23 April 2026
EMADOC-1700519818-3144762
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inaqovi

International non-proprietary name: Decitabine / Cedazuridine

Procedure No. EMA/VR/0000304730

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AML	acute myeloid leukemia
ASTX727	oral decitabine and cedazuridine, INQOVI, INAQOVI
AUC	area under the curve
AUC_{0-24}	area under the curve from time zero to 24 hours post-dose
BCL-2	B-cell lymphoma 2
BIM	Bcl-2 interacting mediator
BLQ	Below the Limit of Quantification
CDA	cytidine deaminase
CI	confidence interval
CMML	chronic myelomonocytic leukemia
CR	complete response
CRh	complete response with partial hematologic recovery
CRi	complete response with incomplete hematologic recovery
CSR	clinical study report
CRCLN	Creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
DoR	duration of response
DNMTi	deoxyribonucleic acid methyltransferase inhibitor
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDC	fixed-dose combination
HMA	hypomethylating agent
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
INQOVI	oral decitabine and cedazuridine, ASTX727, INAQOVI
IRC	Independent Review Committee

IV	Intravenous
KM	Kaplan-Meier
LDAC	low-dose cytarabine
LSM	Least Square Means
MDS	Myelodysplastic Syndromes
mOS	median overall survival
NCCN	National Comprehensive Cancer Network
NE	not evaluable
OBS	observations
OS	overall survival
PBT	Persistent, Bioaccumulative, and Toxic
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
SAE	serious adverse event
SC	Subcutaneous
SCE	Summary of Efficacy
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SOC	standard of care
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
US	United States
USPI	United States Prescribing Information

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Otsuka Pharmaceutical Netherlands B.V. submitted to the European Medicines Agency on 10 October 2025 an application for a variation.

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy for INAQOVI in combination with venetoclax, based on interim results from study ASTX727-07; this is a single-arm, open-label pharmacokinetic, safety, and efficacy study of ASTX727(INAQOVI) in combination with venetoclax in adult patients with acute myeloid leukemia; as a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.3 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and bring editorial changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) EMA/PE/0000246985 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/PE/0000246985 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received scientific advice from the CHMP on 24 February 2022 (EMA/SA/0000073001). The scientific advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	10 October 2025
Start of procedure	1 November 2025
CHMP Rapporteur's preliminary assessment report circulated on	19 December 2025
PRAC RMP advice and assessment overview adopted by PRAC on	15 January 2026
CHMP Rapporteur's updated assessment report circulated on	22 January 2026
Request for supplementary information and extension of timetable adopted by the CHMP on	29 January 2026
MAH's responses submitted to the CHMP on	19 February 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	24 March 2026
PRAC RMP advice and assessