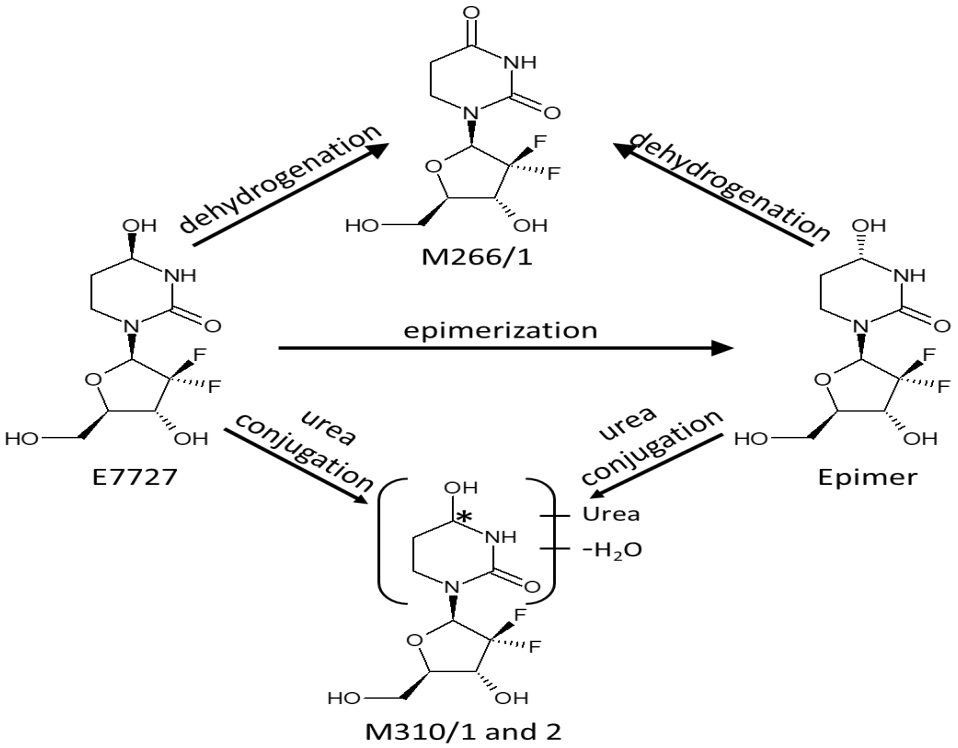
Metabolite profiling in plasma was also performed in study ASTX727-01. Cedazuridine accounted for 48.7% to 51.5% of the total drug related components. Cedazuridine-epimer was the most abundant metabolite/conversion product, accounting for 43.1% to 46.9% of the total drug-related components, while the other metabolites were relatively minor, each accounting for ≤2.9% of the total drug-related components.

The total amount of cedazuridine and cedazuridine-epimer extracted in urine following non-radiolabelled oral administration was reported to be 17.1 mg (17.1 %) and 17.5 mg (17.5 %) of the total dose.

Following a radiolabelled oral dose of cedazuridine, on average 45.7 % and 51.2% was recovered in urine and faeces, respectively. In urine, 20.7% of the total dose was extracted as cedazuridine and 13.8% as cedazuridine-epimer. In faeces, over 20% of the administered dose was in non-extractable material and the recovery of the method was reported to be low. Of the total administered dose, 14.8% was found to be cedazuridine and 11.6 % was found to be cedazuridine-epimer.

Based on the identification of metabolites from the human mass balance study (E7727-01), a proposed metabolic pathway of cedazuridine (E7727) in human plasma is depicted in Figure 5.

Figure 5: Proposed Metabolic Pathway of [^{14}C]-Cedazuridine



E7727=cedazuridine

Pharmacokinetics of metabolites

Cedazuridine has one major metabolite, the epimer. The epimer has been reported to be 1/10th as active as cedazuridine in CDA inhibition and has similar or lower exposure than cedazuridine. It is thus not expected to significantly contribute to the effect of cedazuridine. Rather, conversion to the epimer will lead to lower effect.

Cedazuridine-epimer pharmacokinetic profile largely followed that of cedazuridine, but circulating levels were at approximately 26% to 52% of cedazuridine (study ASTX727-01-A). In the phase III studies ASTX727-02 EU (AML) and NA (MDS/CMML) cedazuridine-epimer to parent (cedazuridine) ratios (EPR) for C_{max}, AUC_{0-8} and AUC_{0-24} were approximately 0.55 (EU) and 0.45 (NA), following a single dose on Day 1, and multiple doses on Day 5.

Interconversion

Cedazuridine can be converted to its epimer, which is considered a major metabolite of decitabine.

Elimination

After a single oral dose of ASTX727 in the Phase 3 Study ASTX727-02 NA MDS/CMML, the geometric mean (CV) $t_{1/2}$ of decitabine was 1.2 hours (23%); the CL/F was 342 L/h at Day 1 and 197 L/h at steady state.

Based on study E7727-01 (period 1, IV tracer dose), CL for cedazuridine (geometric mean [min-max]) was 5.67 L/h (4.23-7.82). The apparent clearance (CL/F) after the oral administration of 100-mg (capsule) was 28.0 L/h (min-max 22.4-48.3).

After a single oral dose of ASTX727 in the Phase 3 Study ASTX727-02 NA MDS/CMML, the geometric mean (CV) $t_{1/2}$ of cedazuridine was 6.33 hours (18%); the CL/F was 30.6 L/h at Day 1 and 25.6 L/h at steady state. Based on the $t_{1/2}$ observed for cedazuridine, it would be expected to clear systemically to below detection levels within 48 to 72 hours.

Mass balance

Study SG-110-05 (mass balance study for guadecitabine, prodrug of decitabine)

Data from study SG-110-05 were included in this application as supportive evidence for characterisation of mass balance and excretion pathways for decitabine. This was Phase I study with guadecitabine, a prodrug of decitabine. Guadecitabine was administered (SC) on days 1 to 5 of a 28-day cycle, with the last dose being radiolabelled.

After SC administration of [^{14}C]-guadecitabine with the radiolabel on the decitabine structure, the mean total excretion of drug related material up to the last point of collection was 90.5%, with 90.2% being excreted in urine and 0.4% in faeces. The mean half-life of decitabine on day 5 was 0.95h. Both guadecitabine and decitabine were almost completely metabolised before excretion, with <1% of cumulative excretion of unchanged drug in urine for both compounds.

Study E7727-01 (Mass balance study for cedazuridine)

This was a Phase I single-dose mass balance study conducted in 8 healthy volunteers (5 male and 3 female) in the fasted state. In period 1 subjects received a single oral dose of 100 mg and a single IV microdose (100 µg ^{14}C-E7727) as a bolus injection. In period 2 of this study, subjects received a single oral dose of 100 mg ^{14}C-E7727 for assessment of mass balance.

The arithmetic mean recovery after a single IV dose of 100 µg ^{14}C-E7727 (period 1) was 81.4%; the major route of excretion of ^{14}C-radioactivity was via urine (80.9%) whereas only a limited amount was excreted via faeces (0.6%).

Upon oral dosing (period 2) with 100 mg ^{14}C-E7727, the mean total recovery was 96.9% (ranging between 93.2% and 100.2%) over the 120-hour collection interval with most of the administered radioactivity recovered in urine and feces in the first 72 hours postdose (92.2%). The renal clearance (CLr) was 4.46 L/h (ranging between 3.01 and 5.47 L/h). The amount of total ^{14}C-radioactivity was somewhat higher in feces (mean of 51.2%) than in urine (mean of 45.7%), indicating that a substantial part of the compound dosed orally may not be absorbed.

Dose proportionality and time dependencies

An approximately dose proportional increase of decitabine peak and total exposure was seen in the dose range of 20 mg to 40 mg when co-administered with 100 mg cedazuridine (study ASTX727-01-A).

A less than dose proportional increase of cedazuridine peak and total exposure was seen in the dose range of 100 mg to 400 mg (study E7727-02). In the range of 40 mg to 100 mg the increase of cedazuridine peak and total exposure is approximately dose proportional, with 1.9-fold increases in AUC and 2.1-fold increases in Cmax at day 5 (study ASTX727-01-A).

After concomitant oral administration of decitabine and cedazuridine capsules, mean decitabine Cmax and AUC was lower on Day 1 than on Days 2 and 5. Steady state was reached with the second dose of the oral combination. Mean decitabine t1/2 following concomitant oral administration of decitabine and cedazuridine was slightly higher compared with IV. Mean decitabine apparent clearance (CL/F)

decreased after multiple doses of concomitant oral administration of decitabine and cedazuridine. This is consistent with the steady state of interaction effect of cedazuridine on decitabine being reached on Day 2. The accumulation ratio on day 5 compared to day 1 was approximately 1.7 to 1.8.

For cedazuridine the accumulation ratios for C_{max} and AUC_{0-8} were in the range of 0.94 to 1.6 (ASTX727-01-A).

Intra- and inter-individual variability

In the phase I study (ASTX727-01-A), with 6 subjects per cohort, the inter-subject variability was higher for orally compared to intravenously administered decitabine. In phase III study (AST727-02-EU AML), with a higher number of subjects, the inter-subject variability of oral decitabine AUC and C_{max} exposure parameters was moderate to high (ranging between 54.4% and 62.7%) and similar to inter-subject variability following IV decitabine infusion.

In the phase III study (ASTX727-02-C EU AML), Inter-subject variability for cedazuridine PK exposure (AUC and C_{max}) parameters following oral administration of ASTX727 was generally low to moderate, ranging between 42.0% to 49.8%.

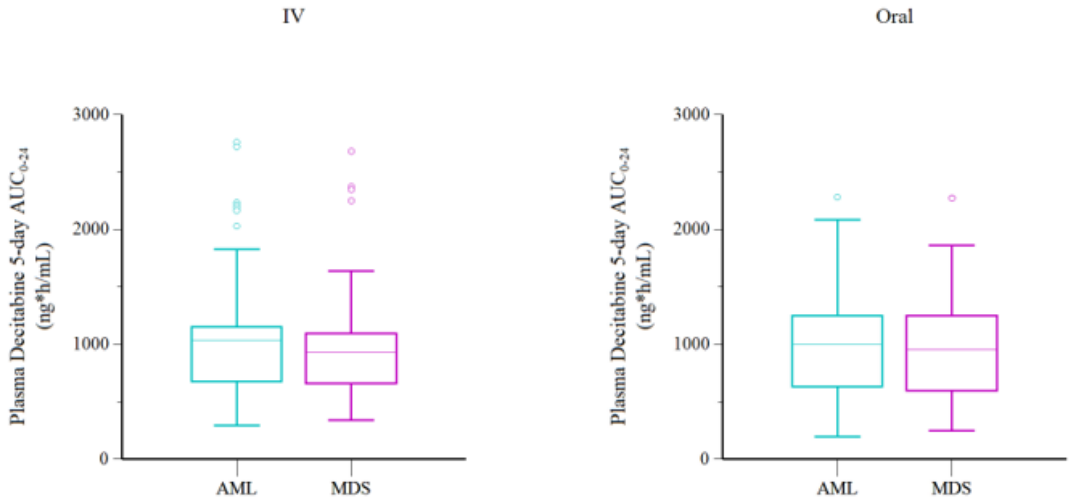
In the phase III study ASTX727-02 EU, the estimated intra-subject CV for Cmax was approximately 30% for both oral decitabine and cedazuridine. For AUC the intra-subject CV was in the range 23-30% for decitabine (both oral and IV) and for cedazuridine.

Pharmacokinetics in target population

All studies with decitabine were performed in patients with either AML or MDS/CMML; two studies with cedazuridine only (mass balance and thorough QT) were performed in healthy volunteers.

The decitabine exposure after administration of ASTX727 determined by NCA was compared graphically for subjects in the MDS/CMML population and the AML population. The primary analysis of decitabine 5 Day AUC_{0-24} showed no apparent difference in exposure between the 2 populations (Figure 6). There was also no apparent difference in cedazuridine exposure in AML versus MDS/CMML population based on graphical comparison.

Figure 6: Box Plots of Plasma Decitabine 5-Day AUC_{0-24} Following Oral and IV Administration in AML versus MDS/CMML Paired Population (Report ASTX-NCA-ASTX727-3006-06112022-02)



AML=acute myeloid leukaemia; AUC_{0-24}=area under the concentration-time curve from time zero to 24 hours postdose; CMML=chronic myelomonocytic leukaemia; IQR=inter-quartile range; IV=intravenous(ly); MDS=myelodysplastic syndrome.

Notes: Median exposure values are designated by a solid line in the centre of the box. Boxes indicate the IQR with whiskers extending to 1.5×IQR. Open circles are outliers.

Source: Report ASTX-NCA-ASTX727-3006-06112022-02, Figure 3

Special populations

Impaired renal function

No dedicated PK study has been performed investigating the effect of renal impairment on decitabine or cedazuridine exposure.

Most subjects in study ASTX727-02 EU (AML patients) had either mild or moderate renal impairment. In the study in the MDS/CMML population, most patients had normal renal function but there were also a rather large proportion of patients with mild and some with moderate renal impairment. Combining both studies, patients with normal (N=65), mild (N=129) and moderate (N=103) renal impairment were included (defined based on absolute GFR). Observed data is presented graphically separately for the AML and MDS/CMML populations respectively. There is a trend that cedazuridine exposure slightly increases with decreasing CrCL. In the MDS/CMML population there is also a trend of slight increase in decitabine exposure with decreasing CrCL, in particular for oral treatment.

Impaired hepatic function

No dedicated PK study has been performed investigating the effect of hepatic impairment on decitabine or cedazuridine exposure.

Very few AML patients with impaired liver function were included in the study. Some MDS/CMML patients had mild liver impairment (defined based only on bilirubin values, ULN to 1.5×ULN) but very few had moderate impairment (defined based only on bilirubin values, 1.5 to 3×ULN).

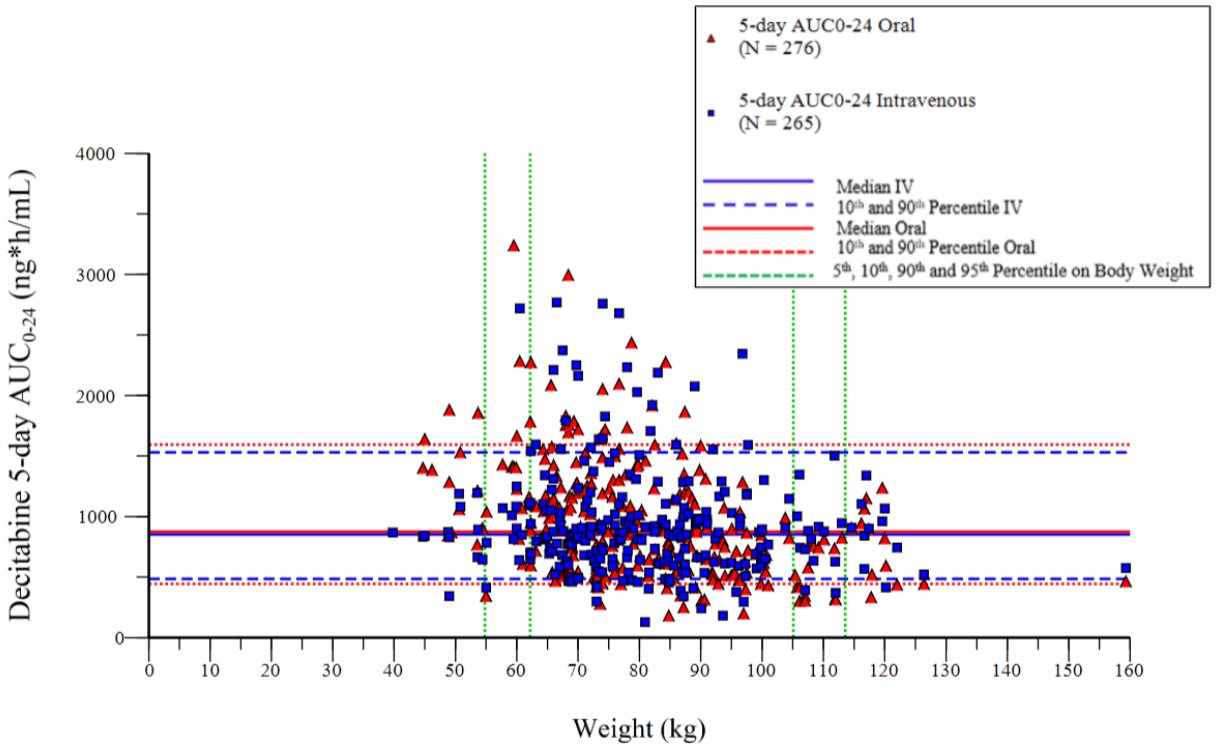
Sex, race/ethnicity, weight, age

Exploratory graphical analyses of sex and decitabine and cedazuridine exposures identified a potential correlation for oral decitabine but this effect was not clinically meaningful.

There were insufficient data to evaluate a potential race covariate.

There is a trend of decreased decitabine 5-day AUC0-24 with increasing weight or BSA with oral decitabine treatment. This is not considered to be clinically relevant (Figure 7).

Figure 7. Decitabine 5-day AUC0-24 in AML, MDS and CMML population (ASTX727-01 and ASTX727-02) across continuous body weight



Based on observed data, there seems to be a trend of increased cedazuridine exposure with increasing age. There is also a trend of increased decitabine exposure with increasing age, at least for oral treatment. The number of older subjects included in studies is summarised below.

Table 22. number of older subjects included in studies

STUDY	Age <65	Age 65-74	Age 75-84	Age 85+	Total
ASTX727-01A Phase 1	8 (18.2%)	19 (43.2%)	15 (34.1%)	2 (4.5%)	44 (100%)
ASTX727-01B Phase 2	17 (21.3%)	34 (42.5%)	25 (31.3%)	4 (5.0%)	80 (100%)
ASTX727-02A MDS/CMML	36 (27.1%)	50 (37.6%)	43 (32.3%)	4 (3.0%)	133 (100%)
ASTX727-02B MDS/CMML	5 (15.2%)	14 (42.4%)	13 (39.4%)	1 (3.0%)	33 (100%)
ASTX727-02C AML	3 (3.4%)	28 (32.2%)	47 (54.0%)	9 (10.3%)	87 (100%)
Total	64 (18.6%)	131 (38.1%)	130 (37.8%)	19 (5.5%)	344 (100%)

Pharmacokinetic interaction studies

Decitabine

Effect of decitabine on the pharmacokinetics of other medicinal products (decitabine as perpetrator)

Drug interaction studies with decitabine have not been conducted. Decitabine did not affect the exposure of cedazuridine at a dose of 100 mg.

Effects of other medicinal products on the pharmacokinetics of decitabine (decitabine as victim)

Drug interaction studies with decitabine have not been conducted. Decitabine is metabolised by CDA and the CDA inhibitor cedazuridine significantly increases the exposure of decitabine as discussed below. Other CDA inhibitors could also increase the exposure of decitabine.

Cedazuridine

Effect of cedazuridine on the pharmacokinetics of other medicinal products (cedazuridine as perpetrator)

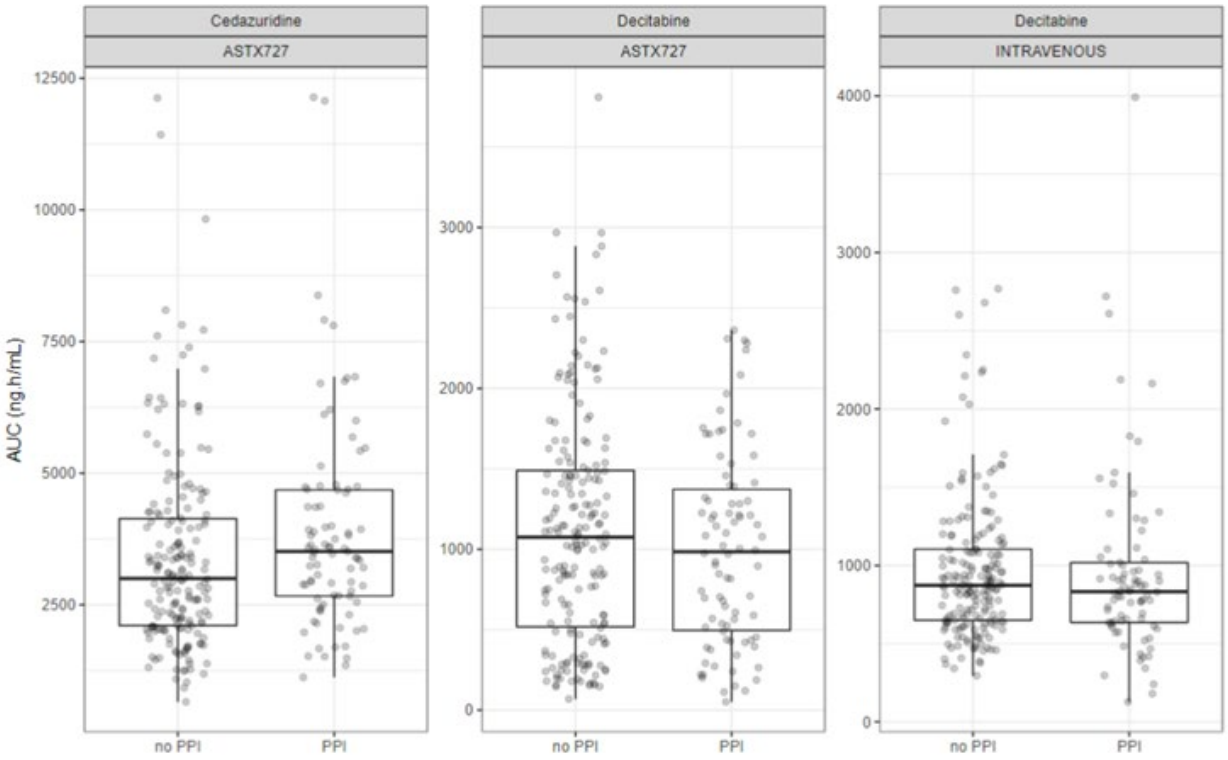
No specific study of the effect of cedazuridine on the PK of other drugs (except decitabine) has been conducted. Cedazuridine is an inhibitor of CDA and it has been demonstrated that cedazuridine significantly affects the exposure of the CDA substrate decitabine, giving up to 12-fold increase in decitabine exposure (study ASTX727-01). It would thus affect the metabolism and exposure of any coadministered drug that is metabolised via this route.

Effects of other medicinal products on the pharmacokinetics of cedazuridine (cedazuridine as victim)

No specific study of the effect of other drugs on the PK of cedazuridine has been conducted. Based on study ASTX727-01, decitabine does not affect the exposure of cedazuridine at a dose of 100 mg.

Concomitant PPI medication was assessed as a potential covariate in the PopPK model because of the possibility that such medications could affect the rate of conversion of cedazuridine into its much less effective epimer. This assessment showed that concomitant PPI medication usage did not have a significant impact on decitabine, cedazuridine, and cedazuridine-epimer parameters and subsequent exposures (Figure8), suggesting that drugs modifying gastric pH are unlikely to affect the PK of cedazuridine or decitabine after ASTX727 administration.

Figure 8: Effect of PPI on IV and oral decitabine exposures



Pharmacokinetics using human biomaterials

Decitabine

The plasma protein binding of decitabine is low and based on previous data, decitabine is not a substrate for CYP enzymes. Decitabine did not inhibit or induce CYP enzymes and did not inhibit P-gp. New in vitro-data was submitted investigating inhibition of CYP3A4, P-gp and BCRP by decitabine at concentrations relevant for intestinal inhibition (60 µM), considering that decitabine is now administered orally instead of intravenously. There was no signal of in vivo relevant inhibition of P-gp, BCRP or CYP3A4 by decitabine at concentrations relevant for intestinal inhibition (all IC50-values being > 100 µM).

Cedazuridine

Effects of cedazuridine on the pharmacokinetics of other medicinal products (cedazuridine as perpetrator)

The following cut-offs have been used for cedazuridine for assessment of interaction potential in vivo:

50´Cmax(u)[a] (µM)	25´Inlet Cmax(u)[b] (µM)	0.1´Dose/250 ml [c] (µM)
42.3	57.8	149.1

a) Input parameters were C_{max} 349 ng/ml (study ASTX727-02, MDS population), fu = 0.65, Mw = 268.21 g/mol. Based on an additional in vitro plasma protein binding study (fu=1) the cut-offs would

instead be 65 µM (50x$C_{max,u}$) and 194 µM (25xinlet $C_{max,u}$) but using these cut-offs instead would not change conclusions.

b) Input parameters F = 0.21 (study E7727-01), k_a = 0.1 min^{-1}, blood/plasma ratio 0.76

c) Dose = 100 mg

Based on in vitro data, there was no signal of in vivo relevant competitive CYP inhibition by cedazuridine. For all studied enzymes (CYP 1A, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A), less than 50% inhibition was observed at the highest studied concentration of 400 µM. This results in a Ki value of > 200 µM which is below both the systemic cut-off and the cut-off relevant for inhibition of intestinal CYP3A4. There was also no clinically relevant time-dependent CYP inhibition by cedazuridine.

A study investigating potential of cedazuridine to induce the activity of CYP enzymes did not indicate significant induction.

Cedazuridine was observed to be an inhibitor of CDA based on in vitro-data.

Based on in vitro data, there was no signal of in vivo relevant inhibition by cedazuridine on P-gp, BCRP, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, CNT1, CNT2, CNT3, ENT1 or ENT2.

Based on in vitro-data, the major metabolite cedazuridine-epimer does not cause clinically relevant CYP inhibition (cut-off below 50 µM and for all studied enzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4) the IC50 values were above 100 µM).

Effects of other medicinal products on the pharmacokinetics of cedazuridine (cedazuridine as victim)

In in vitro studies, cedazuridine was not metabolised by human liver S9 fractions or liver cytosols. These results indicate that cedazuridine is not subject to hepatic metabolism including metabolism by CYP enzymes.

Cedazuridine is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 or MATE2-K. It is however a substrate of the transporters CNT1, CNT3, and ENT2.

2.6.2.2. Pharmacodynamics

Three clinical studies in subjects with AML (Study ASTX727-02 EU AML) and MDS/CMML (Studies ASTX727-01, ASTX727-02 NA MDS/CMML, and ASTX727-04) have contributed to the characterisation of the clinical pharmacology of cedazuridine with decitabine in this submission, and 2 clinical studies in healthy subjects (Studies E7727-01 and E7727-02) have contributed to the characterisation of cedazuridine.

Mechanism of action

Decitabine is a nucleoside metabolic inhibitor that 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. Decitabine- induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA.

Decitabine is a substrate of cytidine deaminase (CDA) which has been shown to have high activity levels in the gastrointestinal (GI) tract and liver of humans. CDA deaminates decitabine and other therapeutic synthetic cytidine analogues to generate pharmacologically inactive metabolites. Therefore,

oral administration of decitabine at relatively lower dose levels is unable to provide pharmacologically relevant systemic exposure levels.

Cedazuridine is a new chemical entity (NCE) and a potent CDA inhibitor. Oral administration of cedazuridine with decitabine increases the systemic exposure of decitabine via inhibition of first pass metabolism of decitabine in the gut and liver by CDA, thereby enabling the pharmacologic effect of decitabine.

Primary and Secondary pharmacology

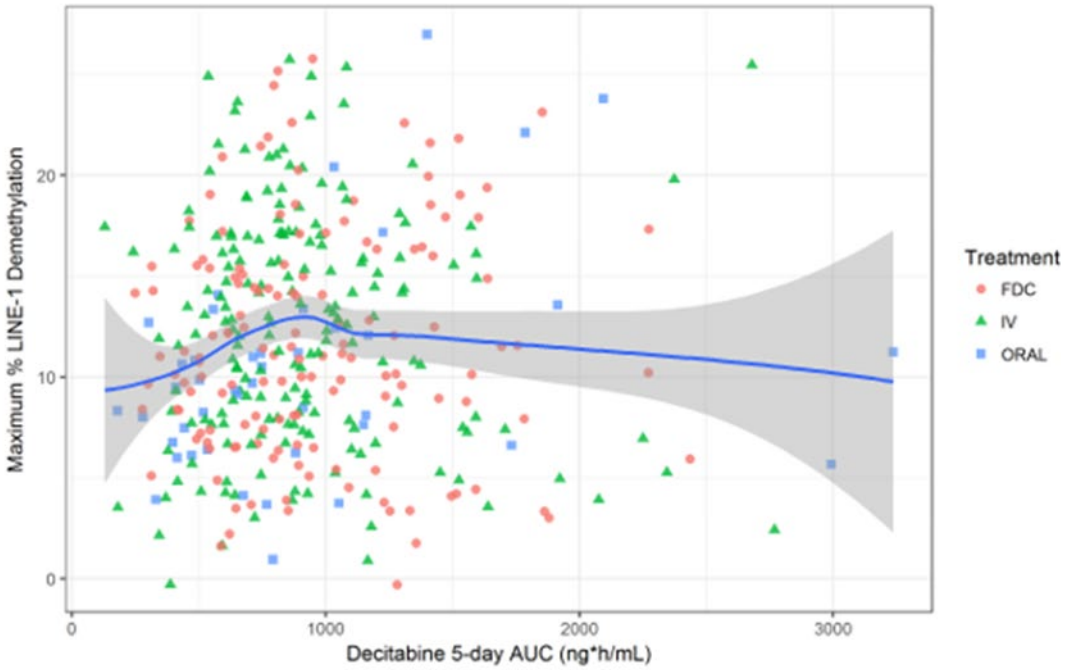
Global DNA demethylation is understood as a marker of the primary pharmacodynamic activity of decitabine. In the ASTX727 studies, this was determined by detection of the percent change from baseline of long interspersed nucleotide elements-1 (LINE-1) demethylation in blood.

Pharmacodynamic data from the 42 subjects in the Dose Escalation Part of Study ASTX727 01 with available LINE-1 methylation measurements for Cycle 1showed that .

LINE-1 demethylation increased with escalating doses of cedazuridine from 40 to 100 mg and then with escalating doses of decitabine from 20 to 40 mg. Maximal demethylation of approximately 12% is consistent with that expected for a cycle of IV decitabine 20 mg/m^2. Cycle 2 reductions were similar but attenuated, as Cycle 2 baseline LINE-1 methylation was lower than the Cycle 1 baseline as a result of incomplete recovery of methylation at the end of Cycle 1.

A PK/PD analysis of the relationship between maximum LINE-1 demethylation and 5-Day decitabine AUC found that there appeared to be a saturable positive PK/PD relationship, with little further increase in response with higher exposures (Figure 9).

Figure 9. Relationship Between Maximum LINE-1 Demethylation and 5-Day Decitabine AUC by Treatment (Studies ASTX727-01 and ASTX727-02 NA MDS/CMML)



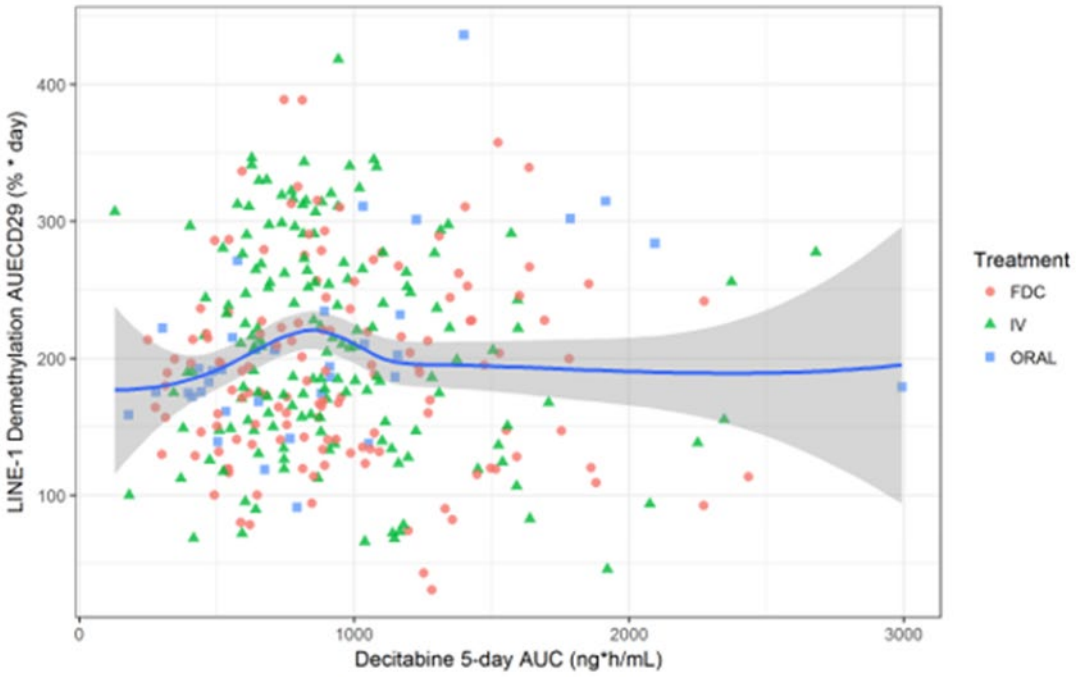
AUC=area under the concentration-time curve; CI=confidence interval; FDC=fixed-dose combination (oral); IV=intravenous(ly); LINE-1=long interspersed nucleotide element-1; LOESS=locally estimated scatterplot; ORAL=oral capsule.

Note: The blue line represents the LOESS smooth regression line for maximum LINE-1 demethylation across decitabine 5-Day AUC and the grey-shaded area is the 95% CI; circles, triangles, and squares are the observed data.

Similarly, the relationship between LINE-1 demethylation AUECD29 and decitabine 5-Day AUC was generally flat and appeared to be treatment-independent based on overlapping data points from the three treatments (Figure 10).

This suggests that a maximal drug effect was achieved over the range of decitabine exposures in the Phase 2 parts of Study ASTX727-01 and in Study ASTX727-02 NA MDS/CMML.

Figure 30. Relationship Between LINE-1 Demethylation AUECD29 and 5-Day Decitabine AUC by Treatment (Studies ASTX727-01 and ASTX727-02 NA MDS/CMML)



AUC=area under the concentration-time curve; AUECD29=area under the effect curve for LINE-1 demethylation from Day 1 to Day 29; CI=confidence interval; CMML=chronic myelomonocytic leukaemia FDC=fixed-dose combination (oral); IV=intravenous(ly); LINE-1=long interspersed nucleotide element-1; MDS=myelodysplastic syndrome; ORAL=oral capsule.

Note: The blue line represents the LOESS smooth regression line for maximum LINE-1 demethylation across decitabine 5-Day AUC and the grey-shaded area is the 95% CI; circles, triangles, and squares are the observed data.

Comparison of LINE-1 Demethylation Between ASTX727 and IV Decitabine

In the pivotal Study ASTX727-02 EU in AML patients and in the supportive study ASTX727-02 NA in MDS/CMML patients, subjects were randomly assigned in a 1:1 ratio to a treatment sequence for the first 2 cycles (Sequence A: ASTX727 in Cycle 1 and IV decitabine Cycle 2 or Sequence B: IV decitabine in Cycle 1 and ASTX727 in Cycle 2).

In these studies, the final, recommended doses of ASTX727 and IV decitabine, respectively, were administered.

Pharmacodynamic variables were based on assessments of %LINE-1 demethylation in blood.

Due to the crossover design of the study and carryover effects of demethylation from Cycle 1 to Cycle 2, the LINE-1 methylation results were presented by treatment (ASTX727 and IV decitabine) in each cycle separately.

Results: Study ASTX727-02 EU (AML)

In the treatment comparisons in Cycle 1 and Cycle 2, maximum %LINE-1 demethylation between decitabine IV and ASTX727 was numerically not different, with a 95% CI that included 0, consistent with both treatments producing similar pharmacodynamic effects (*Table 23*).

Table 23. Comparison of LINE-1 Demethylation Between ASTX727 and Intravenous Decitabine (Study ASTX727-02 EU; AML)

Cycle	n	Treatment	Mean Baseline	Maximum %LINE-1 Demethylation		Difference Between ASTX727 and IV Decitabine	
				LSM	95% CI	Estimate	95% CI
1	33	ASTX727	75.884	9.357	(7.288, 11.426)	1.113	(-1.698, 3.925)
	39	IV Decitabine	76.502	8.243	(6.340, 10.147)		
2	34	ASTX727	74.764	8.037	(6.258, 9.816)	-0.116	(-2.738, 2.507)
	29	IV Decitabine	74.640	8.153	(6.226, 10.079)		

ANOVA=analysis of variance; CI=confidence interval; CSR=clinical study report; IV=intravenous(ly); LINE-1=long interspersed nucleotide element-1; LSM=least squares mean; n=number of subjects.

Notes: Analysis is based on ANOVA model with treatment, period, and sequence as fixed effects, and subject nested in sequence as a random effect (ratio is oral/IV).

Results: Study ASTX727-02 NA (MDS/CMML)

Also in this study, in the treatment comparisons in Cycle 1 and Cycle 2, the difference in maximum %LINE-1 DNA demethylation between IV decitabine and ASTX727 was <1% in absolute value, with a narrow CI that included 0, consistent with similar biological and pharmacodynamic effects between the two treatments (*Table 24*).

Table 24. Comparison of LINE-1 Demethylation Between ASTX727 and Intravenous Decitabine (Study ASTX727-02 NA; MDS/CMML)

Cycle	n	Treatment	Mean Baseline	Maximum %LINE-1 Demethylation		Difference Between ASTX727 and IV Decitabine	
				LSM	95% CI	Estimate	95% CI
1	62	ASTX727	74.858	13.289	(11.798, 14.780)	-0.730	(-2.838, 1.378)
	62	IV Decitabine	75.523	14.019	(12.528, 15.510)		
2	63	ASTX727	73.249	11.151	(9.685, 12.616)	-0.818	(-2.890, 1.255)
	63	IV Decitabine	73.624	11.968	(10.503, 13.434)		

ANOVA=analysis of variance; CI=confidence interval; CSR=clinical study report; IV=intravenous(ly); LINE-1=long interspersed nucleotide element-1; LSM=least squares mean; n=number of subjects.

Notes: Analysis is based on ANOVA model with treatment, period, and sequence as fixed effects, and subject nested in sequence as a random effect (ratio is oral/IV).

Cytidine Plasma Concentrations

An exploratory objective of the Phase 1 Study ASTX727-01 included the assessment of change from baseline in plasma cytidine levels after treatment.

Plasma cytidine levels were evaluated after dosing with oral decitabine alone, IV decitabine, and oral ASTX727 (as decitabine and cedazuridine). The change in circulating plasma cytidine from baseline was calculated.

As expected, administration of decitabine alone (Day −3 [oral] or Day 1 [IV]) did not appear to affect plasma cytidine levels, as decitabine is not known to inhibit CDA. In contrast, on days when cedazuridine was administered at dose levels of 40, 60, or 100 mg, a consistent change manifested as

an increase in plasma cytidine levels. This appeared to be modest (approximately 2-fold) and transient, as evidenced by the trend of recovery towards baseline and full recovery as seen at predose on Cycle 2 Day −3.

Relationship between plasma concentration and effect

Efficacy and safety of decitabine/cedazuridine FDC were to be established based on a PK bridge to previous data for decitabine when administered IV. The Phase 2 and 3 studies (AML and MDS/CMML patients) were not designed to enable a proper assessment of exposure-response. A concentration-QTc analysis of data from the thorough QTc study in healthy volunteers was also conducted (see Section 3.3.7.6.).

2.6.3. Discussion on clinical pharmacology

2.6.3.1. Pharmacokinetics

The most important role of pharmacokinetics in this application is bridging from Inaqovi (ASTX727) to previous efficacy and safety data for IV decitabine based on equivalent decitabine exposure (total AUC over the 5-day cycle). This approach is acceptable, and the PK bridge has been adequately established as further discussed below.

The therapeutic window has not been discussed by the Applicant. For decitabine the aim is to obtain similar exposure as with the approved IV dose and thus similar efficacy and safety. It is noted that the food effect (40% decrease in decitabine AUC with a high-fat meal compared to fasted state) is assumed to be considered clinically relevant hence the product is recommended to be taken in the fasted state (as in the pivotal study comparing oral to IV treatment). Increased cedazuridine exposure might lead to both safety issues for cedazuridine as such (although available data do not indicate a large potential for side effects) and potentially safety issues due to increased decitabine exposure, while decreased cedazuridine exposure would lead to decreased decitabine exposure and thus risk of decreased efficacy. However, no dosage adjustments are currently proposed due to interactions or in special populations, and thus it is considered less critical to define the therapeutic window.

Methods

Bioanalytical methods

The bioanalytical methods used were adequately validated.

Population PK

The popPK analysis is mainly used to support claims regarding the impact of different covariates on decitabine and cedazuridine exposures. The final semi-mechanistic population PK models (IV decitabine, oral decitabine and oral cedazuridine) were combined to describe the PK of decitabine and cedazuridine given alone and in combination, and for the IV and oral formulation of decitabine. The final model parameters were estimated including information from both the AML and MDS population. The high number of BQL samples were handled using the M6 method, which in this application was considered sufficient. The selection of covariates for inclusion in the models is not agreed as many were correlated precluding the possibility to investigate the impact of weight on oral exposure of decitabine. Simulations with a model that includes correlated covariates, where only one covariate is altered, without keeping the correlation to the other covariates intact, can be biased. Due to the limitations of the current models, they are not considered suitable for description of special populations, and conclusions on specific matters related to parameters should be made with caution.

Absorption

The phase III data presented on PK parameters in the SmPC and the clinical pharmacology summary are generated in the MDS/CMML population and not AML. Since the pharmacokinetics of ASTX727 is not depending on diagnosis, this is acceptable. In addition, the MDS/CMML study had a higher number of subjects included compared to the AML study (138 subjects vs. 89 subjects).

Based on available data (including mean fraction absorbed reported as 47.5% for cedazuridine in study ASTX727-01), cedazuridine does not appear to have complete absorption while decitabine possibly is completely absorbed (considering the increase in exposure when first-pass effect is reduced by cedazuridine). However, as the applicant makes no claim regarding BCS class, no firm conclusion will be drawn.

Since the oral bioavailability of decitabine (dose-normalised AUC-ratio compared to IV treatment) was larger than 100% when given with cedazuridine, this indicates that co-administration of cedazuridine does not only affect the first-pass metabolism but also the elimination of decitabine. For example, in ASTX72-01-B (dose confirmation stage) the mean decitabine t1/2 following concomitant oral administration of decitabine and cedazuridine was slightly higher compared with IV (1.08 h), with t1/2 values of 1.14 h, 1.30 and 1.40 h on Day 1, Day 2 and Day 5, respectively. The slightly longer half-life of decitabine indicated that the elimination may be slower in combination with cedazuridine, although the most prominent effect on bioavailability is due to decreased first pass metabolism. The trend with slightly longer half-life at day 2 and 5 for oral administration was also seen in the phase III studies.

It is not entirely clear if increased cedazuridine concentrations (e.g. in special populations or due to interactions) would lead to additional increases in decitabine exposure, as higher cedazuridine doses than the clinical dose of 100 mg has not been studied. Large additional effects on first-pass metabolism are not expected considering the results above.

The CHMP considered in the previous advice that study ASTX727-02 with AUC equivalence to decitabine IV as the primary endpoint and clinical efficacy/safety and biological activity as secondary endpoints, should provide sufficient information to support bridging to the clinical data that supported the approval of IV-decitabine. Bioequivalence for 5-Day AUC_{0-24} between oral and IV decitabine could be concluded for both the AML (EU) and the MDS/CMML (NA) population as well as for pooled data from the two studies. From a PK-perspective, taking in account that this was a cross-over study design, the type of haematological malignance when comparing IV to oral exposure is not crucial. However, for supportive efficacy and safety comparisons it was previously concluded that comparisons in AML patients were needed and the Applicant therefore presents the data from the AML population as pivotal and the data from the MDS/CMML population as supportive. The exposure in both populations was found to be similar.

As expected, there are differences in the decitabine plasma concentration curves between IV and oral administration. For example, differences in extent of exposure (AUC) between oral and IV administration is seen on day 1 which is likely due to less cedazuridine present systemically. This difference is not seen on subsequent days when steady state is expected for cedazuridine. C_{max} is also consistently lower for ASTX727 compared to IV decitabine; on Day 1 the difference was 54% (AML) and 55% (MDS/CMML) and on Day 5 28% (AML) and 22%(MDS/CMML).–

In order to support that the lower C_{max} (and lower AUC on day 1) was not clinically relevant, the applicant has submitted supportive PD data. The PD endpoint, i.e., the maximum percent LINE-1 demethylation, was not significantly different between ASTX727 and IV decitabine in the Phase 3 Study ASTX727-02 in AML or in MDS/CMML patients. This supports that differences in PK profile between ASTX727 and IV decitabine are not expected to affect the primary pharmacodynamic effect.

Based on the results of the food effect study (40% decrease in decitabine AUC with a high-fat meal), it is considered acceptable to recommend intake in the fasted state (no food intake 2 hours before or after administration of Inaqovi) as this was in line with the recommendation in the pivotal study, although this recommendation is not very convenient for the patients. The applicant has made a commitment to submit the results of the additional food effect study (ASTX727-06 food effect substudy) when available and to update the product information as applicable.

Distribution

The concentration range used in the plasma protein binding study was adequate for decitabine, but for cedazuridine the concentrations used were higher than the clinical concentrations. Although it would have been better to investigate a lower concentration range, it is not considered likely that this would affect the conclusion that cedazuridine has low plasma protein binding. Protein-binding of cedazuridine was also investigated in an additional in vitro-experiment, together with cedazuridine-epimer, where the protein binding was found to be even lower (0%). The applicant has not discussed the discrepancy in results, but has kept the previous protein binding value in the SmPC. In both studies, it is however obvious that the protein binding is low and this can be accepted.

Elimination

For decitabine, the major route of elimination is metabolism (followed by renal excretion of metabolites).

För cedazuridine, the two major routes of elimination are renal excretion of unchanged drug and conversion to epimer (followed by renal excretion). The elimination pathways of cedazuridine are considered sufficiently well characterised. Available data (human mass balance study demonstrating that more cedazuridine epimer is formed following oral than IV administration together with quality data) indicate that the conversion from cedazuridine to its epimer mainly occurs due to physiochemical degradation at low pH rather than by enzyme involvement.

After a single dose of 100 mg non-labelled cedazuridine, the total amount of cedazuridine and cedazuridine-epimer extracted in urine was 17.1 mg (17.1 %) and 17.5 mg (17.5 %) respectively of the total dose. Following a radiolabelled oral dose of cedazuridine, on average 45.7 % and 51.2% was recovered in urine and faeces, respectively. In urine, 20.7% of the total radiolabelled dose was extracted as cedazuridine and 13.8% as cedazuridine-epimer. The amount of renally unchanged cedazuridine reported in the SmPC (17.1%) refers to data with unlabelled substance, this can be accepted. Results based on labelled and unlabelled substance is similar. In faeces, the recovery of the method was reported to be low but at least 14.8 % of the total doses was excreted unchanged and at least 11.6% as cedazuridine-epimer. In total, 61% of the totally administered dose has been identified (as cedazuridine and cedazuridine-epimer), corresponding to 63% of the extracted dose. This is less than the 80% recommended in the Guideline on interactions, but no concern is raised, considering that over 20% of the dose was in non-extractable material in faeces.

The renal clearance (CLr) of cedazuridine was 4.46 L/h (ranging between 3.01 and 5.47 L/h) and filtration (fu*GFR) is expected to be around 4.68 L/h, thus active renal secretion does not seem to be included in the renal elimination of cedazuridine.

Dose proportionality and time dependency

The accumulation ratios for decitabine and cedazuridine at steady state were typically 1.8 times and 1.1 times the Day 1 plasma concentrations, respectively, suggesting a slight accumulation. Time dependency was not discussed by the Applicant. However, based on the conclusion that neither decitabine nor cedazuridine is metabolised by cytochrome P450 enzymes, autoinduction is not

expected, and there is thus no clear mechanism for a time dependency. It can be concluded that there is little or no time dependency for Inaqovi.

Special populations

Due to the limitations of the current pop-PK model, it is not considered suitable for description of special populations, and conclusions on specific matters related to parameters should be made with caution.

The graphical analysis of observed data indicates that there is a trend that cedazuridine exposure slightly increases with decreasing CrCL, as expected for a substance for which renal elimination as unchanged drug is a major elimination pathway. However, the graphical analysis is biased as weight and CrCL is correlated and thus it is not possible to draw any firm conclusions. There is also a trend of slight increase in decitabine exposure with decreasing CrCL, in particular for oral treatment. The effect on oral decitabine exposure is likely mainly due to the increase in cedazuridine exposure (due to inhibition of decitabine metabolism caused by increased cedazuridine exposure) as renal excretion of unchanged decitabine is low. Patients with mild renal impairment constituted a significant part of the population on which the overall safety assessment is based and safety data in this population did not warrant any specific recommendations. As it was difficult to draw conclusions regarding possible increase of haematological adverse events in patients with moderate RI, it is agreed to recommend additional monitoring of these patients. There is an ongoing study investigating the PK, safety, and tolerability of oral decitabine and cedazuridine in cancer patients with severe renal impairment compared to patients with normal renal function. The Applicant has made a commitment to submit the results of study ASTX727-17 (RI study) when available. While awaiting these data, it is considered adequate to recommend caution in patients with severe RI.

Based on the mass balance study, renal impairment can be expected to increase the exposure of cedazuridine (as renal elimination of parent drug is major elimination pathway) and potentially also the exposure of decitabine subsequently to increased cedazuridine exposure. However, decitabine itself is mainly metabolised and not excreted renally as unchanged drug.

It is difficult to draw any pharmacokinetic conclusions regarding hepatic impairment based on data obtained with Inaqovi as so few patients in the studies had liver impairment. Large effects of hepatic impairment on decitabine or cedazuridine exposure are not expected but as decitabine affects markers of liver function this may warrant additional caution in these patients. There is an ongoing study investigating the PK, safety, and tolerability of oral decitabine and cedazuridine in cancer patients with moderate and severe hepatic impairment. The Applicant has made a commitment to submit the results of study ASTX727-18 (HI study) when available. Based on available safety data, no dose adjustment or special handling is needed in patients defined by the applicant as having mild hepatic impairment. It is however noted that the Applicant has defined liver function based only on total bilirubin, which is not in accordance with the NCI classification system (which uses total bilirubin and aspartate aminotransferase). Thus, it is not clear that the subjects identified as having "mild HI" can really be considered to have this degree of hepatic impairment. A general recommendation on caution in patients with all degrees of hepatic impairment is adequate.
Large effects of hepatic impairment on decitabine or cedazuridine exposure are not expected as cedazuridine is not hepatically metabolised and as decitabine is metabolised by cytidine deaminase present in several tissues (liver, kidney, intestinal epithelium and blood).

Based on graphical comparison of observed data there is a trend of increased exposure of oral decitabine in women compared to men. As no such trend is observed for IV decitabine (for which the dose is adjusted based on BSA), the trend observed for oral decitabine is likely due to differences in weight rather than due to sex. It is agreed that sex did not have a clinically meaningful effect on the

pharmacokinetics of decitabine or cedazuridine after dosing with Inaqovi and that no dose adjustment is required.

Inaqovi is given as a flat dose (35 mg decitabine) while IV-decitabine is given as a body-surface adjusted dose (20 mg/m2 body surface area). There is a trend of decreased decitabine 5-day AUC_{0-24} with increasing weight or BSA with oral decitabine treatment, but this is not considered to be clinically relevant.

The trend of increased cedazuridine exposure with increasing age may be caused by decreased renal function. The trend of increased decitabine exposure with increasing age, in particular for oral treatment, could be subsequent to the increase in cedazuridine exposure.

The safety and efficacy of Inaqovi in the paediatric population (aged less than 18 years) have not been established. No data are available.

Interactions

The main potential for interactions with cedazuridine is due to its inhibition of CDA. It is agreed that concomitant use with drugs metabolised by CDA should be avoided, as proposed by the Applicant.

Regarding cedazuridine as perpetrator of drug interactions except for CDA inhibition, available in vitro data do not indicate relevant interactions via CYP enzymes (direct or time dependent inhibition or induction) or transporters (inhibition).

There is one major metabolite, cedazuridine-epimer, that has been investigated for potential to inhibit CYP enzymes. It can be concluded that cedazuridine-epimer does not cause clinically relevant CYP inhibition.

Regarding effects of PPI, the Applicant proposes that increased stomach pH might lead to a lower degree of conversion of cedazuridine to its less active epimer and thus an increased effect, possibly leading to increased decitabine exposure. There appears to be some effect on cedazuridine exposure when combined with PPI, however, it does not appear to have a subsequent impact on decitabine exposure. The slightly higher exposure of cedazuridine is not expected to have clinically significant impact.

Cedazuridine is not subject to hepatic metabolism including metabolism by CYP enzymes and is also not a substrate of the most relevant transporter enzymes (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 or MATE2-K). Thus, the potential for cedazuridine as victim of drug-drug interactions is considered low. Cedazuridine was however observed to be a substrate of the transporters CNT1, CNT3, and ENT2. As it is not mandatory to study if new medicinal products are substrates (or inhibitors) of these transporters, the clinical relevance of this finding is unknown. The Applicant does not propose to include this information in the SmPC, which is agreed.

For decitabine, the potential for systemic inhibition/induction will be similar as for IV-decitabine as the exposure is similar (equivalent AUC, lower Cmax). However, as decitabine is now administered orally instead of intravenously, there is also a risk of intestinal interactions. The Applicant submitted additional in vitro data investigating the inhibitory effect of decitabine of CYP3A4, P-gp and BCRP at sufficiently high concentrations in order to exclude intestinal inhibition (i.e. 60 µM), considering that decitabine is now given orally instead of intravenously, and there was no signal of in vivo relevant inhibition of P-gp, BCRP or CYP3A4.

2.6.3.2. Pharmacodynamics

A pharmacokinetic-pharmacodynamic analysis was performed in order to quantify the relationship between decitabine exposures (5 –day total cycle AUC) and LINE-1 demethylation (maximum LINE-1 demethylation and AUEC for LINE-1 demethylation) in subjects with MDS and CMML. The analysis included 79 subjects from ASTX727-01 study (Dose Confirmation and FDC parts) and 133 from ASTX727-02 study.

Maximum LINE-1 demethylation and decitabine exposure showed a positive relationship up to a value of 1000 ng*h/ml, where the system appeared to be saturated and there is no further increase in demethylation with increasing exposure.

Accordingly, over the range of individual AUCs achieved at the recommended dose of 20 mg/m^2 IV decitabine or 35 mg/100 mg oral decitabine/cedazuridine, there was no relationship between individual exposure and PD effect at the recommended dose. The Applicant suggests that this may imply that at the recommended clinical dose of decitabine, a plateau has been reached in terms of the pharmacodynamic effect.

Importantly, a similar degree of %LINE-1 demethylation over a 5-day cycle was shown after administration of the final recommended dose of ASTX727 and after administration of 20 mg/m^2 IV decitabine.

2.6.4. Conclusions on clinical pharmacology

This application is based on a PK bridge, to demonstrate that the known efficacy and safety data for IV decitabine can be extrapolated to ASTX727. Bioequivalence for 5-Day AUC_{0-24} between oral and IV decitabine was shown for both the AML (EU) and the MDS/CMML (NA) population as well as for pooled data from the two studies. AUC_{0-24} for day 1 is lower for oral compared to IV treatment and Cmax is also lower following oral treatment.

The PD endpoint, i.e., the maximum percent LINE-1 demethylation, was numerically not different, given similar AUC for decitabine, between ASTX727 and IV decitabine in the Phase 3 Study ASTX727-02 in AML or in MDS/CMML patients.

This supports that differences in the PK profile (e.g. Cmax) between ASTX727 and IV decitabine are not expected to affect the primary pharmacodynamic effect.

The efficacy of ASTX727 at the proposed dose (35 mg decitabine in combination with 100 mg cedazuridine per day for 5 consecutive treatment days per 28-day cycle) can thus be concluded to be similar to that of IV decitabine at the approved dose (20 mg/m^2 per day for 5 consecutive days per 28-day cycle), in the treatment of adult patients with AML.

Inaqovi is considered approvable from a clinical pharmacology point of view.

The CHMP considers the following measures necessary to address post authorisation the issues related to pharmacology: The Applicant has made a commitment to submit the results of study ASTX727-17 (RI study), study ASTX727-18 (HI study) and study ASTX727-06 (food effect substudy) when available.

2.6.5. Clinical efficacy

The primary data supporting efficacy for the AML indication are from the phase 3 study: ASTX727-02 EU.

During the drug development the efficacy of ASTX727 was initially evaluated in subjects with MDS or CMML in a Phase 1-2 study (ASTX727 01) and in a Phase 3 study (ASTX727-02 NA) which are now considered supportive for the application.

2.6.5.1. Dose response study

Study ASTX727-01 included MDS and CMML subjects who received prior HMA treatment.

In Phase 1 (Dose Escalation Stage; ASTX727-01-A), various doses of cedazuridine and decitabine were given as separate capsules for dose titration. Systemic exposures after oral decitabine alone or with cedazuridine were compared in the same subjects with IV decitabine (20 mg/m^2) to determine the doses of both drugs that closely emulated the IV decitabine exposure. See clinical pharmacology section of the report.

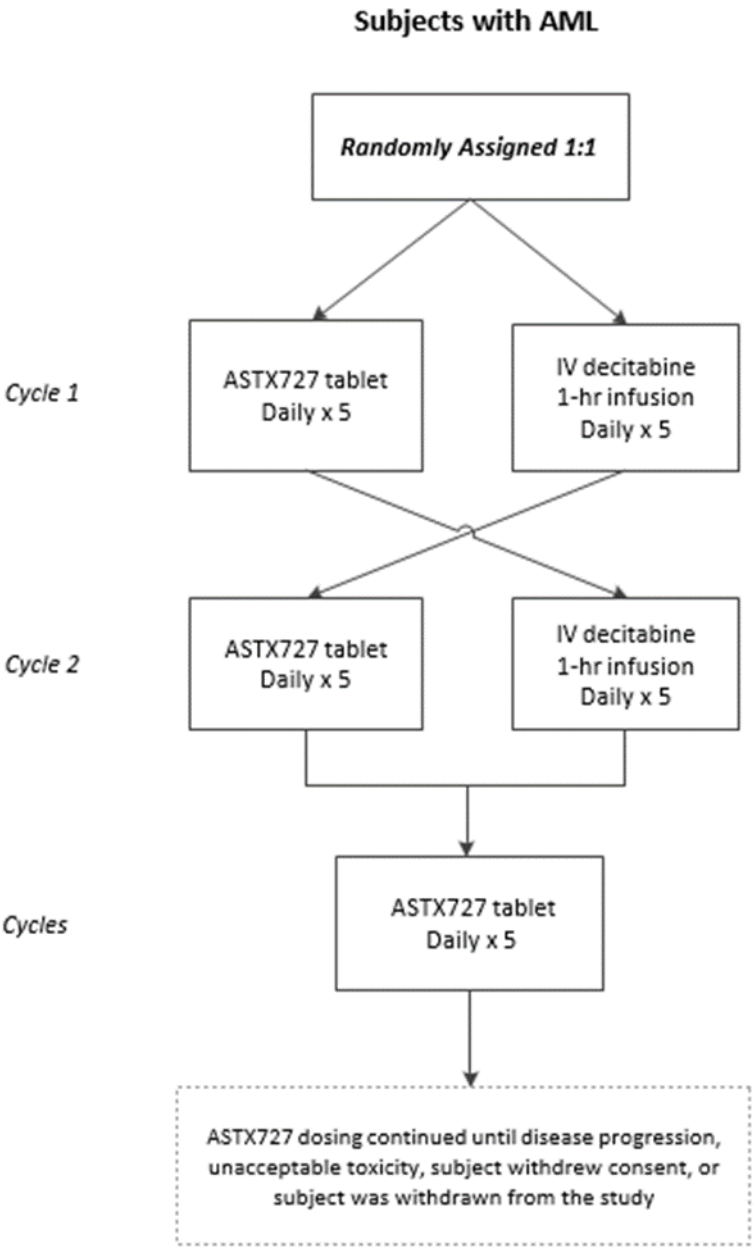
Results from Phase 1 of study ASTX727-01 showed that 100 mg cedazuridine with decitabine doses of 30 mg and 40 mg achieved 5-day cumulative AUC_{0-t} of 81% and 128%, respectively, of that of IV decitabine. In Phase 2 (ASTX727-01-B), the combination of decitabine and cedazuridine at the final recommended doses of 35 mg and 100 mg, respectively, was investigated. See clinical pharmacology section of the report.

2.6.5.2. Main study

Study ASTX727-02 EU

This was a Phase 3 multicentre, randomised, open-label, 2-period, 2-sequence crossover study of ASTX727 versus IV decitabine (study design is depicted in Figure 11). Adult subjects with AML with de novo or secondary AML as defined by World Health Organisation (WHO) criteria, who were not candidates for standard induction chemotherapy and who were candidates to receive IV decitabine were randomised in a 1:1 ratio to receive the ASTX727 FDC tablet Daily×5 in Cycle 1, followed by IV decitabine 20 mg/m2 Daily×5 in Cycle 2 (Sequence A), or the converse order (Sequence B).

Figure 11. Study ASTX727-02 EU design



Methods

Study Participants

Key Efficacy Inclusion Criteria

1. Men or women ≥18 years who are candidates to receive IV decitabine according to FDA or EMA approved indications:

   a, In Europe: Subjects with de novo or secondary AML, as defined by WHO criteria, who are not candidates for standard induction chemotherapy.

b, In Canada: Subjects with de novo or secondary AML, as defined by WHO criteria, who in the judgment of their physician are not deemed candidates for standard induction chemotherapy for AML and for whom there is no available approved standard therapy in Canada.

2. ECOG performance status of 0 to 1.

3. Life expectancy of at least 3 months

Key Efficacy Exclusion Criteria

1. 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.

2. Hospitalisation for more than 2 days for documented febrile neutropenia, pneumonia, sepsis, or systemic infection in the 30 days before screening.

3. Treatment with any investigational drug or therapy within 2 weeks of study treatment, or 5 half-lives, whichever is longer, before the first dose of study treatment, or ongoing clinically significant adverse events (AEs) from previous treatment.

4. Cytotoxic chemotherapy or prior azacitidine or decitabine within 4 weeks of first dose of study treatment.

5. Concurrent MDS therapies, including lenalidomide, erythropoietin, cyclosporine/tacrolimus, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, etc. (Prior treatment with these agents is permitted, provided that completion is at least 1 week before the first dose of study treatment.)

6. Rapidly progressive or highly proliferative disease (total white blood cell 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.

Thirty centres were initiated to conduct this study, of which 27 centres/26 investigators in 9 countries enrolled subjects (2 centres in Canada, 1 in Austria, 3 in Czech Republic, 2 in France, 7 in Germany, 2 in Hungary, 4 in Italy, 8 in Spain, and 1 in the United Kingdom).

Treatments

Subjects received the ASTX727 FDC tablet by mouth Daily×5 in Cycle 1, followed by a 1-hour infusion of IV decitabine 20 mg/m^2 Daily×5 in Cycle 2, or the converse order. In Cycles ≥3, subjects received the ASTX727 tablet Daily×5 in 28-day cycles until disease progression, unacceptable toxicity, or the subject decided to discontinue treatment or was withdrawn from the study.

Table 25. Dosing Schedule by Day and Cycle

Cycle (28 Days)	1						2						≥3					
Cycle Day	1	2	3	4	5	6-28	1	2	3	4	5	6-28	1	2	3	4	5	6-28
If randomized to ASTX727 in Cycle 1, then:																		
ASTX727 tablet	×	×	×	×	×								×	×	×	×	×	
IV decitabine (20 mg/m^2)							×	×	×	×	×							
If randomized to IV decitabine in Cycle 1, then:																		
ASTX727 tablet							×	×	×	×	×		×	×	×	×	×	
IV decitabine (20 mg/m^2)	×	×	×	×	×													

NOTE: On days of ASTX727 administration, subjects should take the FDC tablet at the same time each day

±1 hour (8 AM during the first 2 cycles).

Objectives

Study Objectives:

Primary Objective

- To establish decitabine AUC equivalence of 5-day dosing between ASTX727 and IV decitabine.

Secondary Objectives

To assess the following:

- Long-term safety and efficacy (response rate) of ASTX727.
- Long interspersed nucleotide elements-1 (*LINE-1*) demethylation.
- Additional PK parameters.

Outcomes/endpoints

Study Endpoints:

Primary Endpoint

Comparison between ASTX727 and IV decitabine:

- Total 5-day AUC exposures of decitabine after treatment with ASTX727 versus IV decitabine.

Secondary Endpoints

- Safety as assessed by AEs, concomitant medications, physical examination, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs, ECOG performance status, and electrocardiogram (ECG).
- Maximum %*LINE-1* demethylation.
- Additional secondary PK parameters.
- Clinical response (complete response [CR], CR with incomplete platelet recovery [CRp], and CR with incomplete blood count recovery [CRi] based on modified International Working Group [IWG] 2003 AML response criteria [Cheson et al 2003] and as in the DACO-016 study [ie, CRp as a subset of CRi] [Kantarjian et al 2012]). In addition, CR with partial hematologic recovery (CRh) will also be assessed. CRh will be reported as in Kantarjian et al 2017 and as used in DiNardo et al 2020.
- Time to first response, time to best response, and time to CR.
- Duration of CR and duration of combined CR and CRh, defined respectively as the time interval from the first CR to time of relapse and the time interval from the first CR or CRh to time of relapse.
- Red blood cell (RBC) or platelet transfusion independence (TI).
- Overall survival (OS), defined as the number of days from the date of randomization to the date of death from any cause.
- Survival rates at 6 months, 1 year, and 2 years.
- Event-free survival (EFS), defined as the number of days from the date of randomization to the date of treatment failure or death from any cause, whichever occurs first.
- Progression-free survival (PFS), defined as the number of days from the date of randomization to the date disease progression or death from any cause, whichever occurs first.

Clinical response was adjudicated by Astex medical monitors based on programmed data listings according to the Astex AML Response Assessment Criteria. The evaluation of response was based on Modified IWG 2003 AML Response Criteria (Cheson et al 2003) and included CRp according to Kantarjian et al 2012. Subjects who did not have a valid post-treatment efficacy assessment (ie, no post-treatment bone marrow [BM])/peripheral blood [PB] sample or the quality of BM/PB sample was not adequate for an assessment of efficacy) were classified as not evaluable (NE) for response classifications. Subjects who could not be classified into a response category (CR, CRi, CRp, or partial response [PR]) or into the NE category were classified as non-responders (NR). Progressive disease and stable disease were based on criteria from the European LeukemiaNet (Döhner et al 2017), and CRh was defined as per Kantarjian et al 2017.

Sample size

The primary study objective was to establish decitabine AUC equivalence of 5-day dosing between ASTX727 and IV decitabine.

In an equivalence test of mean using two one-sided tests on data from a two-by-two crossover design, a total sample size of ~70 evaluable subjects achieve 90% power at a 5% significance level assuming a true ratio of the means of 1.0 and a coefficient of variation on the original, unlogged scale of 0.41, and given the equivalence limits of the mean ratio are 0.80 and 1.25.

Accounting for that approximately 20% of subjects may not be evaluable, approximately 85 subjects were to be randomised.

The estimated intra-subject CV from the analysis of 5-day AUC in study ASTX727-02 with MDS and CMML subjects was approximately 0.32. A conservative intra-subject CV value of 0.41 was used for AML sample size justification.

Randomisation and blinding (masking)

The study was open label. Eligible subjects were randomly assigned to Cycle 1 study treatment in a ratio of 1:1 to receive ASTX727 or IV decitabine. Subjects crossed over to the other therapy in Cycle 2. Treatment assignment was determined through a computer-generated randomisation schedule and accessed through an interactive voice response system.

Statistical methods

The submitted statistical analysis plan (SAP version 2.0 dated 15 October 2021) was based on the ASTX727-02 protocol amendment 2.6 Europe (dated 27 January 2021) and describes analysis of AML subjects included in the ASTX727-02 study (ASTX727-02 SAP [AML]).

The analysis for submission purpose was planned to be performed after all subjects had completed 6 months of follow-up or permanently discontinued treatment prior to 6 months of follow up from their first treatment dose. This analysis was to include all available data up to the data cut-off.

An additional analysis will be conducted when all subjects have completed the study.

Unless otherwise specified, all statistical tests and confidence intervals (CIs) as described in the SAP were to be two-sided with alpha = 0.05.

Analysis sets

Primary endpoint PK analysis set according to the SAP: was to include decitabine daily AUC0-t from subjects who were successfully dosed in Cycles 1 and 2 and who met the following criteria for both ASTX727 and IV decitabine dosing.

ASTX727 successful dosing: received full dose of ASTX727 within 3 hours of the intended dosing time, and no vomiting within 6 hours of dosing.

Decitabine successful dosing:

• Subjects in this analysis set were to have at least 2 days of evaluable decitabine AUC0-t measurements in the ASTX727 cycle, i.e., Day 1 and either Day 2 or Day 5:

o For Day 1 to be included, subjects must have been successfully dosed on Day 1.

o For Day 2 to be included: subjects must have been successfully dosed on Day 1 and Day 2.

o For Day 5 to be included: subjects must have been successfully dosed on Day 4 and Day 5. IV decitabine successful dosing: received the full dose as a 1-hour infusion.

• Subjects in this analysis set were to have at least 1 evaluable day of decitabine AUC0-t measurement in the IV decitabine cycle, either Day 1 or Day 5.

Efficacy Analysis Set: was to include data from all subjects who received any amount of study treatment. All data were to be included, and no subjects excluded due to protocol deviations. Subjects were to be included in the treatment sequence according to randomisation.

Safety Analysis Set: was to include data from all subjects who received any amount of study treatment. In the safety analysis, no data exclusion will be allowed because of protocol deviations. Subjects were to be included in the treatment sequence according to the treatment sequence received.

Pharmacodynamic (PD) LINE-1 Analysis Set: was to include data from all subjects who received any amount of study treatment and had LINE-1 methylation data at baseline (Day 1) of Cycle 1 or 2 and on either Day 8 or Day 15 of the respective cycle.

Primary analysis of the primary endpoint

The primary endpoint analysis included data from the following PK assessment days to calculate the 5-day total cycle AUC:

• ASTX727 AUC0-24: Days 1, 2, and/or 5.

• IV decitabine AUC0-24: Days 1 and/or 5.

Efficacy analyses

Efficacy analyses were to be summarised by treatment sequence and all subjects combined (Total), unless otherwise specified. Efficacy variables were to be summarised using descriptive statistics and there were no formal comparison analyses between treatment sequences.

Response Rate

Subjects who did not have a valid post-treatment efficacy assessment (i.e., no post-treatment BM/PB sample or the quality of BM/PB sample was not adequate for an assessment of efficacy) were to be classified as not evaluable (NE) for response classifications. Subjects who could not be classified into a response category (CR, CRi, or PR) or into the NE category were to be classified as non-responders (NR).

Analyses of LINE-1 methylation

Based on that LINE-1 methylation levels often do not completely return to baseline by Day 28 of Cycle 1, and to avoid the confounding effects of differing baselines in Cycle 2 vs Cycle 1, subjects were compared for each of the 2 cycles separately using the baseline values prior to each cycle, thus limiting the evaluation to interpatient comparisons in each of the 2 cycles.

For each of cycles 1 and 2, LINE-1 methylation data were summarised descriptively by visit and treatment. In addition, 95% CIs for mean maximum %LINE-1 demethylation in Cycles 1 and 2 were provided for ASTX727 and IV decitabine, respectively. The 95% CI for the difference in mean maximum %LINE-1 demethylation between ASTX727 and IV decitabine in Cycles 1 and 2 were also estimated based on an analysis of variance (ANOVA) model with treatment as factor.

Safety analyses

Adverse events (AEs) has been summarised by actual treatment received at the onset of the AE.

Laboratory tests, vital signs, ECG, and ECOG performance status has been summarised by treatment sequence and all subjects combined (Total), unless otherwise specified.

Interim analyses

No formal interim analysis was performed in this study to stop the study for futility or lack of efficacy.

Results

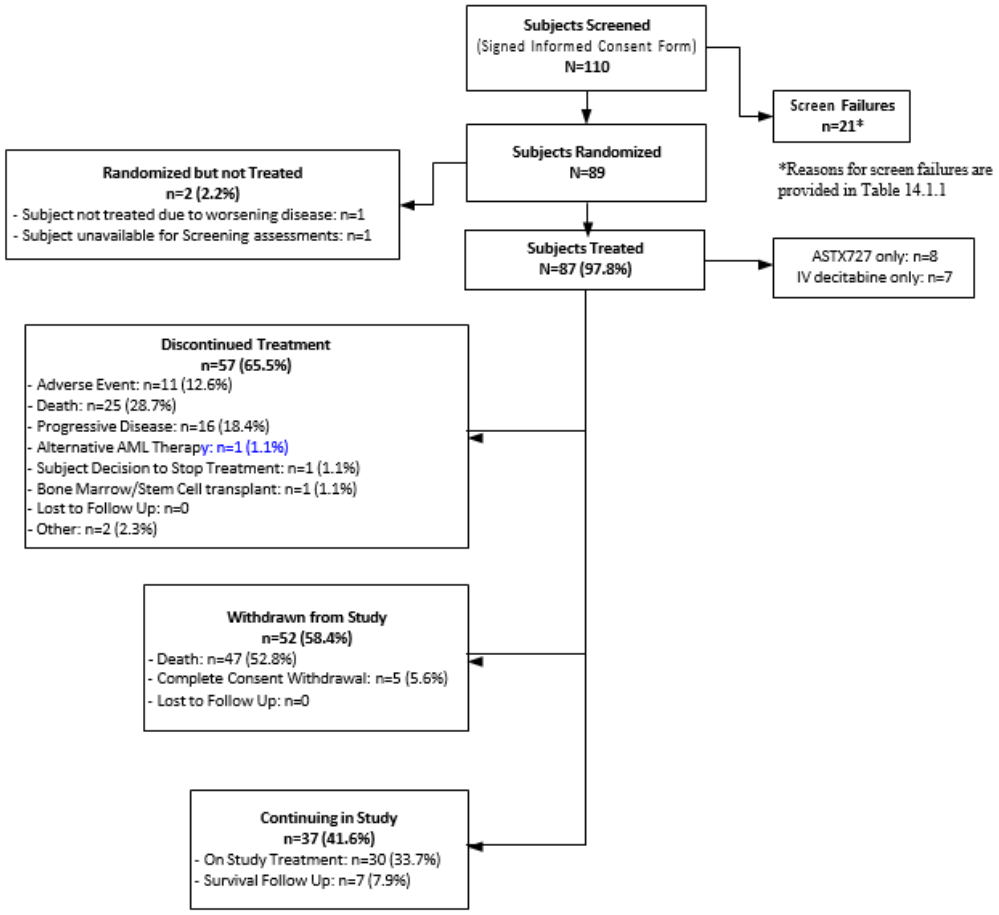
Participant flow

Table 26. Subject Disposition (Randomised Subject Analysis Set)

	Sequence A (N=44) n (%)	Sequence B (N=45) n (%)	Total (N=89) n (%)
Not Treated	1 (2.3)	1 (2.2)	2 (2.2)
Received Treatment	43 (97.7)	44 (97.8)	87 (97.8)
ASTX727 Only	8 (18.2)	0	8 (9.0)
IV Only	0	7 (15.6)	7 (7.9)
ASTX727 and IV	35 (79.5)	37 (82.2)	72 (80.9)
Discontinued Treatment	30 (69.8)	27 (61.4)	57 (65.5)
Adverse Event	7 (16.3)	4 (9.1)	11 (12.6)
Death	12 (27.9)	13 (29.5)	25 (28.7)
Progressive Disease	8 (18.6)	8 (18.2)	16 (18.4)
Alternative AML Therapy[a]	1 (2.3)	0	1 (1.1)
Subject Decision to Permanently Stop Treatment	0	1 (2.3)	1 (1.1)
Bone Marrow/Stem Cell Transplant	0	1 (2.3)	1 (1.1)
Lost to Follow Up	0	0	0
Other	2 (4.7)	0	2 (2.3)
Withdrawn From Study	27 (61.4)	25 (55.6)	52 (58.4)
Death	26 (59.1)	21 (46.7)	47 (52.8)
Complete Consent Withdrawal	1 (2.3)	4 (8.9)	5 (5.6)
Lost to Follow Up	0	0	0
Continuing In Study	17 (38.6)	20 (44.4)	37 (41.6)
On Study Treatment	13 (29.5)	17 (37.8)	30 (33.7)
Survival Follow Up	4 (9.1)	3 (6.7)	7 (7.9)

Percentages for discontinued treatment and reasons for treatment discontinuation are based on number of subjects treated.
Sequence A: ASTX727 in Cycle 1; IV decitabine in Cycle 2.
Sequence B: IV decitabine in Cycle 1; ASTX727 in Cycle 2.
[a] Including subsequent AML therapy.
Source: Table 14.1.4

Figure 12.. Disposition of AML Subjects in Study ASTX727-02 (All Subjects and Randomised Subjects Analysis Sets)



Source: Table 14.1.1, Table 14.1.4, Appendix 16.2.1.1

	All Subjects (N=110)
Screened subjects	110
Screen failed subjects	21
Reasons for screen failure	
Inclusion #01: Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent before the first study-specific procedure	3
Inclusion #02a: Men or women >= 18 years who are candidates to receive IV decitabine according to FDA or EMA approved indications: a) In North America: b) In Europe:	5
Inclusion #03: ECOG performance status of 0 to 1.	2
Inclusion #04: Hepatic: Total or direct bilirubin <=2 x ULN; AST/SGOT and ALT/SGPT <=2.5 x ULN. Renal: serum creatinine <=1.5 x ULN / calculated creatinine clearance / glomerular filtration rate >50 mL/min/1.73m2.	1
Inclusion #06: Life expectancy of at least 3 months.	2
Exclusion #02: Hospitalization for more than 2 days for documented febrile neutropenia, pneumonia, sepsis,or systemic infection in the 30 days before screening.	2
Exclusion #06: Poor medical risk because of other conditions that may put the patient at risk of not being able to complete at least 2 cycles of treatment.	1
Exclusion #08: Rapidly progressive or highly proliferative disease or other criteria that render the subject at high risk of requiring intensive cytotoxic chemotherapy within the next 3 months.	4
Withdrawal by Subject	1

Recruitment

07 January 2020: first subject signed informed consent form (ICF)

06 April 2021: last subject signed ICF

10 January 2020: first subject randomised

22 April 2021: last subject randomised

10 September 2021: data cutoff date

The study is finalised.

Conduct of the study

Protocol amendments

Study ASTX727 02 originally included only subjects with MDS or CMML from North America (NA; US and Canada). Protocol amendment v1.3 (10 December 2018) expanded the subject population to include approximately 70 evaluable subjects with AML in Europe and Canada to extend the PK bridging approach to the AML population as recommended by the CHMP (Scientific Advice EMA/CHMP/SAWP/485806/2018), the indication for which IV decitabine (Dacogen) is approved in the European Union (EU).

Subsequent protocol amendments were produced to address specific national health agency requirements.

Changes to the planned analyses

This Statistical Analysis Plan (SAP) will only describe analysis of AML subjects included in the ASTX727-02 study (ASTX727-02 SAP [AML]). There is a separate SAP which has been approved earlier for analysis of only MDS/CMML subjects included in the ASTX727-02 study (ASTX727-02 SAP).

Response assessment is described in detail in Appendix 1 of the final version of the SAP dated 15 October 2021. The following changes were implemented:

- Response categories were CR, CRi, CRp, PR, NE, and NR. In addition, CR with partial hematologic recovery (CRh) was expected to be reported.
- The reference for CRp (Kantarjian et al 2012) was added. "Complete response with partial hematologic recovery (CRh) will also be assessed as a subset of CRi or CRp" was removed.
- The criteria for CRi were changed to be consistent with IWG 2003 AML Response Criteria (Cheson et al 2003) instead of the protocol.
- Progressive disease and stable disease were added based on the European LeukemiaNet (Döhner et al 2017).
- Changed CRp, CRi to CRi (or CRp) due to CRp being the subset of CRi.
- Duration of CR or CRp was added based on the DACO-016 study (Kantarjian et al 2012)
- Subjects who could not be classified into a response category (CR, CRi/CRp, or PR) or into the NE category were expected to be classified as non-responders (NR). This definition was modified, so that NR was defined as the absence of CR, CRi CRp, CRh, PR (when stable disease and progressive disease were not assessed).

Protocol deviations

Twelve (13.5%) of the 89 randomised subjects had at least 1 important protocol deviation; of these subjects, 7 subjects (7.9%) had deviations related to study drug administration, and 2 subjects (2.2%)

had deviations related to study procedures. All other categories of important protocol deviations included only 1 subject each (eligibility criteria, randomisation/enrolment, and COVID-19).

Table 27. Important Protocol Deviations

Categories	Sequence A (N=44) n (%)	Sequence B (N=45) n (%)	Total (N=89) n (%)
Subjects with at least one important protocol deviation	3 (6.8)	9 (20.0)	12 (13.5)
Eligibility Criteria	0	1 (2.2)	1 (1.1)
Study Drug Administration	1 (2.3)	6 (13.3)	7 (7.9)
Study Procedures	0	2 (4.4)	2 (2.2)
Randomization/Enrollment	1 (2.3)	0	1 (1.1)
Covid-19	1 (2.3)	0	1 (1.1)

Baseline data

Table 28. Demographics Characteristics - Subjects with AML – Study ASTX727-02 EU

Characteristic	Phase 3 Inaqovi (N=89)
Age (years)	
Median (min, max)	78 (61, 92)
Gender (%)	
Male	54 (60.7)
Female	35 (39.3)
ECOG Performance Score (%)	
0	36 (40.4)
1	53 (59.6)
Disease Category (%)	
de novo AML	57 (64.0)
Secondary AML	32 (36.0)
MDS	18 (20.2)
Other antecedent haematological disorder	7 (7.9)
Therapy-related AML	7 (7.9)
Prior HMA Therapy (%)	
Prior azacitidine	2 (2.2)
Transfusion Dependence[a] (%)	
RBC transfusion dependence	37 (41.6)
Platelet transfusion dependence	14 (15.7)

Table 29. Study-Level Summary of ASTX727-02 EU AML Subjects Renal Classification According to the EMA Standard

CRCL (mL/min)	Group	N
15 to 29	Severe	2
30 to 59	Moderate	43
60 to 89	Mild	36
≥90	Normal	6

AML=acute myeloid leukaemia; CRCL=creatinine clearance; EMA=European Medicines Agency; EU=European Union; N=number of subjects.

Source: AXP0103H-Report, Table 7

Numbers analysed

All efficacy endpoints are summarised using the Efficacy Analysis Set (all treated subjects; N=87), unless otherwise specified. Results are summarised by treatment and all subjects combined (Total).

Table 30. Analysis Populations

Analysis Set	Total No. Subjects
Randomized Subject	89
Efficacy	87
Safety	87
Overall PK	87
Pharmacodynamics	78
Primary Paired PK	69

Source: Table 14.1.2, PK Report Table 4

Outcomes and estimation

The analyses presented are based on a data cutoff date of 10 September 2021.

Primary endpoint

ASTX727 (given as an FDC combination of 35 mg decitabine and 100 mg cedazuridine) achieved AUC exposures equivalent to IV infusion of decitabine at 20 mg/m2 (Table 31).

Table 31. Comparison of Decitabine AUC Exposures Between ASTX727 and IV Decitabine in Phase 3 Study ASTX727-02 EU (AML Population)

Analysis		AUC Parameter (ng•h/mL)	N	IV Decitabine Geo. LSM	N	Oral ASTX727 Geo. LSM	Percentage Ratio (%) of Geo. LSM (90% CI)		Intra-Subject (CV%)
Primary	**Paired**	**5-day AUC_{0-24}**	**69**	**907.39**	**69**	**904.13**	**99.64**	**(91.23, 108.8)**	**31.55**
Sensitivity	Unpaired	5-day AUC_{0-24}	71	908.77	71	893.00	98.26	(90.11, 107.2)	31.56
	Paired	5-day AUC_{0-24}	78	896.46	79	885.66	98.80	(90.81, 107.5)	31.31

ANOVA=analysis of variance; AUC_{0-24}=area under the plasma concentration-time curve from time zero to 24 hours; CI=confidence interval; CV=coefficient of variance; IV=intravenous; Geo. LSM=geometric least squares mean

Notes: Paired population: only subjects with data from both IV and oral cycles; Unpaired: included subjects with data from only one cycle.

Analysis is based on ANOVA model with treatment, period, and sequence as fixed effects, and subject nested in sequence as a random effect (ratio is Oral/IV).

Source: Module 2.7.2, Table 19

Exploratory endpoints

Median follow up was 7.95 months (min, max: 4.5, 19.9 months).

Overall Response

Table 32. Overall Response in Subjects with AML – Study ASTX727-02 EU (Efficacy Analysis Set)

	Subjects Evaluable for Response (N=61)		Subjects with ≥6 Months Follow-up or who Discontinued Treatment (N=77)		All Treated Subjects (N=87)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Best Response[a]						
CR	19 (31.1)	(19.9, 44.3)	17 (22.1)	(13.4, 33.0)	19 (21.8)	(13.7, 32.0)
CRi	5 (8.2)	(2.7, 18.1)	4 (5.2)	(1.4, 12.8)	5 (5.7)	(1.9, 12.9)
CRp	2 (3.3)	(0.4, 11.3)	1 (1.3)	(0.0, 7.0)	2 (2.3)	(0.3, 8.1)
PR	4 (6.6)	(1.8, 15.9)	3 (3.9)	(0.8, 11.0)	4 (4.6)	(1.3, 11.4)
Stable disease	33 (54.1)	(40.8, 66.9)	27 (35.1)	(24.5, 46.8)	33 (37.9)	(27.7, 49.0)
NE	—	—	26 (33.8)	(23.4, 45.4)	26 (29.9)	(20.5, 40.6)
Composite Response Rates						
CR + CRi	24 (39.3)	(27.1, 52.7)	21 (27.3)	(17.7, 38.6)	24 (27.6)	(18.5, 38.2)
CR + CRi + PR	28 (45.9)	(33.1, 59.2)	24 (31.2)	(21.1, 42.7)	28 (32.2)	(22.6, 43.1)
CR + CRp	21 (34.4)	(22.7, 47.7)	18 (23.4)	(14.5, 34.4)	21 (24.1)	(15.6, 34.5)
CR + CRh[b]	21 (34.4)	(22.7, 47.7)	19 (24.7)	(15.6, 35.8)	21 (24.1)	(15.6, 34.5)
CRh[b]	2 (3.3)	(0.4, 11.3)	2 (2.6)	(0.3, 9.1)	2 (2.3)	(0.3, 8.1)

BM=bone marrow; CI=confidence interval; CR=complete response; CRh=complete response with partial hematologic recovery; CRi=CR with incomplete blood count recovery; CRp=complete response with incomplete platelet recovery; IWG=International Working Group; NE=not evaluable; PB=peripheral blood; PR=partial response

The 95% CI is the Clopper-Pearson CI.

Subjects who did not have a valid post-treatment efficacy assessment (ie, no post-treatment BM/PB sample or the quality of BM/PB sample was not adequate for an assessment of efficacy) were classified as NE for response classification.

[a] Modified 2003 IWG response criteria (Cheson et al 2003) and Kantarjian et al 2012 were used for CR, CRi, CRp, PR, stable disease, and NE.

[b] Kantarjian et al 2017 was used for CRh assessment.

Source: ASTX727-02 EU CSR Table 14.3.1, Table 14.3.2, Table 14.3.3

Among the subjects with response status of NE, 21 subjects had died as of the data cutoff date (10 September 2021), and 5 remained alive but had discontinued treatment. Among the 33 subjects with best response of stable disease, 16 subjects had died as of the data cutoff date, and of the 17 subjects that were alive, 5 had discontinued treatment.

Table 33. Analysis of Response Rate for the Efficacy and ITT Patient Population

	Efficacy Population (N=87)		**ITT Population (N=89)**	
	n (%)	**95% CI**	**n (%)**	**95% CI**
Best Response (1)				
CR	**19 (21.8)**	**(13.7, 32.0)**	**19 (21.3)**	**(13.4, 31.3)**
CRi	5 (5.7)	(1.9, 12.9)	5 (5.6)	(1.8, 12.6)
CRp	2 (2.3)	(0.3, 8.1)	2 (2.2)	(0.3, 7.9)
PR	4 (4.6)	(1.3, 11.4)	4 (4.5)	(1.2, 11.1)
SD	33 (37.9)	(27.7, 49.0)	33 (37.1)	(27.1, 48.0)
PD	0		0	
NE	26 (29.9)	(20.5, 40.6)	28 (31.5)	(22.0, 42.2)
Composite Response Rates				
CR + CRi	24 (27.6)	(18.5, 38.2)	24 (27.0)	(18.1, 37.4)
CR + CRi + PR*	**28 (32.2)**	**(22.6, 43.1)**	**28 (31.5)**	**(22.0, 42.2)**
CR + CRp	21 (24.1)	(15.6, 34.5)	21 (23.6)	(15.2, 33.8)
CR + CRh	21 (24.1)	(15.6, 34.5)	21 (23.6)	(15.2, 33.8)
CRh (2)	2 (2.3)	(0.3, 8.1)	2 (2.2)	(0.3, 7.9)

The 95% CI is Clopper-Pearson confidence interval.

CI=confidence interval; CR=complete response; CRp=complete response with incomplete platelet recovery. CRp is a subset of CRi; CRh = CR with partial hematologic recovery; CRi=CR with incomplete blood count recovery; PR=partial response; SD = Stable Disease; PD = Progressive Disease; NE=Not evaluable. Subjects who did not have a valid post-treatment efficacy assessment (ie, no post-treatment BM/PB sample or the quality of BM/PB sample is not adequate for an assessment of efficacy) were classified as NE for response classifications.

* As listed in the SmPC "Overall Response included patients with a best response of CR, CRi, and PR"

(1) Modified 2003 IWG response criteria (Cheson et al. 2003) and Kantarjian et al 2012 was used for CR, CRi, CRp, PR, SD, and PD, and NE. (2) Kantarjian et al 2017 was used for the CRh assessment.

Time to Response

Table 34. Time to First Response and Time to Best Response in Subjects with AML – Study ASTX727 -02 EU (Efficacy Analysis Set)

		Total (All Treated Subjects) (N=87)
Time to First Response (Months)	n	28
	Mean	3.29
	SD	1.516
	Median	2.87
	Min, Max	1.8, 6.4
Time to Best Response (Months)	n	28
	Mean	3.74
	SD	1.567
	Median	3.42
	Min, Max	1.8, 7.4

Source: ASTX727-02 EU CSR Table 14.3.6.1

Median time to first response was 2.87 months (min, max: 1.8, 6.4 months), and median time to best response was 3.42 months (range: 1.8, 7.4 months).

Duration of Response

Table 35. Duration of Response for Subjects with AML Who Achieved Complete Response – Study ASTX727 -02 EU CSR (Efficacy Analysis Set)

Characteristics	Total (All Treated Subjects) (N=87)
Number of Subjects, n (%)	19
Censored	9 (47.4)
Event	10 (52.6)
Death	2 (10.5)
Relapse	8 (42.1)
Start of new anticancer therapy (excluding HCT)	0
K-M Estimate, Months, (95% CI)	
25th percentile	3.3 (0.5, 5.3)
Median	5.8 (3.3, NE)
75th percentile	NE (5.3, NE)

CI=confidence interval; CR=complete response; HCT=hematopoietic stem cell transplant; K-M=Kaplan-Meier; NE=not estimable

Source: ASTX727-02 EU CSR Table 14.3.4.1, Table 14.3.1

Ten subjects reached the event of death or relapse. Nine of the 19 subjects who achieved CR (47.4%) were censored. Median duration of response for subjects achieving CR was 5.8 months (95% CI: 3.3, NE). For K-M curve, please refer to the Clinical AR.

Transfusion Independence

Of the 87 treated subjects, 27 of the 41 subjects (65.9%) who were dependent on any transfusion at baseline remained so postbaseline; 14 (34.1%) of the 41 subjects who were dependent on any transfusion at baseline became transfusion independent postbaseline. Conversely, 34 of the 46 subjects (73.9%) who were transfusion independent at baseline became transfusion dependent postbaseline, indicating the disease was not under control; 12 (26.1%) of the 46 subjects who were transfusion independent at baseline remained so postbaseline.

Overall Survival

Table 36. Overall Survival in Subjects with AML – Study ASTX727 -02 EU CSR (Efficacy Analysis Set)

Characteristics	Total (All Treated Subjects) (N=87)
Number of Subjects, n (%)	
Censored	40 (46.0)
Event	47 (54.0)
K-M Estimate, Months (95% CI)	
25th percentile	3.4 (1.4, 5.1)
Median	7.9 (5.9, 13.0)
75th percentile	13.2 (11.3, NE)

CI=confidence interval; K-M=Kaplan-Meier; NE=not estimable
Source: ASTX727-02 EU CSR Table 14.3.8.1

Event-Free Survival

Table 37. Event-Free Survival in Subjects with AML – Study ASTX727-02 EU CSR (Efficacy Analysis Set)

Characteristics	Total (All Treated Subjects) (N=87)
Number of Subjects, n (%)	
Censored	29 (33.3)
Event	58 (66.7)
K-M Estimate, Months, (95% CI)	
25th percentile	2.0 (1.3, 3.3)
Median	5.8 (3.8, 8.3)
75th percentile	9.0 (8.5, 16.9)

CI=confidence interval; K-M=Kaplan-Meier
Source: ASTX727-02 EU CSR Table 14.3.8.2

Progression-Free Survival

Table 38. Progression-Free Survival in Subjects with AML – Total in Study ASTX727-02 EU (Efficacy Analysis Set)

Characteristics	Total (All Treated Subjects) (N=87)
Number of Subjects, n (%)	
Censored	31 (35.6)
Event	56 (64.4)
K-M Estimate, Months (95% CI)	
25th percentile	2.0 (1.3, 3.3)
Median	6.1 (4.0, 8.5)
75th percentile	9.0 (8.7, 16.9)

CI=confidence interval; K-M=Kaplan-Meier
Source: ASTX727-02 EU CSR Table 14.3.8.3

Follow up

Median possible follow-up time overall was 7.95 months (min, max: 4.5, 19.9 months).

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application.

Study ID	Efficacy Objectives	Design	Efficacy Endpoint(s)	Population	Median Treatment Exposure	Response Rate/ Time to Best Response	Median Duration of Response	Median Survival	Median Potential Follow-up
ASTX727-02 EU	Long-term response rate	Phase 3 multicenter, randomised, open-label, 2-period, 2-sequence crossover	Complete response (CR), CR with incomplete platelet recovery (CRp), CR with incomplete blood count recovery (CRi), CR with partial hematologic recovery (CRh)	Males/females ≥18 yrs with de novo or secondary AML not candidates for standard induction therapy	5 cycles (range: 1, 20 cycles)	Best Response: CR[a]: 19 (21.8%) (95% CI 13.7, 32.0) CR+CRp[a]: 21 (24.1%) (95% CI: 15.6, 34.5) CRi[a]: 5 (5.7%) (95% CI: 1.9, 12.9) CRh[a]: 2 (2.3%) (95% CI: 0.3, 8.1) Median Time to Best Response: 3.42 months (range: 1.8, 7.4 months)	CR: 5.8 months (95% CI: 3.3, NE)[b]	OS: 7.9 months (95% CI: 5.9, 13.0) PFS: 6.1 months (95% CI: 4.0, 8.5)[b] EFS: 5.8 months (95% CI: 3.8, 8.3)[b]	7.95 months (range: 4.5, 19.9 months)

Title: A Phase 3, Randomized, Open-Label, Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) versus IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukemia (CMML), and Acute Myeloid Leukemia (AML)		
Study identifier	Protocol Number: ASTX727-02 Study Identifier ASTX727-02 EU CSR Number: ASTX727-02-C Trial Registry Number: NCT03306264 EudraCT Number: 2018-003395-12	
Design	Phase 3, multicentre, randomised, open-label, 2-period, 2-sequence crossover study comparing decitabine AUC equivalence of ASTX727 and IV decitabine	
	Duration of main phase:	After completion of the first two 28-day treatment cycles, subjects continued to receive treatment with ASTX727 in 28-day cycles until disease progression, unacceptable toxicity, or the subject decides to discontinue treatment or withdraw from the study. The study is ongoing.
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	The primary objective of this study was to establish AUC equivalence of 5-day dosing between ASTX727 and IV decitabine in adult subjects with AML who were candidates to receive IV decitabine	
Treatments groups	Sequence A	ASTX727 tablet (35 mg decitabine plus 100 mg cedazuridine) Daily×5 in Cycle 1 and IV decitabine (20 mg/m^2) 1-hour infusion Daily×5 in Cycle 2. Cycle 3 and beyond: All subjects received 28-day cycles of ASTX727 tablet Daily×5.
	Sequence B	IV decitabine (20 mg/m^2) 1-hour infusion Daily×5 in Cycle 1 and ASTX727 tablet (35 mg decitabine plus 100 mg cedazuridine) Daily×5 in Cycle 2. Cycle 3 and beyond: All subjects received 28-day cycles of ASTX727 tablet Daily×5.

Endpoints and definitions	Primary endpoint		The primary endpoint was total 5-day (total cycle) AUC exposures of decitabine after treatment with ASTX727 versus IV decitabine
	Secondary efficacy endpoints		• % Maximum long interspersed nucleotide elements 1 (*LINE-1*) demethylation • Clinical response (complete response [CR], CR with incomplete platelet recovery [CRp], and CR with incomplete blood count recovery [CRi] based on modified International Working Group (IWG) 2003 AML response criteria (Cheson et al 2003) and as in the DACO-016 study (ie, CRp as a subset of CRi) (Kantarjian et al 2012). In addition, complete response with partial haematologic recovery (CRh) will also be assessed. CRh will be reported as in Kantarjian et al 2017 and as used in DiNardo et al 2020. • Time to first response, time to best response, and time to CR. • Duration of CR and duration of combined CR and CRh, defined respectively as the time interval from the first CR to time of relapse and the time interval from the first CR or CRh to time of relapse. • Red blood cell (RBC) or platelet transfusion independence (TI). • Overall survival (OS), defined as the number of days from the date of randomisation to the date of death from any cause. • Survival rates at 6 months, 1 year, and 2 years. • Event-free survival (EFS), defined as the number of days from the date of randomisation to the date of treatment failure or death from any cause, whichever occurs first. • Progression-free survival (PFS), defined as the number of days from the date of randomisation to the date disease progression or death from any cause, whichever occurs first.
Results	Primary endpoint		ASTX727 demonstrated equivalent decitabine PK AUC to IV decitabine 20 mg/m2 when both were administered over 5 days.
Database lock	10 September 2021 (data cutoff date)		

Results and Analysis	
Analysis description	**Primary Analysis**
Analysis population and time point description	Analysis Populations: • All Subject Analysis Set: all screened subjects. • Randomised Subject Analysis Set: all randomised subjects. Subjects were included in the treatment group (Sequence A or Sequence B) according to their randomly assigned treatment sequence. • Primary Endpoint PK Analysis Set: included decitabine daily area under the curve from time zero to 24 hours postdose (AUC_{0-24}) from subjects who received the 5-day dosing of IV decitabine and ASTX727 in Cycles 1 and 2 and who met the criteria for both ASTX727 and IV decitabine dosing and PK assessments. • Overall PK Analysis Set: included subjects who may not have been included in the Primary Endpoint PK Analysis Set and who received any amount of treatment; complied with the protocol sufficiently to ensure PK samples were collected as intended; and provided sufficient samples to measure plasma concentrations of decitabine, cedazuridine, and cedazuridine-epimer. • Pharmacodynamics (PD) Analysis Set: included subjects who received any amount of treatment and who had *LINE-1* methylation data at baseline (Day 1) of Cycle 1 or 2 and on either Day 8 or Day 15 of that cycle. • Efficacy Analysis Set: all subjects who received any amount of study treatment. Subjects were included in the treatment sequence according to their randomly assigned treatment sequence. • Safety Analysis Set: all subjects who received any amount of study treatment. Subjects were included in the treatment sequence according to the treatment sequence received. Time Point Description: Analyses were performed after all evaluable subjects had completed Cycles 1 and 2 and included the primary analyses of all PK endpoints, maximum %*LINE-1* demethylation, and all available clinical response and safety data up to the data cutoff date of 10 September 2021.

Descriptive statistics and estimate variability	**Treatment Group**			**Total**
	Primary Endpoint			
	Number of subjects (Primary PK Endpoint Analysis Set)		69 (primary pairable reliable 5-day AUC_{0-24})	
	Plasma Decitabine AUC Equivalence Assessment for the Primary Exposure Variable AUC_{0-24}		99.64% ratio of geometric LSM (91.23, 108.8) 90% CI 31.55 Intra-subject CV%	
	Secondary Efficacy Endpoints			
	Number of subjects (ITT Analysis Population)		89	
	Complete response, n (95% CI)		21 [13.4, 31.3]	
	Time to CR for subjects who achieved CR in months, median (range)		3.0 (1.8, 7.4)	
	Median duration of CR for subjects who achieved CR[c], months (95% CI)		n=19 5.8 (3.3, NE)	
	Overall rResponse† (%) [95% CI]		32 [22.0, 42.2]	
Notes	The study is ongoing. Because 40 subjects were still censored at the time of data cut, the median overall survival time may change as the data mature. At the time of data cutoff, the median possible follow-up time overall was 7.95 months (min, max: 4.5, 19.9 months).			

2.6.5.3. Clinical studies in special populations

There are no clinical studies in special populations.

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

A retrospective comparison between efficacy results in subjects with AML treated in Study ASTX727-02 EU and subjects with AML treated with single-agent IV decitabine in the open-label, randomised, multicentre, Phase 3 pivotal decitabine AML registration study (Study DACO-016) and the open-label, Phase 2 supportive decitabine study (Study DACO-017) is summarised in Table 39.

Table 39. Retrospective Comparison of Efficacy Parameters of ASTX727 vs Decitabine for Subjects with AML

	ASTX727		IV Decitabine
Efficacy Endpoint	**Study ASTX727-02 EU (AML) N=87**	**Study DACO-016 (AML) N=242**	**Study DACO-017 (AML) N=55**
CR, n (%)	19 (21.8)[a] (95% CI: 13.7, 32.0)	38 (15.7)	13 (23.6) (95% CI: 13.2, 37.0)
CR + CRp, n (%)	21 (24.1)[a] (95% CI: 15.6, 34.5)	43 (17.8)	13 (23.6) (95% CI: 13.2, 37.0)
CRi, n (%)	5 (5.7)[a] (95% CI: 1.9, 12.9)	24 (9.9)	1 (1.8) (95% CI: 0.0, 9.7)
Time to best response (median), months	3.42[b] (Range: 1.8, 7.4)	4.3[c] (95% CI: 3.8, 5.1)	4.1[b] (95% CI: 2.3, 5.1)
OS median, months	7.9 (95% CI: 5.9, 13.0)	7.7 (95% CI: 6.2, 9.2)	7.6 (95% CI: 5.7, 11.5)
PFS median, months	6.1 (95% CI: 4.0, 8.5)[b]	3.7 (95% CI: 2.7, 4.6)	--
EFS median, months	5.8 (95% CI: 3.8, 8.3)[b]	3.5 (95% CI: 2.5, 4.1)	--

CI=confidence interval; CMML=CR=complete response; CRi=CR with incomplete blood count recovery; CRp=complete response with incomplete platelet recovery; EFS=event-free survival; IWG=International Working Group; NE=not evaluable; OS=overall survival; PFS=progression-free survival; PR=partial response

[a] Modified 2003 IWG response criteria (Cheson et al 2003) and Kantarjian et al 2012 were used for CR, CRi, CRp, PR, stable disease, and NE.

[b] For CR

[c] For CR + CRp

Source: ASTX727-02 EU CSR, Table 14.3.1, 14.3.6.1, 14.3.8.1, 14.3.8.2, 14.3.8.3; Dacogen SmPC; EMA 2012; Nieto et 2016

2.6.5.5. Supportive study(ies)

The efficacy of ASTX727 was initially evaluated in subjects with MDS or CMML in a Phase 1-2 study (ASTX727 01) and in a Phase 3 study (ASTX727-02 NA). The efficacy results from the Phase 2 stages of ASTX727-01 (ie, ASTX727-01-B), and efficacy results from Phase 3 Study ASTX727-02 NA are supportive for this submission.

Study ASTX727-01-B Phase 2 was designed to evaluate the dose combination of 35 mg decitabine and 100 mg cedazuridine in a crossover design to confirm that the dose combination yielded PK exposures and DNA demethylation similar to IV decitabine. CR was observed in 17.5% of all treated subjects. Median duration of response for subjects with a best response of CR was 285 days (interquartile range: 155, 413 days). Of subjects who were RBC transfusion dependent at baseline, 50% were RBC transfusion free for any consecutive 56-day period post baseline. Similarly, of the subjects who were platelet transfusion dependent at baseline, 50% were platelet transfusion free for any consecutive 56 day period post-baseline. Median time to AML or death was 364 days (95% CI: 305.0, 654.0), and median survival time was 589 days (95% CI: 392.0, 864.0).

Study ASTX727-02 NA was a Phase 3 multicentre, randomised, open-label, 2-period, 2 sequence crossover study comparing decitabine AUC equivalence of ASTX727 and IV decitabine in subjects with MDS and CMML. The study design was identical to that of ASTX727 02 EU in that subjects were randomly assigned in a 1:1 ratio to a treatment sequence for the first two cycles (Sequence A: ASTX727 in Cycle 1 and IV decitabine Cycle 2; or Sequence B: IV decitabine in Cycle 1 and ASTX727 in

Cycle 2). After completion of the first 2 treatment cycles, subjects continued to receive treatment with ASTX727 in 28-day cycles until disease progression, unacceptable toxicity, treatment discontinuation for other reasons, or they were withdrawn from the study. CR was observed in 21.8% of all treated subjects and in 24.8% of subjects evaluable for response. Median duration of best response was 371.0 days (95% CI: 289.0, 439.0). More than half (51.9%) of the 54 subjects who were RBC transfusion dependent at baseline were RBC transfusion independent for any consecutive ≥56-day period post-baseline. A similar overall rate of platelet transfusion independence (50%) for any consecutive ≥56-day period post-baseline was observed for subjects with platelet transfusion dependence at baseline. Median survival time was 966.0 days (95% CI: 809.0, NE), and median follow-up time was 966.0 days (range, 868 to 1208 days).

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Clinical efficacy was intended to be demonstrated by a PK bridging approach to the clinical data for IV decitabine from pivotal study ASTX727-02 EU, a multicentre, open-label, 2-sequence crossover study of oral ASTX727 versus IV decitabine in patients with AML. This strategy was accepted during CHMP scientific advice meeting.

Study population

The inclusion and exclusion criteria allowed selection of a study population in line with the proposed target indication. Inclusion/exclusion criteria were in line with that of Dacogen clinical studies and its approved indications across regions.

Endpoints

The primary endpoint was total 5-day AUC exposure of decitabine after treatment with ASTX727 versus IV decitabine.

All secondary efficacy endpoint (like CR, time to first response, OS) were exploratory. Efficacy was explored based on complete response (CR) and rate of conversion from transfusion dependence to transfusion independence. Both parameters are considered adequate given the current clinical context. The response criteria for evaluation of AML - and assessment of the main efficacy endpoint- are based on the IWG criteria published by Cheson et al (2003), and are considered adequate.

The median treatment duration was 5 months (range 0 to 18 months).

Sample size

The sample size estimation was based on the primary PK endpoint and appears appropriate.

No sample size considerations were made regarding the assessment of efficacy or safety. The ASTX727 efficacy and safety assessment is referred to cycle 1 or, for long-term follow-up of ASTX727 treatment, beyond cycle 2 and is, from cycle 3 and onward hampered by the open label single arm design as well as that all subjects also were to receive IV decitabine (either in cycle 1 or cycle 2). Although the sample size is considered adequate in terms of statistical assumptions regarding the primary endpoint, the database is limited for generating evidence in terms of efficacy and safety in AML patients. However, efficacy was a secondary objective in the current study and the reported data are only provided as supportive, which is acceptable.

Randomisation

According to study schedule of events, randomisation was to be performed during screening. As described, randomisation could have been performed at least up to 14 days before initiation of study treatment administration although the CSP also stated that subjects were to initiate study treatment as soon as possible after randomisation. In the end, a total of 89 subjects were randomised whereof 2.2% (2/89) never received any study treatment due to worsening disease (n=1) and that screening assessments could not be performed (n=1).

Statistical analysis

The statistical methods appear reasonable. Efficacy endpoints were summarised using descriptive statistics.

However, all summaries of efficacy had been based on randomised and treated subjects (i.e., 87/89). In a single-arm trial, clinical response data should be presented based on the ITT population. Thus, the applicant was requested to present new estimates and corresponding 95% CI using the Randomised Subject Analysis Set. In response, new analyses have been provided for the endpoints proposed to be presented in the SmPC 5.1.

Efficacy data and additional analyses

Study population

A total of 110 patients were screened, 21 were screen failures, 89 patients were randomised, and finally 87 patients were treated (AST727 only: 8; IV decitabine only: 7); 37 patients are continuing in study (on study treatment n=30; survival follow up n=7). All efficacy endpoints are summarised using the Efficacy Analysis Set (all treated subjects; N=87).

Patients included (n=87) had a median age of 78 years (range 61-92) with 97% of subjects ≥65 years, and 61% were male. Poor and intermediate risk cytogenetics were noted in 38% and 52% of subjects, respectively. Fifty-two percent of subjects had severe or moderate renal failure, as would be anticipated given the age range studied.

Primary endpoint

ASTX727 demonstrated equivalent decitabine PK AUC to IV decitabine 20 mg/m2 when both were administered over 5 days. For further assessment of PK endpoints, please refer to the PK AR.

Secondary endpoints

The PD endpoint, i.e., the maximum percent LINE-1 demethylation, was numerically comparable between ASTX727 and IV decitabine in the Phase 3 Study ASTX727-02 in AML as well as MDS/CMML patients. This supports that differences in Cmax are not anticipated to result in different efficacy.

After a median follow-up of 7.95 months, the CR rate in patients receiving ASTX727 was 21.8% (95% CI 13.7, 32.0), the median duration of CR was 5.8 months (95% CI 3.3, NE) and the median time to first response was 2.87 months (min, max: 1.8, 6.4). Of the 41 patients dependent on transfusions at baseline, 34.1% of patients became independent of transfusions post-baseline. Among 46 patients who were independent of transfusions at baseline, 26.1% of patients remained so post-baseline.

Median duration of treatment (to the data cut-off date of 10 September 2021) was 4.86 months (range 0 to 18 months), with 37.5% of subjects treated for >6 months and 6.3% of subjects treated for >12 months.

Median EFS time was 5.8 months (95% CI: 3.8, 8.3), median PFS time was 6.1 months (95% CI: 4.0, 8.5) and median OS time was 7.9 months (95% CI: 5.9, 13.0).

None of the clinical endpoint directly isolate the effect of the test agents, as both test and reference agent were given before the assessment of ORR, and as a single arm trial does not isolate treatment effects on PFS or OS.

Analysis performed across trials

A retrospective comparison of results in subjects with AML being treated in study ASTX727-02 EU and subjects with AML treated with single-agent IV decitabine in the Phase 3 pivotal decitabine AML registration study (Study DACO-016) and the open-label, Phase 2 supportive decitabine study (Study DACO-017) was presented by the Applicant:

CR rate of 21.8% with ASTX727 compared to 15.7% in study DACO-016 and 23.6% in study DACO-017. Median survival of 7.9 months compared to 7.7 months in DACO-016 and 7.6 months in DACO-017. Thus, the efficacy results achieved with ASTX727 were similar to the efficacy results of IV decitabine.

Supportive studies

The efficacy results from the Phase 2 stages of ASTX727-01 (ie, ASTX727-01-B), and from Phase 3 Study ASTX727-02 NA showed clinical efficacy in MDS and CMML. The results from these studies support the present application.

2.6.7. Conclusions on the clinical efficacy

Since AUC is similar for oral decitabine in combination with cedazuridine and for decitabine given IV at the respective recommended doses, it can be inferred that the efficacy of ASTX727 at the proposed dose is similar to that of IV decitabine at the approved dose, in the treatment of adult patients with AML.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Studies supporting the safety evaluation

In support of the safety evaluation of ASTX727 the Applicant discussed primarily the results of three studies, in which decitabine + cedazuridine were administered according to the currently proposed dosing schedule (i.e., 35 mg decitabine/100 mg cedazuridine for 5 consecutive days of each 28-day cycle):

- Study ASTX727-02 EU: Pivotal Phase 3 study in adult patients with AML (n=87, 80 of whom received ASTX727)
- Study ASTX727-02 North America (NA): Supportive data, Phase 3 study in adult patients with MDS/CMML (N=133)
- Study ASTX727-01-B (dose confirmation phase): Supportive data from the extension phase, adult patients with in MDS/CMML (n=80)

The data presented from these studies are those up to the data cutoff dates that were used for the primary analyses for the individual clinical study reports (CSRs):

- 10 September 2021 for ASTX727-02 EU (pivotal)

- 07 June 2021 for ASTX727-02 NA (supportive)
- 16 September 2020 for ASTX727-01-B (supportive)

In these three studies, oral decitabine + cedazuridine and IV decitabine were administered in Cycle 1 and 2 in a crossover fashion. Thus, all patients in these studies received one cycle of IV decitabine.

In addition, data are available from a completed thorough QT study of cedazuridine in adult healthy subjects.

Extent of exposure

A total of 502 subjects have received ASTX727 and/or IV decitabine in the ASTX727 clinical programme, and 40 subjects have received cedazuridine only.

The pooled population from the studies mentioned above is referred to as the "integrated population". The integrated population, thus, includes all subjects who received at least 1 dose of study treatment (35 mg decitabine and 100 mg cedazuridine) administered orally in the pivotal Phase 3 study ASTX727-02 or in the Phase 2 stage of study ASTX727-01, regardless of the formulation used (separate capsules or FDC tablets).

Overall study drug exposure for the integrated population is summarised in Table 40.

Table 40. Study Drug Exposure in the Integrated Population as of CSR Cutoff Dates (Phase 2 and Phase 3 Subjects)

Characteristic		**ASTX727-02 EU [AML] (N=80)**	**ASTX727-01-B / ASTX727-02 NA [MDS/CMML] (N=208)**	**All Subjects (N=288)**
Total Number of Cycles Received		480	2246	2726
Number of Cycles Received[a]	N	80	208	288
	Mean	6.0	10.8	9.5
	SD	4.11	8.65	7.95
	Median	6.0	8.0	7.0
	Min, Max	1, 20	1, 44	1, 44
Number of Cycles[a], n (%)	1	8 (10.0)	6 (2.9)	14 (4.9)
	2	11 (13.8)	16 (7.7)	27 (9.4)
	3-5	20 (25.0)	49 (23.6)	69 (24.0)
	6-8	24 (30.0)	36 (17.3)	60 (20.8)
	9-11	10 (12.5)	29 (13.9)	39 (13.5)
	≥12	7 (8.8)	72 (34.6)	79 (27.4)
Number of Delayed Cycles[b], n (%)	At least 1	55 (68.8)	142 (68.3)	197 (68.4)

Characteristic		ASTX727-02 EU [AML] (N=80)	ASTX727-01-B / ASTX727-02 NA [MDS/CMML] (N=208)	All Subjects (N=288)
	1-3	47 (58.8)	69 (33.2)	116 (40.3)
	4-6	8 (10.0)	31 (14.9)	39 (13.5)
	>6	0	42 (20.2)	42 (14.6)
Number of Reduced Dose Cycles[c], n (%)	At least 1	6 (7.5)	105 (50.5)	111 (38.5)
	1-3	5 (6.3)	52 (25.0)	57 (19.8)
	4-6	1 (1.3)	14 (6.7)	15 (5.2)
	>6	0	39 (18.8)	39 (13.5)

[a] Completed or partially completed cycle.

[b] Delayed treatment cycle is identified by investigators.

[c] Dose-reduced cycle is based on any missing treatment in Cycles 1 and 2, dose adjustment by investigator or any drug return by subject for cycles >2; last treatment cycle > Cycle 2 was not included in calculation of dose reduction.

Subject disposition

Subject disposition of the integrated population is summarised in Table 33.

Table 5. Subject Disposition of the Integrated Population (Phase 2 and Phase 3 Subjects)

Characteristic	ASTX727-02 EU [AML] (N=80)	ASTX727-01-B / ASTX727-02 NA [MDS/CMML] (N=208)	All Subjects (N=288)
Received Treatment, n (%)	80 (100.0)	208 (100.0)	288 (100.0)
At least 1 dose of ASTX727[a]	80 (100.0)	208 (100.0)	288 (100.0)
At least 1 dose of IV decitabine	72 (90.0)	202 (97.1)	274 (95.1)
Discontinued Treatment[b], n (%)	51 (63.8)	208 (100.0)	259 (89.9)
Adverse Event	11 (13.8)	16 (7.7)	27 (9.4)
Death	20 (25.0)	21 (10.1)	41 (14.2)
Progressive Disease	15 (18.8)	58 (27.9)	73 (25.3)
Alternative MDS/CMML Therapy	0	3 (1.4)	3 (1.0)
Subject Decision to Permanently Stop	1 (1.3)	11 (5.3)	12 (4.2)
Bone Marrow/Stem Cell Transplant	1 (1.3)	39 (18.8)	40 (13.9)
Lost to Follow-up	0	0	0
Alternative AML Therapy	1 (1.3)	0	1 (0.3)

Characteristic	ASTX727-02 EU [AML] (N=80)	ASTX727-01-B / ASTX727-02 NA [MDS/CMML] (N=208)	All Subjects (N=288)
Other	2 (2.5)	60 (28.8)	62 (21.5)
Withdrawn from Study, n (%)	44 (55.0)	207 (99.5)	251 (87.2)
Death	41 (51.3)	106 (51.0)	147 (51.0)
Adverse Event	0	1 (0.5)	1 (0.3)
Progressive Disease	0	4 (1.9)	4 (1.4)
Withdrawal by Subject	3 (3.8)	6 (2.9)	9 (3.1)
Lost to Follow-up	0	1 (0.5)	1 (0.3)
Rollover to Study ASTX727-06	0	28 (13.5)	28 (9.7)
Study Terminated by Sponsor	0	40 (19.2)	40 (13.9)
Other	0	21 (10.1)	21 (7.3)
Duration of Follow-up, days[c]			
Mean	287.7	1185.3	935.9
SD	125.63	278.47	471.66
Median	242.0	1069.5	966.0
Min, Max	137, 606	868, 1710	137, 1710
Continuing in Study, n (%)	36 (45.0)	1 (0.5)[d]	37 (12.8)
Ongoing study treatment	29 (36.3)	0	29 (10.1)
On study for survival follow-up	7 (8.8)	1 (0.5)[d]	8 (2.8)

[a] ASTX727 includes decitabine and cedazuridine as separate capsules and ASTX727 FDC tablets.

[b] Percentages are based on the number of subjects who received treatment.

[c] Number of follow-up days is calculated as database cutoff date minus first treatment date regardless of survival status.

[d] One subject in Study ASTX727-02 NA , shown to be in survival follow up, discontinued treatment; no further information was available, as the study centre was closed soon after

2.6.8.2. Adverse events

A treatment-emergent adverse event (TEAE) is defined as any new AE or any worsening of an existing condition with an onset date on or after the first study drug administration date (Cycle 1 Day 1 [C1D1]) and up to 30 days after the last dose of study treatment or the start of an alternative anti-cancer treatment (for MDS/CMML or AML), whichever occurred first.

Events that occurred more than 30 days after the last dose of study treatment or the start of an alternative anti-cancer treatment (for MDS/CMML or AML) were also considered treatment-emergent if they were both serious and related to the study treatment.

In the following tables and text, the term 'AE' will generally refer to a TEAE, unless otherwise specified.

Relatedness to study treatment (decitabine and cedazuridine in FDC tablets or separate capsules) as assessed by investigators was used for the Applicant's Summary of Clinical Safety.

An overview of treatment-emergent AEs in the integrated population is presented in Table 41.

Table 41. Overall Summary of Adverse Events in the Integrated Population (Phase 2 and Phase 3 Subjects)

	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
All Adverse Events			
Subjects with any AE	80 (100)	208 (100)	288 (100)
Subjects with any AE Grade ≥3	71 (88.8)	199 (95.7)	270 (93.8)
Subjects with an AE Leading to Discontinuation of Study Treatment	11 (13.8)	13 (6.3)	24 (8.3)
Subjects with any SAE	59 (73.8)	151 (72.6)	210 (72.9)
Death	19 (23.8)	21 (10.1)	40 (13.9)
Other Subjects with SAEs[a]	40 (50.0)	130 (62.5)	170 (59.0)
AE Related to Any Study Medication			
Subjects with any AE	49 (61.3)	171 (82.2)	220 (76.4)
Subjects with any AE Grade ≥3	38 (47.5)	138 (66.3)	176 (61.1)
Subjects with an AE Leading to Discontinuation of Study Treatment	3 (3.8)	4 (1.9)	7 (2.4)
Subjects with any SAE	18 (22.5)	35 (16.8)	53 (18.4)
Death	1 (1.3)	5 (2.4)	6 (2.1)
Other Subjects with SAEs[a]	17 (21.3)	30 (14.4)	47 (16.3)

AE=adverse event; SAE=serious adverse event

2.6.8.3. Common adverse events

In subjects with AML (N=80), the AEs with the highest incidence (≥20% of subjects), regardless of relationship to study medication, were anaemia, febrile neutropenia, neutropenia, thrombocytopenia, nausea, asthenia, pyrexia, and pneumonia.

In subjects with MDS/CMML (N=208), the AEs with highest incidence (≥20% of subjects), regardless of relationship to study medication, were anaemia, febrile neutropenia, leukopenia, thrombocytopenia, neutropenia, constipation, diarrhoea, nausea, asthenia, fatigue, oedema peripheral, pyrexia, pneumonia, decreased appetite, arthralgia, dizziness, headache, cough, and dyspnoea.

Grade ≥3 adverse events

In the subjects with AML (N=80), 88.8% reported at least one Grade ≥3 AE. The Grade ≥3 AEs that occurred with highest incidence (>20% of subjects) were thrombocytopenia, anaemia, febrile neutropenia, neutropenia, and pneumonia.

In the MDS/CMML subject group (N=208), 95.7% reported at least one Grade ≥3 AE. The most frequently reported Grade ≥3 AEs (>20% of subjects) were thrombocytopenia, neutropenia, anaemia, febrile neutropenia, and leukopenia.

Treatment-related adverse events (as assessed by investigator)

In subjects with AML (N=80), 61.3% reported at least one treatment-related AE. The treatment-related AEs that occurred with highest incidence (>10% of subjects) were thrombocytopenia, neutropenia, anaemia, febrile neutropenia, and nausea.

Treatment-related Grade ≥3 AEs reported in ≥2 subjects with AML were thrombocytopenia, neutropenia, anaemia, and febrile neutropenia.

In the MDS/CMML subject group (N=208), 82.2% reported at least one treatment-related AE. The most frequently reported treatment-related AEs (12% of subjects) were thrombocytopenia, neutropenia, anaemia, leukopenia, fatigue, and nausea.

Treatment-related Grade ≥3 AEs reported in ≥2 subjects with MDS/CMML were neutropenia, thrombocytopenia, anaemia, and leukopenia.

Adverse events in studies with cedazuridine alone

Two studies in healthy subjects were performed administration of cedazuridine only. Study E7727-01 was a mass-balance study with administration of a single 100 mg dose of cedazuridine. No AEs assessed as related to treatment were reported from this study.

Study E7727-02 was a thorough QT study, which is further discussed below. Single doses of 100 mg and 400 mg cedazuridine, 400 mg moxifloxacine and placebo were administered to 31 subjects (one additional subject withdrew after the first period and was only treated with placebo). AEs were reported in 20/32 subjects (after cedazuridine or moxifloxacine). The most commonly reported AEs were dizziness (n=9), headache (n=4), medical device site reaction (n=4) and abdominal pain (n=4). Treatment-related AEs were reported in a total of 7/32 subjects (21.9%). Four (4) of the 7 AEs that were assessed as treatment-related were reported after administration of moxifloxacine or placebo. For cedazuridine (100 or 400 mg) the only treatment-related AEs were 2 cases of abdominal pain and one case of headache. All these reactions were of Grade 1 severity.

2.6.8.4. Serious adverse event/deaths/other significant events

Deaths

Treatment-emergent AEs with an outcome of death are summarised in Table 35 for the integrated population.

In subjects with AML (N=80), 19 subjects (23.8%) had TEAEs with an outcome of death during the treatment period. Only 1 of the fatal TEAEs, was considered related to study treatment by the investigator.

In subjects with MDS/CMML (N=208), 21 subjects (10.1%) had TEAEs with an outcome of death during the treatment period. Five subjects had TEAEs with an outcome of death considered treatment-related by the investigator: myocarditis, pneumonia , sepsis , and septic shock . Three of these subjects had events considered related to IV decitabine (sepsis, pneumonia, and septic shock). The other TEAE of fatal pneumonia was considered related to ASTX727 by the investigator's causality assessment. The event of myocarditis was considered by the investigator as related to ASTX727; however, the Applicant assessed the myocarditis as not related to study treatment because of concomitant positive blood culture. The Applicant also took into consideration that decitabine has no known cardiac liabilities, and there has been no clinical incidences of cardiac toxicity or nonclinical cardiac liabilities reported for cedazuridine.

One subject died due to gastrointestinal perforation (Viscera perforation).. The event of viscera perforation was assessed as unrelated to ASTX727.

Table 42. Treatment-Emergent Adverse Events with an Outcome of Death in the Integrated Population (Phase 2 and Phase 3 Subjects)

MedDRA System Organ Class MedDRA Preferred Term	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
Subjects with any AE	19 (23.8)	21 (10.1)	40 (13.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (1.3)	0	1 (0.3)
Febrile neutropenia	1 (1.3)	0	1 (0.3)
CARDIAC DISORDERS	1 (1.3)	2 (1.0)	3 (1.0)
Cardiac arrest	0	1 (0.5)	1 (0.3)
Cardiac failure congestive	1 (1.3)	0	1 (0.3)
Myocarditis	0	1 (0.5)	1 (0.3)
GASTROINTESTINAL DISORDERS	1 (1.3)	0	1 (0.3)
Gastrointestinal perforation	1 (1.3)	0	1 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (5.0)	1 (0.5)	5 (1.7)
General physical health deterioration	1 (1.3)	0	1 (0.3)
Multiple organ dysfunction syndrome	2 (2.5)	0	2 (0.7)
Sudden death	1 (1.3)	1 (0.5)	2 (0.7)
INFECTIONS AND INFESTATIONS	9 (11.3)	12 (5.8)	21 (7.3)
Pneumonia	6 (7.5)	4 (1.9)	10 (3.5)
Sepsis	2 (2.5)	5 (2.4)	7 (2.4)
Septic shock	1 (1.3)	3 (1.4)	4 (1.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (1.3)	0	1 (0.3)
Subdural haematoma	1 (1.3)	0	1 (0.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	2 (1.0)	2 (0.7)
Pancreatic carcinoma metastatic	0	1 (0.5)	1 (0.3)
Small cell lung cancer	0	1 (0.5)	1 (0.3)
NERVOUS SYSTEM DISORDERS	1 (1.3)	1 (0.5)	2 (0.7)
Cerebral haemorrhage	1 (1.3)	1 (0.5)	2 (0.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (1.3)	3 (1.4)	4 (1.4)
Pneumothorax	0	1 (0.5)	1 (0.3)
Respiratory distress	1 (1.3)	0	1 (0.3)
Respiratory failure	0	2 (1.0)	2 (0.7)

Other Serious adverse events (SAEs)

Serious AEs occurring in ≥2% of either the AML or the MDS/CMML patients in the integrated population are summarised in Table 36.

In subjects with AML (N=80), a total of 59 subjects (73.8%) had at least 1 SAE. The most commonly reported SAEs (>10% of subjects) were febrile neutropenia and pneumonia. *Treatment-related* SAEs occurred in 18 subjects (22.5%). Treatment-related SAEs were most commonly reported within SOC Blood and lymphatic system disorders (N=11) and Infections and infestations (N=6).

In subjects with MDS/CMML (N=208), a total of 151 subjects (72.6%) had at least 1 SAE. The most commonly reported SAEs (>10% of subjects) were febrile neutropenia, pneumonia, and sepsis. *Treatment-related* SAEs occurred in 35 subjects (16.8%). Treatment-related SAEs were most commonly reported within SOC Blood and lymphatic system disorders (N=24) and Infections and infestations (N=12).

Table 43. Serious Adverse Events Occurring in ≥2% of Subjects in Any Group in the Integrated Population (Phase 2 and Phase 3 Subjects)

MedDRA System Organ Class MedDRA Preferred Term	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
Subjects with any Serious Treatment-Emergent Adverse Event[a]	59 (73.8)	151 (72.6)	210 (72.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	25 (31.3)	71 (34.1)	96 (33.3)
Anaemia	3 (3.8)	3 (1.4)	6 (2.1)
Febrile neutropenia	20 (25.0)	62 (29.8)	82 (28.5)
CARDIAC DISORDERS	3 (3.8)	7 (3.4)	10 (3.5)
Cardiac failure	2 (2.5)	0	2 (0.7)
GASTROINTESTINAL DISORDERS	9 (11.3)	18 (8.7)	27 (9.4)
Gastrointestinal haemorrhage	1 (1.3)	5 (2.4)	6 (2.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (10.0)	16 (7.7)	24 (8.3)
Asthenia	2 (2.5)	5 (2.4)	7 (2.4)
Multiple organ dysfunction syndrome	2 (2.5)	1 (0.5)	3 (1.0)
Pyrexia	1 (1.3)	7 (3.4)	8 (2.8)
INFECTIONS AND INFESTATIONS	33 (41.3)	76 (36.5)	109 (37.8)
Cellulitis	3 (3.8)	11 (5.3)	14 (4.9)
Escherichia bacteraemia	2 (2.5)	0	2 (0.7)
Infection	6 (7.5)	0	6 (2.1)
Pneumonia	16 (20.0)	31 (14.9)	47 (16.3)
Sepsis	4 (5.0)	23 (11.1)	27 (9.4)
NERVOUS SYSTEM DISORDERS	3 (3.8)	11 (5.3)	14 (4.9)
Cerebral haemorrhage	2 (2.5)	1 (0.5)	3 (1.0)
Syncope	0	6 (2.9)	6 (2.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (5.0)	17 (8.2)	21 (7.3)
Dyspnoea	0	5 (2.4)	5 (1.7)
Pleural effusion	3 (3.8)	1 (0.5)	4 (1.4)

[a] Includes serious adverse events with outcome of death.

2.6.8.5. Adverse event of special interest

From data in the AML population (n=80), the Applicant discussed the following adverse events of special interest:

- *Myelosuppression events*

In the SOC Blood and Lymphatic System Disorders, all grades TEAEs were reported by 85.0% of subjects, and CTCAE Grade 3 or 4 events were reported by 72.5% of the subjects with AML. The reported TEAEs for myelosuppression events (all grades) are as follows: leukopenia (11.3%); neutropenia (26.3%), and thrombocytopenia (58.8%).

Febrile neutropenia is a distinct TEAE that was reported by 28.8% subjects; a majority of these events were CTCAE Grade 3 or 4 (26.3%).

Anaemia was a grouped term in 62.5% subjects, which included distinct terms of anaemia (60%) and haematotoxicity (7.5%). Most of these grouped anaemia events were CTCAE Grade 3 or 4. One subject (1.3%) with AML had a CTCAE Grade 5 event of febrile neutropenia, which was considered unrelated to ASTX727 by the investigator.

Serious AEs were reported by 31.3% of the 80 subjects with AML receiving ASTX727. The most commonly reported distinct SAEs (≥5% subjects) was febrile neutropenia (25.0%). Related SAEs in this SOC were reported by 13.8% of subjects, most commonly febrile neutropenia (11.3%).

- *Bleeding/haemorrhagic events*

Among subjects with AML (N=80), grouped haemorrhagic TEAEs reported by ≥5% of subjects are haematoma (12.5%), GI haemorrhage (8.8%), and epistaxis (6.3%). The majority of these TEAEs were low CTCAE grade. CTCAE Grade 3 or higher events are cerebral haemorrhage (1 subject) and gastrointestinal haemorrhage (3 subjects).

Haemorrhagic SAEs in subjects with AML are gastrointestinal haemorrhage, haemorrhoidal haemorrhage, subdural haematoma, and haematoma (1 subject each; 1.3%) and cerebral haemorrhage (2 subjects; 2.5%).

SAEs that were assessed as treatment-related were two cases of cerebral haemorrhage (2.5%).

- *Infection events*

Among subjects with AML (N=80), infection TEAEs (all grades) were reported by 70% of subjects, and CTCAE Grade 3 or 4 events were reported by 41.3% of subjects.

Serious AEs in the Infections and Infestations SOC were reported by 41.3% of the 80 subjects with AML receiving ASTX727. Related infection SAEs were reported for 6 subjects (7.5%): pneumonia (3 subjects, 3.8%) and anal abscess, enterococcal bacteraemia, Escherichia bacteraemia, Escherichia urinary tract infection, pseudomonal bacteraemia, and sinusitis aspergillus (1 subject each, 1.3%)

Reported CTCAE Grade 5 infection events in patients with AML were pneumonia (6 subjects, 7.5%), sepsis (1 subject, 1.3%), and septic shock (1 subject, 1.3%) as distinct ungrouped AEs. As described above, none of the fatal infections events in the AML population was assessed as related to ASTX727.

- *Gastrointestinal/hepatobiliary events*

Among subjects with AML (N=80), gastrointestinal TEAEs (all grades) were reported by 48.8% of subjects and CTCAE Grade 3 or 4 events were reported by 8.8% of subjects.

Grouped gastrointestinal TEAEs reported by ≥5% of subjects with AML are nausea (21.3%), constipation (18.8%), diarrhoea (13.8%), vomiting (12.5%), stomatitis (10.0%), and gastrointestinal disorder and oral discomfort (5.0% each). Most of these reported TEAEs were low grade (Grade ≤3). CTCAE Grade 3 events were gastritis, neutropenic colitis, and stomatitis (1 subject each, 1.3%).

There was one CTCAE Grade 5 event of gastrointestinal perforation in a subject with AML who received ASTX727; the event led to discontinuation of study drug, but was considered by the investigator to be unrelated to study drug.

TEAEs reported as related by 5% or more of the subjects are nausea (11.3%), constipation and diarrhoea (6.3% subjects each), and vomiting (5.0%).

Two SAEs of CTCAE Grade 2 constipation and CTCAE Grade 2 diarrhoea were reported by 1 subject each, both unrelated to study treatment.

In the Investigations SOC, a grouped TEAE of hepatic enzyme increased was reported for 10.0% of subjects with AML (all grades), and 2 subjects (2.5%) reported CTCAE Grade 3 or 4 events.

Among subjects with AML (N=80), 23.3% to 43.7% of the subjects experienced a worsening of any grade for all of the above laboratory abnormalities. These abnormalities were low grade with 2.8% and 2.7% subjects reporting CTCAE Grade 3 or 4 worsening for AST increased and ALT increased,

respectively. None of the subjects reported a worsening to CTCAE Grade 3 or 4 for alkaline phosphatase increased or bilirubin increased.

- *Cardiac events*

Among subjects with AML (N=80), cardiac TEAEs (all grades) were reported by 15.0% and CTCAE Grade 3 or 4 events were reported by 6.3% of subjects. Grouped TEAEs reported by 5% or more subjects are cardiac failure (8.8%) and arrhythmia (7.5%).

The majority of reported cardiac TEAEs were low grade, non-serious, and not assessed as related to study treatment. CTCAE Grade 3 or higher events are distinct ungrouped AEs of cardiac failure (2 subjects, 2.5%), cardiac failure congestive (3 subjects, 3.8%) and cardiogenic shock (1 subject, 1.3%).

Serious TEAEs were reported by 3 (3.8%) subjects with AML: CTCAE Grade 3 cardiac failure (2 subjects, 2.5%), CTCAE Grade 5 cardiac failure congestive, and CTCAE Grade 1 tachycardia (1 subject each, 1.3%). None of the reported SAEs were considered related to treatment by the investigator.

Two subjects had TEAEs of ECG QT prolonged, both of which were Grade 1 and 1 subject had CTCAE Grade 3 ejection fraction decreased. There was one related TEAE of CTCAE Grade 1 ECG QT prolonged.

Among all subjects with AML who received ASTX727 (N=80), QTcF change from baseline of >60 ms was noted in 4 (5.0%) subjects, and QTcF > 500 ms among those subjects with QTcF ≤500 ms at baseline was noted in 2 (2.5%) subjects. The incidence of QTcF prolongation was comparable between ASTX727 and IV decitabine.

- *Renal and urinary events*

Among subjects with AML (N=80), renal TEAEs (all grades) were reported by 18.8% and CTCAE Grade 3 or 4 events were reported by 7.5% of subjects. The most commonly reported grouped TEAE was acute kidney injury, reported by 11.3% (all grades) and 3.8% (CTCAE Grade 3 or 4).

The following laboratory parameters were reported very commonly as worsening of any grade: creatinine increased, hyponatremia, hyperkalaemia, hypokalaemia. All, except for hyperkalaemia, were reported commonly as worsening to CTCAE Grade 3 or 4.

- *Hypersensitivity events*

In the AML population (N=80), 1 subject (1.3%) reported a non-serious TEAE of hypersensitivity while on treatment with ASTX727 that was considered not related to study treatment by the investigator.

- *Skin events*

Among subjects with AML (N=80), a total of 13 (16.3%) reported TEAEs of skin and subcutaneous tissue disorders. These included the grouped terms blister, dermatitis, erythema nodosum, hyperhidrosis, petechiae and rash. All distinct skin and subcutaneous TEAEs were reported by ≤5% of subjects with AML. All of the reported events in the AML population were non-serious and exclusively low grade (Grade ≤3).

2.6.8.6. Thorough QT (TQT) study with cedazuridine

Study E7727-02 was a Phase 1 study to determine QTc Effects of cedazuridine.

The study was a randomised, double-blinded, double-dummy, placebo-controlled thorough QTc study with single therapeutic (100 mg) and supratherapeutic (400 mg) doses of cedazuridine in 32 healthy subjects. Subjects were randomised into one of 12 treatment sequences using a 3-Williams squares design. On each dosing day (Day 1 of each treatment period), subjects were administered 100 mg

cedazuridine, 400 mg cedazuridine, 400 mg moxifloxacin, or placebo with a 5-day washout between dosing.

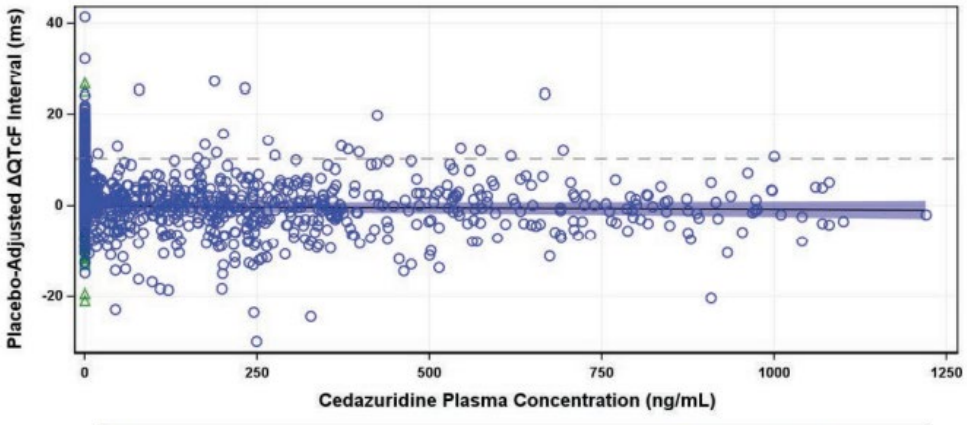
The results on QTc were evaluated using both concentration-QTc modelling and by-timepoint analysis, however, the primary analysis was based on concentration-QTc (C-QTc) modelling of the relationship between plasma concentrations of cedazuridine (and its metabolite cedazuridine-epimer) and change from baseline QTcF (ΔQTcF) with the intent to exclude an effect of placebo-corrected ΔQTcF (ΔΔQTcF) >10 msec at clinically relevant plasma levels.

Assay sensitivity was demonstrated by the positive control moxifloxacin.

The concentration-time profiles, and exposure values in terms of C_{max} and AUC, were similar for cedazuridine and the cedazuridine-epimer at both dose levels administered. The exposures increased in a less than dose-proportional manner after single doses of 100 mg and 400 mg cedazuridine (2.6-fold [C_{max}] and 2.7-fold [AUC] higher exposure at 400 mg compared to 100 mg).

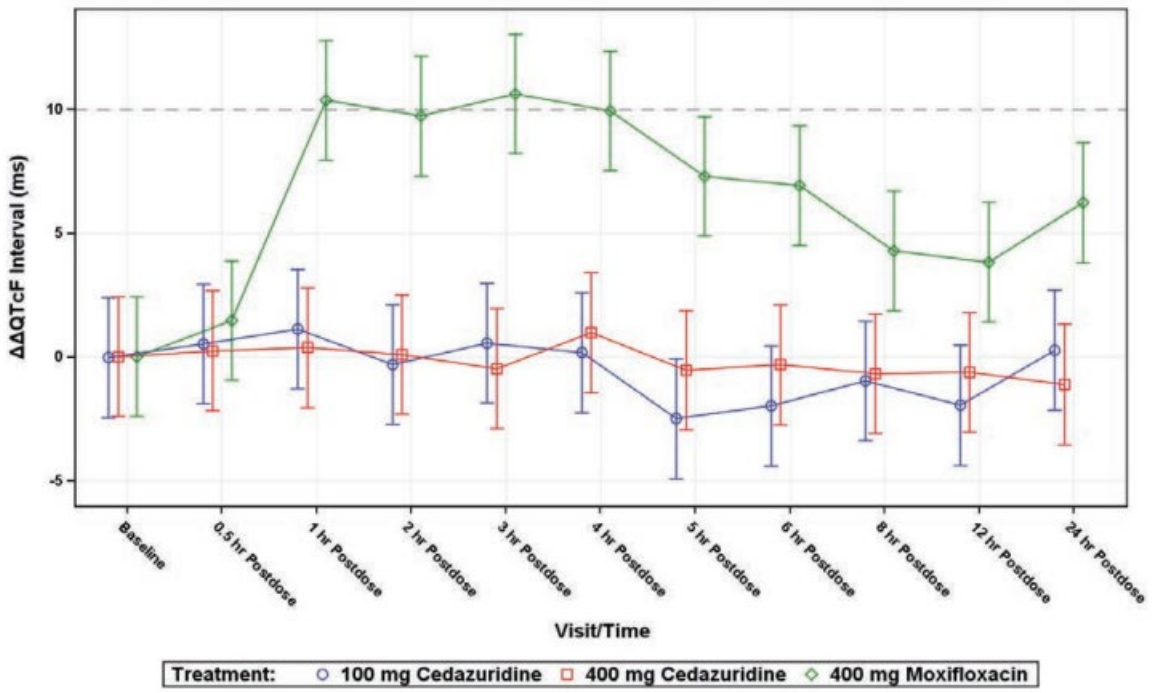
The model-estimated slope of cedazuridine plasma concentration in the concentration-QTc relationship was slightly negative and not statistically significant (-0.00068 ms per ng/mL [90% CI: -0.00 to 0.00]) with a not statistically significant treatment effect-specific intercept of -0.11280 ms (P=0.8844). The effect on ΔΔQTcF at the geometric mean peak cedazuridine concentration can be predicted to -0.21 ms (90% CI: -0.75 to 0.33) and -0.54 ms (90%CI: -1.93 to 0.84) for the 100 mg (309.1 ng/mL; cedazuridine-epimer: 327 ng/mL) and 400 mg (791.2 ng/mL; cedazuridine-epimer: 837 ng/mL) dose groups, respectively (Figure 13).

Figure 13. Scatter plot of observed cedazuridine plasma concentrations and estimated placebo-adjusted ΔQTcF (PK/QTc analysis set)



In the by-time point analysis on the QTcF interval, LS mean, SE, and 2-sided 90% CI of change-from baseline QTcF (ΔQTcF) and placebo-corrected ΔQTcF (ΔΔQTcF) were calculated for each active dose group and moxifloxacin group as well as on placebo for ΔQTcF at each post-dose time point (Figure 14).

Figure 14. Placebo-corrected change-from-baseline QTcF (ΔΔQTcF) across time points with statistical modelling (QT/QTc analysis set)



2.6.8.7. Laboratory findings

Worsening to any grade increased liver function markers, hyperglycaemia, hyponatremia and increased creatinine were very common. However, worsening of these parameters to grade 3 or 4 was generally seen in < 5% of AML patients, which is in the same range as that reported for Dacogen (EPAR).

Potential Hy's law cases

Laboratory data for the integrated population of Phase 2 and Phase 3 subjects were evaluated for potential Hy's Law cases by identifying subjects with ALT >3×ULN and total bilirubin ≥2×ULN with alkaline phosphatase <2×ULN.

None of the subjects in the AML population were potential Hy's Law cases.

Six subjects in the MDS population (3 subjects from the Phase 2 study for MDS and 3 subjects from the Phase 3 study for MDS) were identified as potential Hy's Law cases, but further medical review found it unlikely that these cases represent liver injury related to treatment, because all 6 cases occurred in the setting of fatal AEs (myocarditis, sepsis, or cardiac failure).

2.6.8.8. Safety in special populations

Age

The safety profile of IV decitabine in elderly patients can be considered well established.

In the AML study (ASTX727-02 EU; N=80), the majority of subjects were elderly with 49 subjects (61.3%) ≥75 years, 28 subjects (35.0%) ≥65 and <75 years of age, and 3 subjects (0.4%) younger

than 65 years of age. No differences in safety were observed between age groups ≥65 years; the group of subjects < 65 years of age is too small to draw any conclusions.

Table 44. safety profile in elderly patients

	Number (%) of Subjects								
	AML			MDS/CMML			All Subjects		
MedDRA SOC MedDRA Term	<65 (N=3)	≥65-<75 (N=28)	≥75 (N=49)	<65 (N=52)	≥65-<75 (N=82)	≥75 (N=74)	<65 (N=55)	≥65-<75 (N=110)	≥75 (N=123)
Number of subjects who reported at least one TEAE	3 (100)	28 (100)	49 (100)	52 (100)	82 (100)	74 (100)	55 (100)	110 (100)	123 (100)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (33.3)	21 (75.0)	46 (93.9)	49 (94.2)	68 (82.9)	65 (87.8)	50 (90.9)	89 (80.9)	111 (90.2)
Anaemia	0	16 (57.1)	32 (65.3)	26 (50.0)	37 (45.1)	34 (45.9)	26 (47.3)	53 (48.2)	66 (53.7)
Febrile neutropenia	0	10 (35.7)	13 (26.5)	23 (44.2)	23 (28.0)	23 (31.1)	23 (41.8)	33 (30.0)	36 (29.3)
Haematotoxicity	0	0	6 (12.2)	0	0	0	0	0	6 (4.9)
Leukopenia	1 (33.3)	2 (7.1)	6 (12.2)	17 (32.7)	22 (26.8)	21 (28.4)	18 (32.7)	24 (21.8)	27 (22.0)
Neutropenia	0	6 (21.4)	15 (30.6)	29 (55.8)	45 (54.9)	45 (60.8)	29 (52.7)	51 (46.4)	60 (48.8)
Thrombocytopenia	0	16 (57.1)	31 (63.3)	34 (65.4)	53 (64.6)	44 (59.5)	34 (61.8)	69 (62.7)	75 (61.0)
Thrombocytopenic purpura	1 (33.3)	0	0	0	0	0	1 (1.8)	0	0
CARDIAC DISORDERS	0	4 (14.3)	7 (14.3)	11 (21.2)	15 (18.3)	13 (17.6)	11 (20.0)	19 (17.3)	20 (16.3)
Cardiac failure	0	3 (10.7)	0	0	0	1 (1.4)	0	3 (2.7)	1 (0.8)
GASTROINTESTINAL DISORDERS	2 (66.7)	15 (53.6)	24 (49.0)	48 (92.3)	69 (84.1)	65 (87.8)	50 (90.9)	84 (76.4)	89 (72.4)
Abdominal pain	0	0	1 (2.0)	7 (13.5)	8 (9.8)	12 (16.2)	7 (12.7)	8 (7.3)	13 (10.6)
Constipation	0	7 (25.0)	8 (16.3)	25 (48.1)	35 (42.7)	33 (44.6)	25 (45.5)	42 (38.2)	41 (33.3)
Diarrhoea	1 (33.3)	4 (14.3)	6 (12.2)	23 (44.2)	31 (37.8)	27 (36.5)	24 (43.6)	35 (31.8)	33 (26.8)
Gingival swelling	1 (33.3)	0	0	0	1 (1.2)	0	1 (1.8)	1 (0.9)	0
Haemorrhoids	1 (33.3)	0	3 (6.1)	7 (13.5)	2 (2.4)	4 (5.4)	8 (14.5)	2 (1.8)	7 (5.7)
Nausea	0	6 (21.4)	11 (22.4)	35 (67.3)	33 (40.2)	24 (32.4)	35 (63.6)	39 (35.5)	35 (28.5)
Stomatitis	0	2 (7.1)	1 (2.0)	9 (17.3)	11 (13.4)	11 (14.9)	9 (16.4)	13 (11.8)	12 (9.8)
Tongue ulceration	1 (33.3)	2 (7.1)	1 (2.0)	0	1 (1.2)	0	1 (1.8)	3 (2.7)	1 (0.8)
Vomiting	1 (33.3)	4 (14.3)	5 (10.2)	18 (34.6)	10 (12.2)	9 (12.2)	19 (34.5)	14 (12.7)	14 (11.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (100)	14 (50.0)	29 (59.2)	36 (69.2)	62 (75.6)	55 (74.3)	39 (70.9)	76 (69.1)	84 (68.3)
Asthenia	1 (33.3)	5 (17.9)	11 (22.4)	11 (21.2)	16 (19.5)	21 (28.4)	12 (21.8)	21 (19.1)	32 (26.0)
Chills	0	0	2 (4.1)	4 (7.7)	10 (12.2)	5 (6.8)	4 (7.3)	10 (9.1)	7 (5.7)
Fatigue	0	0	7 (14.3)	21 (40.4)	40 (48.8)	42 (56.8)	21 (38.2)	40 (36.4)	49 (39.8)
Oedema peripheral	1 (33.3)	7 (25.0)	5 (10.2)	11 (21.2)	23 (28.0)	19 (25.7)	12 (21.8)	30 (27.3)	24 (19.5)
Peripheral swelling	1 (33.3)	0	0	3 (5.8)	4 (4.9)	2 (2.7)	4 (7.3)	4 (3.6)	2 (1.6)
Pyrexia	2 (66.7)	3 (10.7)	14 (28.6)	18 (34.6)	18 (22.0)	10 (13.5)	20 (36.4)	21 (19.1)	24 (19.5)

	Number (%) of Subjects								
	AML			MDS/CMML			All Subjects		
MedDRA SOC MedDRA Term	<65 (N=3)	≥65-<75 (N=28)	≥75 (N=49)	<65 (N=52)	≥65-<75 (N=82)	≥75 (N=74)	<65 (N=55)	≥65-<75 (N=110)	≥75 (N=123)
INFECTIONS AND INFESTATIONS	2 (66.7)	18 (64.3)	34 (69.4)	35 (67.3)	56 (68.3)	52 (70.3)	37 (67.3)	74 (67.3)	86 (69.9)
Cellulitis	1 (33.3)	1 (3.6)	5 (10.2)	5 (9.6)	8 (9.8)	13 (17.6)	6 (10.9)	9 (8.2)	18 (14.6)
Infection	0	2 (7.1)	5 (10.2)	0	0	0	0	2 (1.8)	5 (4.1)
Pneumonia	1 (33.3)	6 (21.4)	11 (22.4)	10 (19.2)	16 (19.5)	17 (23.0)	11 (20.0)	22 (20.0)	28 (22.8)
Sepsis	0	3 (10.7)	2 (4.1)	3 (5.8)	9 (11.0)	12 (16.2)	3 (5.5)	12 (10.9)	14 (11.4)
Upper respiratory tract infection	0	0	1 (2.0)	10 (19.2)	10 (12.2)	7 (9.5)	10 (18.2)	10 (9.1)	8 (6.5)
Urinary tract infection	0	4 (14.3)	4 (8.2)	4 (7.7)	9 (11.0)	11 (14.9)	4 (7.3)	13 (11.8)	15 (12.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (33.3)	3 (10.7)	9 (18.4)	18 (34.6)	34 (41.5)	38 (51.4)	19 (34.5)	37 (33.6)	47 (38.2)
Contusion	0	0	0	4 (7.7)	13 (15.9)	18 (24.3)	4 (7.3)	13 (11.8)	18 (14.6)
Fall	1 (33.3)	0	5 (10.2)	6 (11.5)	10 (12.2)	13 (17.6)	7 (12.7)	10 (9.1)	18 (14.6)
INVESTIGATIONS	1 (33.3)	11 (39.3)	12 (24.5)	23 (44.2)	37 (45.1)	37 (50.0)	24 (43.6)	48 (43.6)	49 (39.8)
Alanine aminotransferase increased	0	4 (14.3)	2 (4.1)	12 (23.1)	11 (13.4)	12 (16.2)	12 (21.8)	15 (13.6)	14 (11.4)
Aspartate aminotransferase increased	0	3 (10.7)	2 (4.1)	7 (13.5)	9 (11.0)	10 (13.5)	7 (12.7)	12 (10.9)	12 (9.8)
Blood bilirubin increased	0	0	0	7 (13.5)	6 (7.3)	6 (8.1)	7 (12.7)	6 (5.5)	6 (4.9)
Blood creatinine increased	1 (33.3)	2 (7.1)	2 (4.1)	2 (3.8)	12 (14.6)	15 (20.3)	3 (5.5)	14 (12.7)	17 (13.8)
C-reactive protein increased	0	3 (10.7)	1 (2.0)	0	0	0	0	3 (2.7)	1 (0.8)
Weight Decreased	0	0	4 (8.2)	4 (7.7)	8 (9.8)	10 (13.5)	4 (7.3)	8 (7.3)	14 (11.4)
METABOLISM AND NUTRITION DISORDERS	2 (66.7)	8 (28.6)	15 (30.6)	33 (63.5)	46 (56.1)	52 (70.3)	35 (63.6)	54 (49.1)	67 (54.5)
Decreased appetite	1 (33.3)	3 (10.7)	8 (16.3)	13 (25.0)	20 (24.4)	25 (33.8)	14 (25.5)	23 (20.9)	33 (26.8)
Hyperglycaemia	1 (33.3)	1 (3.6)	1 (2.0)	6 (11.5)	9 (11.0)	8 (10.8)	7 (12.7)	10 (9.1)	9 (7.3)
Hypoalbuminaemia	0	0	0	5 (9.6)	9 (11.0)	11 (14.9)	5 (9.1)	9 (8.2)	11 (8.9)
Hypocalcaemia	0	1 (3.6)	0	5 (9.6)	8 (9.8)	14 (18.9)	5 (9.1)	9 (8.2)	14 (11.4)
Hypokalaemia	0	5 (17.9)	7 (14.3)	9 (17.3)	15 (18.3)	13 (17.6)	9 (16.4)	20 (18.2)	20 (16.3)
Hypomagnesaemia	1 (33.3)	0	2 (4.1)	4 (7.7)	15 (18.3)	6 (8.1)	5 (9.1)	15 (13.6)	8 (6.5)
Hyponatraemia	1 (33.3)	0	1 (2.0)	7 (13.5)	9 (11.0)	7 (9.5)	8 (14.5)	9 (8.2)	8 (6.5)

	Number (%) of Subjects								
	AML			MDS/CMML			All Subjects		
MedDRA SOC MedDRA Term	<65 (N=3)	≥65-<75 (N=28)	≥75 (N=49)	<65 (N=52)	≥65-<75 (N=82)	≥75 (N=74)	<65 (N=55)	≥65-<75 (N=110)	≥75 (N=123)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (66.7)	4 (14.3)	13 (26.5)	31 (59.6)	50 (61.0)	50 (67.6)	33 (60.0)	54 (49.1)	63 (51.2)
Arthralgia	1 (33.3)	1 (3.6)	4 (8.2)	15 (28.8)	24 (29.3)	16 (21.6)	16 (29.1)	25 (22.7)	20 (16.3)
Back pain	1 (33.3)	3 (10.7)	2 (4.1)	13 (25.0)	11 (13.4)	17 (23.0)	14 (25.5)	14 (12.7)	19 (15.4)
Muscle spasms	0	0	0	5 (9.6)	9 (11.0)	3 (4.1)	5 (9.1)	9 (8.2)	3 (2.4)
Myalgia	0	0	1 (2.0)	7 (13.5)	13 (15.9)	11 (14.9)	7 (12.7)	13 (11.8)	12 (9.8)
Osteoarthritis	1 (33.3)	0	1 (2.0)	0	2 (2.4)	0	1 (1.8)	2 (1.8)	1 (0.8)
Pain in extremity	1 (33.3)	0	0	7 (13.5)	9 (11.0)	11 (14.9)	8 (14.5)	9 (8.2)	11 (8.9)
NERVOUS SYSTEM DISORDERS	1 (33.3)	4 (14.3)	11 (22.4)	36 (69.2)	47 (57.3)	47 (63.5)	37 (67.3)	51 (46.4)	58 (47.2)
Dizziness	1 (33.3)	0	5 (10.2)	12 (23.1)	29 (35.4)	29 (39.2)	13 (23.6)	29 (26.4)	34 (27.6)
Headache	0	1 (3.6)	1 (2.0)	26 (50.0)	22 (26.8)	15 (20.3)	26 (47.3)	23 (20.9)	16 (13.0)
Somnolence	1 (33.3)	0	0	0	0	0	1 (1.8)	0	0
PSYCHIATRIC DISORDERS	0	6 (21.4)	9 (18.4)	16 (30.8)	24 (29.3)	14 (18.9)	16 (29.1)	30 (27.3)	23 (18.7)
Anxiety	0	1 (3.6)	0	4 (7.7)	9 (11.0)	5 (6.8)	4 (7.3)	10 (9.1)	5 (4.1)
Insomnia	0	4 (14.3)	5 (10.2)	10 (19.2)	11 (13.4)	8 (10.8)	10 (18.2)	15 (13.6)	13 (10.6)
RENAL AND URINARY DISORDERS	0	6 (21.4)	6 (12.2)	14 (26.9)	14 (17.1)	18 (24.3)	14 (25.5)	20 (18.2)	24 (19.5)
Haematuria	0	0	1 (2.0)	6 (11.5)	4 (4.9)	4 (5.4)	6 (10.9)	4 (3.6)	5 (4.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (33.3)	10 (35.7)	13 (26.5)	35 (67.3)	60 (73.2)	55 (74.3)	36 (65.5)	70 (63.6)	68 (55.3)
Cough	0	1 (3.6)	4 (8.2)	13 (25.0)	24 (29.3)	21 (28.4)	13 (23.6)	25 (22.7)	25 (20.3)
Dyspnoea	0	1 (3.6)	4 (8.2)	13 (25.0)	22 (26.8)	31 (41.9)	13 (23.6)	23 (20.9)	35 (28.5)
Dyspnoea exertional	1 (33.3)	1 (3.6)	0	3 (5.8)	6 (7.3)	5 (6.8)	4 (7.3)	7 (6.4)	5 (4.1)
Epistaxis	0	2 (7.1)	3 (6.1)	7 (13.5)	7 (8.5)	13 (17.6)	7 (12.7)	9 (8.2)	16 (13.0)
Oropharyngeal pain	0	0	1 (2.0)	14 (26.9)	13 (15.9)	9 (12.2)	14 (25.5)	13 (11.8)	10 (8.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (33.3)	5 (17.9)	6 (12.2)	30 (57.7)	46 (56.1)	33 (44.6)	31 (56.4)	51 (46.4)	39 (31.7)
Blister	1 (33.3)	0	0	0	0	0	1 (1.8)	0	0
Erythema	1 (33.3)	0	1 (2.0)	4 (7.7)	4 (4.9)	3 (4.1)	5 (9.1)	4 (3.6)	4 (3.3)
Petechiae	0	1 (3.6)	1 (2.0)	6 (11.5)	5 (6.1)	6 (8.1)	6 (10.9)	6 (5.5)	7 (5.7)
Rash	0	1 (3.6)	0	3 (5.8)	10 (12.2)	6 (8.1)	3 (5.5)	11 (10.0)	6 (4.9)
Rash maculo-papular	0	1 (3.6)	1 (2.0)	6 (11.5)	6 (7.3)	11 (14.9)	6 (10.9)	7 (6.4)	12 (9.8)
Skin ulcer	1 (33.3)	0	0	0	0	0	1 (1.8)	0	0

	Number (%) of Subjects								
	AML			MDS/CMML			All Subjects		
MedDRA SOC MedDRA Term	<65 (N=3)	≥65-<75 (N=28)	≥75 (N=49)	<65 (N=52)	≥65-<75 (N=82)	≥75 (N=74)	<65 (N=55)	≥65-<75 (N=110)	≥75 (N=123)
VASCULAR DISORDERS	1 (33.3)	5 (17.9)	16 (32.7)	10 (19.2)	29 (35.4)	25 (33.8)	11 (20.0)	34 (30.9)	41 (33.3)
Haematoma	1 (33.3)	2 (7.1)	6 (12.2)	2 (3.8)	3 (3.7)	4 (5.4)	3 (5.5)	5 (4.5)	10 (8.1)
Hypertension	0	1 (3.6)	6 (12.2)	3 (5.8)	8 (9.8)	6 (8.1)	3 (5.5)	9 (8.2)	12 (9.8)
Hypotension	0	0	2 (4.1)	2 (3.8)	12 (14.6)	9 (12.2)	2 (3.6)	12 (10.9)	11 (8.9)

Sex

In the integrated population there were 95 females and 193 males. There were no obvious differences and, in general, the most frequently reported TEAEs (>20% of subjects) were the same in both groups (e.g., anaemia, thrombocytopenia, neutropenia, febrile neutropenia, pyrexia, and asthenia).

Race

The Applicant explains that although AE data by race were summarised for the integrated population as per the statistical analysis plan (SAP), collection of race and ethnicity data in certain countries in Europe (where the majority of sites were located in Study ASTX727-02 EU in subjects with AML) was prohibited. Therefore, the results of the analysis were deemed clinically irrelevant.

Renal impairment

The rates of reported anaemia, thrombocytopenia, neutropenia, and febrile neutropenia seemed to increase among subjects with AML as a function of renal dysfunction. However, among MDS subjects in a larger sample size (N=208), no significant increase in the same AEs was noted with worsening renal function.

The rate of reported neutropenia among both AML and MDS populations is comparable among subjects with normal and mild renal dysfunction; however, there is a 20% increase in reported neutropenia with worsening of renal function from normal to moderate. Despite this increased rate of neutropenia, there is no corresponding increase in the rate of pneumonia when comparing normal and moderate renal dysfunction reported among both AML and MDS populations.

Hepatic impairment

The reported rate of diarrhoea and constipation among both AML and MDS populations did not increase with worsening hepatic function. While there was an increase in reported nausea and vomiting when comparing subjects with normal hepatic function to mild hepatic dysfunction, none of the reported events were CTCAE Grade 3 or higher. Despite an increased rate of neutropenia among subjects with moderate hepatic dysfunction for both subpopulations, there is no corresponding increase in the rate of pneumonia when comparing normal and moderate hepatic dysfunction reported among both AML and MDS populations.

Body surface area

The rates of all of the reviewed TEAEs for both AML or MDS subjects were consistent across BSA quartiles. No apparent increase was evident with decrease of BSA. Similar results were observed for TEAEs CTCAE Grade 3 or higher.

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

Drug-drug interaction studies have not been conducted with cedazuridine or decitabine.

2.6.8.10. Discontinuation due to adverse events

Discontinuation due to adverse events

In subjects with AML (N=80), 11 subjects (13.8%) permanently discontinued treatment due to AEs. Discontinuation AEs reported for more than 1 subject were pneumonia (4 subjects; 5.0%) and asthenia (2 subjects; 2.5%). Three subjects with AML had discontinuation AEs considered related to treatment by the investigator: asthenia in 2 subjects (2.5%) and stomatitis in 1 subject (1.3%).

In subjects with MDS/CMML (N=208), a total of 13 subjects (6.3%) permanently discontinued treatment due to AEs. Discontinuation AEs reported for more than 1 subject were febrile neutropenia (2 subjects; 1.0%) and pneumonia (2 subjects; 1.0%). Four subjects with MDS/CMML had altogether six discontinuation AEs considered related to treatment by the investigator; the reactions were febrile neutropenia (2 subjects; 1.0%) and Pure red cell aplasia (1 subject), and hypersensitivity, cardiogenic shock and myocarditis (1 subject).

Dose modifications due to adverse events

In study ASTX727-02, it was important that subjects completed Cycle 1 and 2 (ASTX727 and IV decitabine in a cross-over fashion) in order to fulfil the primary objective of the study. If dose reductions were necessary during Cycle 1 and 2, subjects were not included in the primary pharmacokinetic evaluation.

From Cycle 3, dose reductions could be made by reducing the number of treatment days per cycle. According to protocol, dose reductions were to be considered if myelosuppression was suspected to be drug-related rather than disease-related. Dose delays (delaying the next cycle) to allow recovery of blood counts from drug-related myelosuppression were allowed at the discretion of the investigator.

In subjects with **AML** (N=80), drug interruptions and dose reductions due to a TEAE occurred in 47.5% of subjects. The most common AEs (≥3% of subjects) that resulted in drug interruption or dose reduction during treatment with ASTX727 were neutropenia (10 subjects; 12.5%), haematotoxicity (6 subjects; 7.5%), febrile neutropenia (4 subjects; 5.0%), pneumonia (4 subjects; 5.0%), and pleural effusion and thrombocytopenia (2 subjects each; 2.5%).

In subjects with **MDS/CMML** (N=208), drug interruptions and dose reductions due to a TEAE occurred in 104 subjects (50.0%). Also in this group, the most common reason was haematologic toxicity including febrile neutropenia, followed by infections (most common: pneumonia).

2.6.8.11. Post marketing experience

The most recent Development Safety Update Report (DSUR) for ASTX727 is based on a reporting period from 17 January 2021 to 16 January 2022. No new information from the postmarketing setting was obtained during the reporting period for ASTX727 that changes the benefit-risk profile of ASTX727.

2.6.8.12. Comparison of ASTX727 and IV decitabine

In study ASTX727-02 EU and ASTX727-02 NA (AML and MDS/CMML patients, respectively) ASTX727 and IV decitabine were administered in a crossover fashion in Cycle 1 and 2. Thus, half of the patients received ASTX727 and half of the patients received IV decitabine in the first two cycles. In the Clinical study reports, comparisons of AEs observed in Cycle 1 and 2 were presented for the two respective treatments. This comparison might, however, be somewhat confounded by carry-over effects from Cycle 1 to Cycle 2.

The overall rate of AEs, Grade ≥3 AEs and discontinuations due to AEs was similar for the two treatments during Cycle 1 and Cycle 2.

In both study populations, the rate of SAEs was higher after ASTX727 than after IV decitabine. SAEs were reported in 24% of AML patients after IV decitabine and 44% of AML patients after ASTX727 (Table). In MDS/CML patients, SAEs were reported in 18% of patients after IV decitabine and 31% after ASTX727 (Table). Confidence intervals for the rates of SAEs and treatment-related SAEs, were, however wide and largely overlapping (Table and Table).

For **AML** patients, treatment related SAEs were reported in 15.2% of patients after ASTX727 and 6.4% of patients after IV decitabine. The total number of related events were 17 and 5, respectively. The most commonly reported treatment-related SAEs after ASTX727 in Cycle 1 or 2 were febrile neutropenia (n=5), pneumonia, anaemia and cerebral haemorrhage (n=2 each).

For **MDS/CMML** patients, treatment related SAEs were reported in 8.5% of patients after ASTX727 and 3.0% of patients after IV decitabine. The difference in the number of related events was, however, smaller in the MDS/CMML study (14 vs. 10 events for ASTX727 and IV decitabine, respectively). The most commonly reported treatment-related SAEs after ASTX727 in Cycle 1 or 2 were febrile neutropenia (n=7) and sepsis (n=2).

*Table 45. Treatment-Emergent Serious Adverse Events in ≥2 Subjects in different cycles (Study ASTX727-02 EU; **AML**)*

	Number (%) of Subjects			
MedDRA Preferred Term[a]	**IV Decitabine Cycle 1 or 2 (N=78) n (%)**	**ASTX727 Cycle 1 or 2 (N=79) n (%)**	**ASTX727 Cycle ≥ 3 (N=60) n (%)**	**ASTX727 Total[b] (N=80) n (%)**
Total Number of TEAEs	24	49	60	127
Number of subjects who reported at least one TEAE	19 (24.4)	35 (44.3)	31 (51.7)	59 (73.8)
Febrile neutropenia	4 (5.1)	9 (11.4)	11 (18.3)	20 (25.0)
Pneumonia	4 (5.1)	9 (11.4)	7 (11.7)	16 (20.0)
Infection	1 (1.3)	2 (2.5)	3 (5.0)	6 (7.5)
Sepsis	1 (1.3)	0	3 (5.0)	4 (5.0)
Anaemia	0	3 (3.8)	0	3 (3.8)
Cellulitis	1 (1.3)	1 (1.3)	1 (1.7)	3 (3.8)
Pleural effusion	0	2 (2.5)	1 (1.7)	3 (3.8)
Asthenia	0	2 (2.5)	0	2 (2.5)
Cardiac failure	0	0	2 (3.3)	2 (2.5)
Cerebral haemorrhage	0	2 (2.5)	0	2 (2.5)
Escherichia bacteraemia	2 (2.6)	0	2 (3.3)	2 (2.5)
Multiple organ dysfunction syndrome	0	1 (1.3)	1 (1.7)	2 (2.5)
Acute kidney injury	1 (1.3)	1 (1.3)	0	1 (1.3)

*Table 46. Treatment-Emergent Serious Adverse Events in ≥2 Subjects in different cycles (Study ASTX727-02 NA; **MDS/CMML**)*

	Number (%) of Subjects			
MedDRA Preferred Term[a]	**IV Decitabine Cycle 1 or 2 (N=132)**	**ASTX727 Cycle 1 or 2 (N=130)**	**ASTX727 Cycles ≥3 (N=119)**	**ASTX727 Total[b] (N=130)**
Total Number of SAEs	38	51	57	108
Number of subjects reporting at least 1 SAE	24 (18.2)	40 (30.8)	30 (25.2)	54 (41.5)
Febrile neutropenia	7 (5.3)	16 (12.3)	12 (10.1)	23 (17.7)
Pneumonia	5 (3.8)	7 (5.4)	6 (5.0)	11 (8.5)
Sepsis/septic shock[c]	1 (0.8)	5 (3.8)	3 (2.5)	8 (6.2)
Anaemia	0	1 (0.8)	1 (0.8)	2 (1.5)
Cellulitis	2 (1.5)	2 (1.5)	0	2 (1.5)
Diverticulitis	0	1 (0.8)	1 (0.8)	2 (1.5)
Fall	0	2 (1.5)	0	2 (1.5)
Myocardial infarction	0	1 (0.8)	1 (0.8)	2 (1.5)
Pyrexia	1 (0.8)	2 (1.5)	0	2 (1.5)
Syncope	1 (0.8)	0	2 (1.7)	2 (1.5)

Denominators are numbers of subjects who received at least one dose of study treatment. SAEs are treatment emergent.
Subjects are counted only once for each AE PT.
[a] Coded using MedDRA v22.0.
[b] Data sorted in descending order of incidence for ASTX727 Total (all oral cycles). Includes AEs from all cycles in which subjects received ASTX727.
[c] Event occurred in Cycle 2 with ASTX727, but investigator assessed event as related to IV decitabine in Cycle 1.

Table 47. Summary of Subjects Experiencing Treatment Emergent Adverse Events with Confidence Interval (Study ASTX727-02 EU; AML)

	IV Decitabine Cycle 1 or 2 (N=78) n (%) (95% CI)	ASTX727 Cycle 1 or 2 (N=79) n (%) (95% CI)
All Adverse Events		
Subjects with any AE	70 (89.7%) (80.79, 95.47)	70 (88.6%) (79.47, 94.66)
Subjects with any AE Grade ≥3	43 (55.1%) (43.44, 66.41)	52 (65.8%) (54.29, 76.13)
Subjects with an AE Leading to Discontinuation of Treatment	1 (1.3 %) (0.03, 6.94)	5 (6.3 %) (2.09, 14.16)
Subjects with any SAE	19 (24.4%) (15.35, 35.40)	35 (44.3%) (33.12, 55.92)
Death	3 (3.8 %) (0.80, 10.83)	9 (11.4%) (5.34, 20.53)
Other Subjects with an SAE[a]	16 (20.5%) (12.20, 31.16)	26 (32.9%) (22.75, 44.40)
AE Related to Any Study Medication		
Subjects with any AE	31 (39.7%) (28.83, 51.46)	34 (43.0%) (31.94, 54.67)
Subjects with any AE Grade ≥3	17 (21.8%) (13.24, 32.59)	25 (31.6%) (21.63, 43.08)
Subjects with an AE Leading to Discontinuation of Treatment	0 (0.0, 4.62)	1 (1.3 %) (0.03, 6.85)
Subjects with any SAE	5 (6.4 %) (2.11, 14.33)	12 (15.2%) (8.10, 25.03)
Death	0 (0.0, 4.62)	1 (1.3 %) (0.03, 6.85)
Other Subjects with an SAE	5 (6.4 %) (2.11, 14.33)	11 (13.9%) (7.16, 23.55)

[a] Excluding subjects with SAEs that led to death.

Adverse events are coded using MedDRA v22.0 and graded using CTCAE v4.03

The 95% CI is Clopper-Pearson confidence interval.

Table 48. Summary of Subjects Experiencing Treatment Emergent Adverse Events with Confidence Interval (Study ASTX727-02 NA; MDS/CMML)

	IV Decitabine Cycle 1 or 2 (N=132) n (%) 95% CI	ASTX727 Cycle 1 or 2 (N=130) n (%) 95% CI
All Adverse Events		
Subjects with any AE	127 (96.2%)	127 (97.7%)
	(91.38, 98.76)	(93.40, 99.52)
Subjects with any AE Grade ≥ 3	89 (67.4%)	97 (74.6%)
	(58.73, 75.32)	(66.24, 81.84)
Subjects with an AE Leading to Discontinuation of Treatment	1 (0.8 %)	1 (0.8 %)
	(0.02, 4.15)	(0.02, 4.21)
Subjects with any SAE	24 (18.2%)	40 (30.8%)
	(12.01, 25.83)	(22.98, 39.46)
Death	2 (1.5 %)	1 (0.8 %)
	(0.18, 5.37)	(0.02, 4.21)
Other Subjects with an SAE[a]	22 (16.7%)	39 (30.0%)
	(10.75, 24.14)	(22.28, 38.66)
AE Related to Any Study Medication		
Subjects with any AE	86 (65.2%)	92 (70.8%)
	(56.37, 73.23)	(62.15, 78.41)
Subjects with any AE Grade ≥ 3	61 (46.2%)	68 (52.3%)
	(37.50, 55.10)	(43.37, 61.14)
Subjects with an AE Leading to Discontinuation of Treatment	1 (0.8 %)	1 (0.8 %)
	(0.02, 4.15)	(0.02, 4.21)
Subjects with any SAE	4 (3.0 %)	11 (8.5 %)
	(0.83, 7.58)	(4.30, 14.64)
Death	2 (1.5 %)	1 (0.8 %)
	(0.18, 5.37)	(0.02, 4.21)
Other Subjects with an SAE[a]	2 (1.5 %)	10 (7.7 %)
	(0.18, 5.37)	(3.75, 13.69)

[a] Excluding subjects with SAEs that led to death.
Adverse events are coded using MedDRA v22.0 and graded using CTCAE v4.03
The 95% CI is Clopper-Pearson confidence interval.

To avoid potential carry-over effects from Cycle 1 to Cycle 2, the Applicant presented a comparison of AEs in Cycle 1 only, after ASTX727 and IV decitabine, respectively. This comparison was only made for AML patients and is therefore hampered by the low number of subjects per group (n=42 for ASTX727 and n=38 for IV decitabine).

In general, the incidence of all adverse drug reactions is consistent between the 2 groups (Table 41).

The rates of nausea, diarrhoea and vomiting appeared higher after ASTX727 than after IV decitabine in Cycle 1 in patients with AML. When looking at the integrated population (Cycle 1 and Cycle 2 data), a similar trend was seen in AML patients but not in MDS/CMML patients, for which GI events were overall

more commonly reported than for AML patients. Gastrointestinal AEs of Grade ≥3 were reported in < 2% of patients after both treatments, in AML as well as MDS/CMML patients.

Fatigue was more commonly reported for ASTX727 than for IV decitabine in Cycle 1 in patients with AML. This was also seen in MDS/CMML patients when comparing both Cycle 1 and Cycle 2. The Applicant suggests fatigue may be secondary to other events, such as pneumonia, which was observed at a higher rate in the ASTX727 group, but considered a chance finding.

Table 49. A Cycle 1 Comparison of Adverse Drug Reactions for Subjects With AML (Grouped Event Terms)

	ASTX727 Cycle 1 (N=42)		**Intravenous Decitabine Cycle 1 (N=38)**	
	All CTCAE Grades	**CTCAE Grade 3-4**	**All CTCAE Grades**	**CTCAE Grade 3-4**
MedDRA SOC MedDRA Term	**n (%) Frequency**	**n (%) Frequency**	**n (%) Frequency**	**n (%) Frequency**
INFECTIONS AND INFESTATIONS				
Pneumonia	6 (14.3) Very Common	4 (9.5) Common	1 (2.6) Common	1 (2.6) Common
Sepsis	1 (2.4) Common	0 N/A	1 (2.6) Common	1 (2.6) Common
Cellulitis	4 (9.5) Common	2 (4.8) Common	1 (2.6) Common	1 (2.6) Common
Urinary tract infection	4 (9.5) Common	0 N/A	1 (2.6) Common	0 N/A
Viral infection	2 (4.8) Common	1 (2.4) Common	3 (7.9) Common	0 N/A
Bacteraemia	2 (4.8) Common	2 (4.8) Common	0 N/A	0 N/A
Polyserositis	1 (2.4) Common	1 (2.4) Common	0 N/A	0 N/A
Sinusitis fungal	0 N/A	0 N/A	0 N/A	0 N/A
Infection	1 (2.4) Common	1 (2.4) Common	3 (7.9) Common	1 (2.6) Common
Anorectal infection	0 N/A	0 N/A	0 N/A	0 N/A
Upper respiratory infection	0 N/A	0 N/A	3 (7.9) Common	0 N/A

	ASTX727 Cycle 1 (N=42)		Intravenous Decitabine Cycle 1 (N=38)	
	All CTCAE Grades	CTCAE Grade 3-4	All CTCAE Grades	CTCAE Grade 3-4
MedDRA SOC MedDRA Term	**n (%) Frequency**	**n (%) Frequency**	**n (%) Frequency**	**n (%) Frequency**
Oropharyngitis fungal	0 N/A	0 N/A	1 (2.6) Common	0 N/A
Periodontitis	2 (4.8) Common	0 N/A	1 (2.6) Common	0 N/A
Enterocolitis viral	1 (2.4) Common	0 N/A	0 N/A	0 N/A
Bacterial infection	0 N/A	0 N/A	0 N/A	0 N/A
Ear infection	0 N/A	0 N/A	0 N/A	0 N/A
Respiratory tract infection	0 N/A	0 N/A	0 N/A	0 N/A
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Leukopenia[b]	1 (2.4) Common	1 (2.4) Common	4 (10.5) Very Common	3 (7.9) Common
Thrombocytopenia[b]	15 (35.7) Very Common	13 (31.0) Very Common	21 (55.3) Very Common	17 (44.7) Very Common
Anaemia[b]	15 (35.7) Very Common	10 (23.8) Very Common	20 (52.6) Very Common	15 (39.5) Very Common
Neutropenia[b]	4 (9.5) Common	3 (7.1) Common	7 (18.4) Very Common	7 (18.4) Very Common
Febrile neutropenia	7 (16.7) Very Common	5 (11.9) Very Common	3 (7.9) Common	3 (7.9) Common
METABOLISM AND NUTRITION DISORDERS				
Hyperglycaemia[b]	0 N/A	0 N/A	0 N/A	0 N/A
NERVOUS SYSTEM DISORDERS				

	ASTX727 Cycle 1 (N=42)		Intravenous Decitabine Cycle 1 (N=38)	
	All CTCAE Grades	CTCAE Grade 3-4	All CTCAE Grades	CTCAE Grade 3-4
MedDRA SOC MedDRA Term	**n (%) Frequency**	**n (%) Frequency**	**n (%) Frequency**	**n (%) Frequency**
Cerebral haemorrhage	1 (2.4) Common	0 N/A	0 N/A	0 N/A
Cerebral Haematoma	0 N/A	0 N/A	0 N/A	0 N/A
Subdural haematoma	0 N/A	0 N/A	0 N/A	0 N/A
Dizziness	3 (7.1) Common	0 N/A	1 (2.6) Common	0 N/A
Headache	0 N/A	0 N/A	0 N/A	0 N/A
EYE DISORDERS				
Eye haemorrhage	1 (2.4) Common	0 N/A	1 (2.6) Common	0 N/A
VASCULAR DISORDERS				
Haematoma	3 (7.1) Common	0 N/A	2 (5.3) Common	0 N/A
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Pleural effusion	4 (9.5) Common	2 (4.8) Common	0 N/A	0 N/A
Hypoxia	0 N/A	0 N/A	0 N/A	0 N/A
Dyspnoea	1 (2.4) Common	0 N/A	2 (5.3) Common	0 N/A
Cough	1 (2.4) Common	0 N/A	0 N/A	0 N/A
Epistaxis	2 (4.8) Common	0 N/A	1 (2.6) Common	0 N/A
GASTROINTESTINAL DISORDERS				
Stomatitis	2 (4.8) Common	0 N/A	1 (2.6) Common	0 N/A

	ASTX727 Cycle 1 (N=42)		Intravenous Decitabine Cycle 1 (N=38)	
	All CTCAE Grades	CTCAE Grade 3-4	All CTCAE Grades	CTCAE Grade 3-4
MedDRA SOC MedDRA Term	**n (%) Frequency**	**n (%) Frequency**	**n (%) Frequency**	**n (%) Frequency**
Nausea	7 (16.7) Very Common	0 N/A	1 (2.6) Common	0 N/A
Diarrhoea	8 (19.0) Very Common	0 N/A	1 (2.6) Common	0 N/A
Vomiting	4 (9.5) Common	0 N/A	1 (2.6) Common	0 N/A
Gastrointestinal haemorrhage	1 (2.4) Common	1 (2.4) Common	2 (5.3) Common	0 N/A
Neutropenic colitis	0 N/A	0 N/A	0 N/A	0 N/A
Mouth haemorrhage	0 N/A	0 N/A	0 N/A	0 N/A
Oral discomfort	3 (7.1) Common	0 N/A	0 N/A	0 N/A
HEPATOBILIARY DISORDERS				
Hepatic enzyme increased	1 (2.4) Common	0 N/A	2 (5.3) Common	0 N/A
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Rash	0 N/A	0 N/A	1 (2.6) Common	0 N/A
Petechiae	1 (2.4) Common	0 N/A	0 N/A	0 N/A
RENAL AND URINARY DISORDERS				
Haematuria	0 N/A	0 N/A	0 N/A	0 N/A
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Pyrexia	4 (9.5) Common	0 N/A	4 (10.5) Very Common	0 N/A

	ASTX727 Cycle 1 (N=42)		Intravenous Decitabine Cycle 1 (N=38)	
	All CTCAE Grades	CTCAE Grade 3-4	All CTCAE Grades	CTCAE Grade 3-4
MedDRA SOC MedDRA Term	**n (%) Frequency**	**n (%) Frequency**	**n (%) Frequency**	**n (%) Frequency**
Fatigue	8 (19.0) Very Common	2 (4.8) Common	3 (7.9) Common	0 N/A

The Applicant also presented an indirect comparison of the safety data for ASTX727 (N=80 for AML and N=288 for the integrated population) with published data for Dacogen (N=293 for AML; EPAR, SmPC).

The frequencies for nearly all ADRs reported with Dacogen were comparable in rate and severity to the ASTX727 dataset among subjects with AML. The most frequently observed ADRs in subjects with AML in the Dacogen group were directly related to myelosuppression or its consequences of fever and infection. A similar pattern of frequently observed ADRs was noted among subjects with AML treated with ASTX727.

Furthermore, ADRs leading to dose delays were primarily due to myelosuppression or infection for both Dacogen and ASTX727.

The most common AEs leading to death in subjects with AML for both treatments were infection events.

When comparing ASTX727 and Dacogen in subjects with AML, there appears to be an isolated increase in anaemia reported with ASTX727 (60% vs. 38% [all grades] and 45% vs. 31% [CTCAE Grade 3 or 4]). This increase is not accompanied by a suppression of a similar magnitude among all other cell lines (neutrophils, platelets). This may be a consequence of differences in sample size (N=80 for ASTX727 vs. N=293 for Dacogen). However, anaemia and all other cytopenias were reported as occurring very commonly in both subjects treated with ASTX727 and historical control Dacogen.

The incidence of events reported in the GI SOC (diarrhoea, vomiting, nausea, and stomatitis) in subjects receiving ASTX727 is not worse compared with Dacogen.

2.6.9. Adverse Drug Reactions for the label

The Applicant proposes to base the ADR table in section 4.8 of the SmPC primarily on previous experience with Dacogen, but with frequencies estimated from the group of 80 AML patients included in study ASTX727-02 EU.

The following table is proposed for the SmPC, section 4.8:

Table 50. Adverse Drug Reactions for Subjects With AML (Including Distinct Terms and Grouped Event Terms)

MedDRA SOC	MedDRA Term [a]	AML (N=80)			
		All CTCAE Grades		CTCAE Grade 3-4	
		%	Frequency	%	Frequency
Infections and infestations	All other infections (viral, bacterial, fungal) [b]	50.0	Very common	25.0	Very common
	Pneumonia [c]	23.8	Very common	18.8	Very common
	Sepsis [d]	10.0	Very common	6.3	Common
	Urinary tract infection [e]	17.5	Very common	2.5	Common
	Sinusitis (including fungal [f] and bacterial [g])	2.5	Common	2.5	Common
Blood and lymphatic system disorders	Leukopenia [h]	81.3	Very common	67.5	Very common
	Thrombocytopenia [h,i]	73.8	Very common	67.5	Very common
	Anaemia [h]	67.5	Very common	60.0	Very common
	Neutropenia [h,j]	41.8	Very common	41.8	Very common
	Febrile neutropenia	28.8	Very common	26.3	Very common
	Pancytopenia [k]	Not known	Uncommon [k]	Not known	Uncommon [k]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Differentiation syndrome [l]	Not known	Not known	Not known	Not known
Metabolism and nutrition disorders	Hyperglycaemia [h,m]	61.1	Very common	4.2	Common
Nervous system disorders	Headache [n]	2.5	Common	Not known	Common [n]
Cardiac disorders	Cardiomyopathy [o]	Not known	Uncommon	Not known	Uncommon
	Epistaxis [n]	6.3	Common	Not known	Common [n]

Respiratory, thoracic and mediastinal disorders	Interstitial lung disease [l]	Not known	Not known	Not known	Not known
Gastrointestinal disorders	Stomatitis [p]	10.0	Very common	1.3	Common
	Nausea [q]	21.3	Very common	Not known	Uncommon [q]
	Diarrhoea [r]	13.8	Very common	Not known	Common [r]
	Vomiting [r]	12.5	Very common	Not known	Common [r]
	Neutropenic colitis [s]	1.3	Common	1.3	Common
Hepatobiliary disorders	Aspartate aminotransferase increased [h,t]	30.6	Very common	2.8	Common
	Alanine aminotransferase increased [h,u]	28.8	Very common	2.7	Common
	Alkaline phosphatase increased [h,v]	43.7	Very common	0	Not applicable
	Bilirubin increased [h,w,q]	23.3	Very common	Not known	Uncommon[f]
Skin and subcutaneous tissue disorders	Acute febrile neutrophilic dermatosis (Sweet's syndrome) [x]	Not known	Uncommon [x]	Not applicable [y]	Not applicable [y]
General disorders and administration site conditions	Pyrexia [z]	23.8	Very common	1.3	Common

[a] The corresponding frequency category for each adverse drug reaction is based on the CIOMS III convention

[b] Grouped terms include anal abscess, anorectal infection, bacteraemia, cellulitis, cellulitis staphylococcal, corona virus infection, coronavirus test positive, enterococcal bacteraemia, enterocolitis viral, erythema, Escherichia bacteraemia, folliculitis, furuncle, gingival swelling, herpes virus infection, infection, klebsiella bacteraemia, nasal congestion, nasopharyngitis, oral candidiasis, oral herpes, oropharyngeal candidiasis, otitis externa, periodontitis, pharyngitis, polyserositis, pseudomonal bacteraemia, staphylococcal bacteraemia, staphylococcal infection, streptococcal bacteraemia, respiratory tract infection, skin infection, tooth abscess, tooth infection, upper respiratory tract infection, varicella zoster virus infection

[c] Grouped terms include bronchitis, pneumonia

[d] Grouped terms include sepsis, septic shock, systemic candida, urosepsis

[e] Grouped terms include bacteriuria, cystitis, dysuria, Escherichia urinary tract infection, urinary tract infection, urinary tract infection enterococcal

[f] Grouped terms include sinusitis aspergillus, sinusitis fungal

[g] Sinusitis bacterial was not observed in the clinical trial with Inaqovi, however sinusitis (organism not specified) was observed in clinical trials with IV decitabine at a frequency of common (3%, 1%)

[h] Based on laboratory values

[i] Thrombocytopaenia may lead to bleeding and haemorrhagic reactions that may be fatal

[j] Neutrophils decreased (n=79)

[k] Pancytopenia, including fatal events, was not observed in the clinical trial with Inaqovi, however it was observed in clinical trials with IV decitabine at a frequency of uncommon (< 1%)

[l] Differentiation syndrome and interstitial lung disease were not observed in the clinical trial with Inaqovi, however they were observed in post-market setting with the use of IV decitabine

[m] Hyperglycemia (n=72)

[n] Headache and epistaxis Grade 3-4, were not observed in the clinical trial with Inaqovi, however they were observed in clinical trials with IV decitabine at a frequency of common (1% and 2%)

[o] Cardiomyopathy was not observed in the clinical trial with Inaqovi, however it was observed in clinical trials with IV decitabine at a frequency of uncommon (< 1%)

[p] Grouped terms include aphthous ulcer, glossitis, oral discomfort, oropharyngeal discomfort, oropharyngeal pain, stomatitis, tongue ulceration, toothache

[q] Nausea and bilirubin increased, Grade 3-4, were not observed in the clinical trial with Inaqovi, however it was observed in clinical trials with IV decitabine at a frequency of uncommon (< 1%)

[r] Diarrhoea and vomiting, Grade 3-4, were not observed in the clinical trial with Inaqovi, however they were observed in clinical trials with IV decitabine at a frequency of common (2% and 1%)

[s] Caecitis (including fatal events) was not observed in the clinical trial with Inaqovi, however they were observed in post-market setting with the use of IV decitabine

[t] Aspartate aminotransferase increased (n=72)

[u] Alanine aminotransferase increased (n=73)

[v] Alkaline phosphatase increased (n=71)

[w] Bilirubin increased (n=73)

[x] Acute febrile neutrophilic dermatosis was not observed in the clinical trial with Inaqovi, however it was observed in clinical trials with IV decitabine (all Grades) at a frequency of uncommon (< 1%)

[y] Not applicable (Grade 3-4): Adverse drug reaction has not been observed with either Inaqovi or IV decitabine in both clinical trials and post-market

[z] Grouped terms include chills and pyrexia

CTCAE= Common Terminology Criteria for Adverse Events

2.6.10. Discussion on clinical safety

This application concerns ASTX727, a fixed-dose combination (FDC) of a known substance, decitabine, and the cytidine deaminase (CDA) inhibitor cedazuridine, which is a new chemical entity (NCE). The application involves a new route of administration for decitabine.

The combination of decitabine and cedazuridine has been shown to increase systemic decitabine exposure (based on area under the curve; AUC) following oral administration relative to that observed with oral decitabine alone.

Decitabine is previously approved as an intravenous (IV) formulation, Dacogen, for the same indication as that proposed for Inaqovi. The systemic toxicity of decitabine in AML patients has, thus, been previously established in studies with IV decitabine. The systemic safety profile of decitabine administered as ASTX727 may therefore be supported by a pharmacokinetic (PK) bridge from IV decitabine, under the assumption that a similar systemic exposure (plasma AUC) to decitabine will lead to a similar systemic safety profile. This approach has been agreed by the CHMP in scientific advice procedures and results described above.

A safety assessment is still necessary in order to identify potential additional or different toxicity due to the oral administration of decitabine, e.g. local toxicity in the gastrointestinal (GI) tract, as well as the potential added toxicity from cedazuridine.

The safety assessment is primarily based on the integrated population from Study ASTX727-02 EU in AML patients (n=80) and from Study ASTX727-02 NA and study ASTX727-01B in MDS/CMML patients (n=208), in which the final dose of ASTX727 was administered, i.e. 35 mg decitabine + 100 mg cedazuridine for 5 consecutive days of each 28-day cycle.

The use of data from patients with MDS/CMML as well as AML to make an overall safety assessment is agreed, in order to increase the sample size. The differences in cytogenic profiles might not be expected to have a major impact on the safety profile and tolerability of ASTX727. However, as some AEs of decitabine might also be manifestations of the underlying disease, pooling of data from the AML and MDS/CMML studies may not be appropriate. Accordingly, in most analyses, the Applicant presented AML and MDS/CMML data separately. Further, the information in section 4.8 of the SmPC, on adverse drug reactions observed in the Inaqovi studies, is based on the AML population (n=80).

Among a total of median 6 cycles (AML) or 7-8 cycles (MDS/CMML), all patients in the integrated population received one cycle of IV decitabine in Cycle 1 or Cycle 2, in a cross-over fashion with ASTX727. The safety profile over the whole treatment period therefore reflects both treatments.

The Applicant also presented a direct comparison of AEs after ASTX727 and IV decitabine in Cycle 1 for AML patients and in Cycle 1 and Cycle 2 for the both AML and MDS/CMML patients. this analysis has several limitations: The study design, primarily aiming at comparing pharmacokinetics, was not optimised to detect treatment differences in safety. The data is based on only one cycle of each treatment. Further, the analysis of Cycle 1 only includes a limited number of patients, as it is based on only AML patients, and only half of the patients received either treatment in Cycle 1 (approximately 40 patients per treatment group). The comparison of AEs using data from both Cycle 1 and Cycle 2 might, on the other hand, be diluted by carry-over effects from Cycle 1 to Cycle 2 in terms of treatment-related AEs as well as AEs due to underlying disease or co-morbidities.

Adverse events (AEs)

In line with the demonstration of a similar exposure to decitabine after administration of ASTX727 and IV decitabine, the overall safety profile observed in the Phase 2/Phase 3 studies with ASTX727 in AML or MDS/CMML patients was similar to what has been previously reported for Dacogen and what could be expected in these patient populations. Thus, haematologic suppression and gastrointestinal (GI) disorders were very commonly reported, as were different types of infections. Haematological toxicity and infections were also the most commonly reported AEs of Grade 3 or higher. No new, important safety issues were identified that could be attributed to cedazuridine.

In a direct comparison of ASTX727 and IV decitabine in Cycle 1 and 2 of study ASTX727-02, where the two treatments were administered in a cross-over manner, the rate of serious adverse events (SAEs) was about twice as high after ASTX727 than after IV decitabine. This was seen also in terms of SAEs that were considered treatment-related by the investigator, although the latter might possibly, to same extent, be attributed to the open-label design of the study. For AML patients, but not for MDS/CMML patients, a similar imbalance was seen for fatal AEs. As discussed above, however, the study design was not optimised for comparing safety between the two treatments. With relatively small groups, and small numbers of SAEs and fatal AEs, the confidence intervals for the estimated rates of such events were wide and largely overlapping between groups.

Over the complete treatment period, SAEs (assessed as unrelated or related) were most commonly reported within SOCs Infections and infestations and Blood and lymphatic tissue disorders, followed by gastrointestinal disorders. During Cycle 1 and 2, when the comparison of treatments was made, the

most commonly reported PTs were febrile neutropenia, pneumonia and sepsis (observed after both treatments). Other SAEs reported during the first two cycles included cellulitis (3 cases each after ASTX727 and IV decitabine), asthenia (2 cases, for ASTX727 only), anaemia, multiple organ failure (one case for ASTX727), acute renal failure (one case each after ASTX727 and IV decitabine), cerebral haemorrhage (2 cases for ASTX727). There were 9 and 3 fatal AEs after ASTX727 and IV decitabine, respectively, during the first two cycles. Only one of these fatal AEs (cerebral haemorrhage, observed after ASTX727) was considered treatment-related. Other fatal AEs included pneumonia (n=2 per treatment) and septic shock (n=1 per treatment), multiple organ failure, febrile neutropenia, general physical health deterioration, respiratory distress and sudden death (n=1 each, all for ASTX727). The sudden death was reported as related to significant co-morbidity. The pattern of SAEs and fatal AEs may be considered as expected for the patient population and/or decitabine treatment, and it is acknowledged that most SAEs and fatal AEs were not considered treatment-related.

Considering the new, oral route of administration of decitabine, it is of particular interest to look at the GI adverse events for potential local toxicity. In AML patients (n=80), the rate of GI events indeed seemed higher after ASTX727 than after IV decitabine in Cycles 1 and 2. This trend was, however, not seen in the larger group of MDS/CMML patients. Further, the overall rate of GI events was not higher in the ASTX727 studies than what is reported in the Dacogen SmPC. The events were generally of Grade 1-2 in severity.

Importantly, the GI adverse events appear to have been tolerated in the ASTX727 studies, as they did not lead to dose modification or treatment discontinuations, except in one case of stomatitis. Thus, altogether, the potential difference between ASTX727 and IV decitabine in terms of reported GI events in the ASTX727 studies is not considered to negatively impact the B/R balance specific to oral decitabine in combination with cedazuridine, or to cancel the benefits of having an orally administered treatment option for these patients.

Gastrointestinal haemorrhage was reported in altogether 8.0% (Grade ≥3 in 2.7%) of the integrated population. Bleeding events were generally considered treatment-related, and due to thrombocytopenia. Such events have been reported also for Dacogen. The gastrointestinal haemorrhagic events reported for ASTX727 are not considered likely to be directly related to the local exposure to decitabine at oral administration, but rather to thrombocytopenia induced by the systemic exposure to decitabine.

Fatigue was more commonly reported for ASTX727 than for IV decitabine in Cycle 1 in patients with AML. This was also seen in MDS/CMML patients when comparing both Cycle 1 and Cycle 2. Fatigue was reported as reason for treatment discontinuation in altogether two patients (both with AML). Fatigue is not listed as ADR in the SmPC for Dacogen. The Applicant suggests that fatigue and some other ADRs observed in the ASTX727 studies but not listed for Dacogen (e.g. rash, pleural effusion, cough, hypoxia) are more likely secondary to other events, such as infections, than a direct effect of ASTX727 treatment.

Overall, the reasons for treatment discontinuation and dose modification do not lead to new concerns for ASTX727 in comparison with Dacogen.

Special populations

As expected for patients with AML and MDS/CMML, the majority of patients in the integrated safety population were elderly. The safety profile of decitabine in elderly patients can be considered well established, both in the ASTX727 studies and previously for Dacogen. There is no reason to expect a different safety profile for ASTX727 by age than for IV decitabine.

Decitabine is not eliminated unchanged in urine to any relevant extent. However, for cedazuridine, the renal route is a major elimination pathway. An increase in cedazuridine levels at decreased renal

function could theoretically lead to an increase in decitabine levels, if CDA inhibition increases. As expected for an elderly patient population, the ASTX727 integrated safety population included a relevant number of patients with mild renal impairment. It is agreed that no specific recommendations for patients with mild renal impairment are necessary, other than what is recommended for all patients (AE monitoring and dose adjustment). However, the number of patients with moderate renal impairment was low, and there were no patients with severe renal impairment.

In the proposed SmPC for Inaqovi, the normal starting dose is recommended for patients with moderate renal impairment but due to an increased risk for AEs, patients with moderate renal impairment should be monitored. Given the theoretical risk of increased CDA inhibition and thereby increased decitabine levels, this appears to be a reasonable recommendation. A warning has been introduced in Section 4.4 regarding patients with severe renal impairment, due to the lack of data in this patient group.

The number of patients with hepatic impairment was low, and it is difficult to draw conclusions on the risk for increased toxicity based on AE data only. Large effects of hepatic impairment on cedazuridine exposure are not expected as cedazuridine is not hepatically metabolised. Thus, there appears to be no theoretical reason to expect a different safety profile for ASTX727 in patients with hepatic impairment than for IV decitabine. Taking into account potential hepatotoxic effects of decitabine, recommendations for moderate to severe hepatic impairment have been introduced in the SmPC, in line with the Dacogen SmPC.

Cedazuridine

There is very little clinical data on the administration of cedazuridine alone. As described in the non-clinical assessment report, there were large margins between the No-effect level in toxicology studies and clinical exposure to cedazuridine.

Further, as discussed above, there were no new, unexpected findings in the ASTX727 studies compared with the known safety profile for Dacogen that could potentially be attributed to cedazuridine.

The impact of cedazuridine exposure on the QTc prolongation was studied in healthy subjects (Study E7727-02) with supratherapeutic doses 100 and 400 mg. The results showed a non-statistically significant treatment effect. The results (ΔΔQTcF) lie within the accepted ranges.

The concentration-QTc relationship has also been evaluated in patients (Study ASTX727-02). The analysis explored the relationship between the change from baseline in QTc interval and mean plasma concentrations of decitabine, cedazuridine, and cedazuridine-epimer. The linear regression showed that the slope of the relationship between the change from baseline of QTcF and cedazuridine and cetabine was very flat. The model predicted QTcF change at 3h in subjects treated with ASTX727 was 6.96 ms (-1.14-15.07) as a function of cedazuridine concentration and 5.33 ms (-2.11-12.76). In the case of patient treated with IV decitabine, the predicted QTcF change to day 3 at 1h was 1.98 (-4.25-8.02).In conclusion, cedazuridine is considered unlikely to relevantly affect the safety profile for ASTX727 compared with IV decitabine.

SmPC

The systemic safety profile of decitabine is assumed to be the same after administration of ASTX727 and Dacogen, given a similar systemic exposure. Potential differences in the safety profile between ASTX727 and Dacogen would therefore be expected to be due to either the new route of administration of decitabine (such as local GI toxicity) or to cedazuridine. The data presented, however, indicates no apparent differences between the safety profile for ASTX727 and that previously known for Dacogen, that could potentially be attributed to either the oral administration route of decitabine or to

cedazuridine. Accordingly, the Inaqovi SmPC includes largely the same safety information as the Dacogen SmPC (in sections 4.3, 4.4, 4.6, 4.7, 4.8, 4.9). The exception is information directly related to the IV formulation or route of administration, and information concerning the paediatric population, which has been deferred for Inaqovi.

The proposed SmPC section 4.2 includes recommendations for missed or vomited doses. These recommendations are in line with the study protocol recommendations and are considered appropriate.

2.6.11. Conclusions on the clinical safety

In line with the demonstration of a similar exposure to decitabine after administration of ASTX727 and IV decitabine, the overall safety profile observed for ASTX727 in AML and MDS/CMML patients, respectively, was similar to what has been previously reported for Dacogen and what could be expected in these patient populations. There were no new findings in the ASTX727 studies compared with the known safety profile for Dacogen that could possibly be attributed to cedazuridine or to the new, oral route of administration of decitabine. Thus, from a safety perspective, no objections to approval of Inaqovi have been identified.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 2.8-6 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])

2.7.2. Pharmacovigilance plan

No Additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 5.3-7 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		

Table 5.3-7 V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
• **Safety Concern**	• **Risk Minimisation Measures**	• **Pharmacovigilance Activities**
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
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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities:

Table 5.3-7 V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
• **Safety Concern**	• **Risk Minimisation Measures**	• **Pharmacovigilance Activities**
	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	• None
Use in severe cardiac disease (e.g., 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

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 06 July 2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Inaqovi (decitabine / cedazuridine) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication for ASTX727 is "Inaqovi as monotherapy is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy."

3.1.2. Available therapies and unmet medical need

Curative therapies, including intensive chemotherapy and allogeneic stem cell transplantation, are generally applicable to the minority of patients who are younger, while most older individuals exhibit poor prognosis and survival.

Patients not suitable for induction therapy (generally >65 years old and/or with significant co-morbidities) are often treated with HMAs administered parenterally which imposes a significant treatment burden. The HMAs decitabine (Dacogen) and azacitidine (Vidaza) are approved by the EMA for adult patients with AML who are not candidates for standard induction chemotherapy.

An orally available HMA would reduce the burden of chronic treatment for patients and their caregivers.

3.1.3. Main clinical studies

The primary data supporting the safety and efficacy for the AML indication are from the phase 3 study ASTX727-02 EU. This was a Phase 3 multicentre, randomised, open-label, 2-period, 2-sequence crossover study of oral ASTX727 versus IV decitabine.

Adult subjects with AML who were candidates to receive IV decitabine were randomised in a 1:1 ratio to receive the ASTX727 FDC tablet Daily×5 in Cycle 1, followed by IV decitabine 20 mg/m2 Daily×5 in Cycle 2, or the converse order. Eighty-nine subjects with AML were randomised and 87 were treated (80 of whom received at least 1 dose of ASTX727) as of the data cutoff date (10 September 2021).

The primary aim of the study was to demonstrate similar AUC for decitabine delivered through oral ASTX727 at the proposed dose as for IV decitabine at the approved dose, in the treatment of adult patients with AML.

Thus, the present application is based on a PK bridge to IV decitabine, assuming that previous efficacy and safety data for this dose and route of administration can be extrapolated to ASTX727 if the decitabine plasma exposure (total AUC over the 5-day cycle) is similar.

3.2. Favourable effects

The geometric mean ratio (GMR) of 5-day total decitabine AUC0-24hr between Inaqovi and IV decitabine was 99% for patients with MDS/CMML and 100% for patients with AML (90% confidence interval [CI] 93% - 106% and 91% - 109% for MDS/CMML and AML, respectively).

Thus, bioequivalence for 5-Day AUC_{0-24} between oral and IV decitabine was convincingly demonstrated. AUC_{0-24} for day 1 is lower for oral compared to IV treatment and C_{max} is also lower following oral treatment (22-28% lower on day 5). To support the assumption that Cmax differences do not matter, the applicant recorded the maximum percent LINE-1 demethylation in peripheral blood. This was comparable between Inaqovi and IV decitabine in the Phase 3 Study ASTX727-02 in AML as well as MDS/CMML patients.

The complete response (CR) rate in patients treated sequentially with Inaqovi and IV decitabine (with either then one or the other given first) was 21% [13.4, 31.3]. The duration of CR was 5.8 months [3.3, NE]. These figures are roughly similar to what was historically seen with IV decitabine alone

3.3. Uncertainties and limitations about favourable effects

Inaqovi is given as a flat dose (35 mg decitabine) while IV-decitabine is given as a body-surface adjusted dose (20 mg/m^2). There is a trend of decreased decitabine 5-day AUC_{0-24} with increasing weight or BSA with oral decitabine treatment, but this is not considered to be clinically relevant.

Cmax is not bioequivalent, and as anticipated somewhat higher with IV decitabine administration. However, theoretical considerations on the role of AUC versus plasma Cmax, as well as the impact on LINE-1 demethylation, support that this would not impact the efficacy of Inaqovi relative to IV decitabine.

Since all patients in the pivotal trial received one cycle of IV decitabine (cycle 1 or 2), the CR rate do not completely isolate the effect of Inaqovi. Moreover, the pivotal trial is essentially a single arm trial with a nested cross-over of two decitabine formulations. Single arm trials do not isolate the effect of the test agent on time dependent endpoints such as PFS and OS.

3.4. Unfavourable effects

The safety assessment is primarily based on the integrated population from Study ASTX727-02 EU in AML patients (n=80) and from Study ASTX727-02 NA and study ASTX727-01B in MDS/CMML patients (n=208).

The overall safety profile observed in the Phase 2/Phase 3 studies with ASTX727 in AML or MDS/CMML patients was similar to what has been previously reported for Dacogen and what could be expected in these patient populations. Thus, haematologic suppression and gastrointestinal (GI) disorders were very commonly reported, as were different types of infections. Haematological toxicity and infections were also the most commonly reported adverse events (AEs) of Grade 3 or higher.

Considering the new, oral route of administration of decitabine the overall rate of GI events was not higher in the ASTX727 studies than what is reported in the Dacogen SmPC. The events were generally of Grade 1-2 in severity and did not lead to dose modification or treatment discontinuation.

A direct safety comparison with decitabine IV is issued from data of the Cycle 1 in the cross-over study ASTX727-02 EU (N=42 for ASTX727 and 38 for IV decitabine). In general, the incidence of all ADRs is consistent between the 2 groups, but incidence of pneumonia, cellulitis, urinary tract infection, bacteraemia, polyserositis, periodontitis, pleural effusion and gastrointestinal symptoms (nausea, diarrhoea, vomiting) was higher in the ASTX727 group while cytopenias were higher in the IV decitabine group (except from febrile neutropenia). The comparison is, however, based on a very limited number of subjects and should be interpreted with caution. The potential difference between ASTX727 and IV decitabine in terms of these reported events is not considered to outweigh the benefits of having an orally administered treatment option for these patients.

In a thorough QT study with cedazuridine in healthy volunteers, no clinically relevant effects of single doses of 100 mg or 400 mg (supratherapeutic dose) cedazuridine on studied ECG parameters were observed. There were also no apparent differences in QTcF changes after administration of ASTX727 and IV decitabine, respectively, in Studies ASTX727-01B and ASTX727-02 (EU, NA).

Overall, the safety profile of Inaqovi is globally in accordance with what could be expected from a cytotoxic compound in such a setting. Most common adverse events are already known for decitabine IV and manageable. Decitabine in ASTX727 has known risks of cytotoxicity, mainly haematologic toxicity (myelosuppression) and infection consequences due to neutropenia. ASTX727 also contains a new chemical entity, the CDA inhibitor cedazuridine, which has not shown additional risks.

3.5. Uncertainties and limitations about unfavourable effects

The key uncertainty is based on the limits of the size of the safety database for new chemical entity cedazuridine, whereby rare side effects may remain unidentified. There are no signals from non-clinical studies with cedazuridine alone used in higher doses than the one clinically proposed that warrants further clinical investigation. Routine pharmacovigilance is considered sufficient to capture signal of eventual rare side effects.

3.6. Effects Table

Table 51. Effects Table for Inaqovi (ASTX727) in the treatment of AML (data cut-off: 10 September 2021)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects (in ITT population N=89)						
Complete Response		% [95% CI]	21 [13.4, 31.3]	N/A	Secondary endpoint Descriptive	
Median Duration of CR*	* From start of CR until relapse or death	months [95% CI]	5.8 [3.3, NE]	N/A	Secondary endpoint Descriptive	
Median Time to CR		months [range]	3.0 [1.8, 7.4]	N/A	Secondary endpoint Descriptive	
Overall Response †	† OR included patients with a best response of CR, CRi, and PR	% [95% CI]	32 [22.0, 42.2]	N/A	Secondary endpoint Descriptive	

Unfavourable Effects						
Effect	**Description**	**Subjects with AE (%)**	**Treatment**	**Control**	**Uncertainties/ Strength of evidence**	**References**
Haematologic toxicity		85.0%	ASTX727 (35 mg decitabine + 100 mg cedazuridine) x 5 days per 28-day cycle + one cycle of IV decitabine 20 mg/m^2 x 5 days	N/A	Small dataset (n=80) All subjects received one cycle of IV decitabine (20 mg/m^2 x 5 days) of a total median of 6 cycles No control arm	Study ASTX727-02 EU
Infections		67.5%	"	"	"	"
Gastrointestinal disorders		51.3%	"	"	"	"

Treatment-related Grade ≥3 AEs	Treatment-relatedness as assessed by investigator	47.5%	"	"	"	"
Treatment-related SAEs	Treatment-relatedness as assessed by investigator	22.5%	"	"	"	"
Discon-tinuation due to treatment-related AE	Treatment-relatedness as assessed by investigator	3.8%	"	"	"	"
Fatal treatment-related AE	Treatment-relatedness as assessed by investigator	1.3% (1 sub-ject)	"	"	"	"

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Since AUC over one treatment cycle (5 consecutive treatment days per 28-day cycle) is similar for oral decitabine (35 mg decitabine in combination with 100 mg cedazuridine) and for decitabine given IV at the recommended dose (20 mg/m^2 per day for 5 consecutive days per 28-day cycle), it can be inferred that the efficacy of ASTX727 at the proposed dose is similar to that of IV decitabine at the approved dose, in the treatment of adult patients with AML.

The overall safety profile observed for ASTX727 in AML and MDS/CMML patients, respectively, was manageable, acceptable, and roughly similar to what has been previously reported for Dacogen in the relevant patient populations. There were no new findings in the ASTX727 studies compared with the known safety profile for Dacogen that could be attributed to cedazuridine or to the new, oral route of administration of decitabine.

3.7.2. Balance of benefits and risks

The benefit/risk balance for ASTX727 (Inaqovi) administered orally at the proposed dose, i.e. 35 mg decitabine + 100 mg cedazuridine per day, for 5 consecutive days per 28-day cycle) is therefore supported to be the same as for IV decitabine, administered as 20 mg/m^2 per day, for 5 consecutive days per 28-day cycle and previously been deemed positive by the CHMP.

The final indication for Inaqovi is acceptable.

3.8. Conclusions

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

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Inaqovi is not similar to Dacogen, Mylotarg, Xospata, Daurismo, Vyxeos liposomal, Rydapt and Tibsovo within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

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

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.

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

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

New Active Substance Status

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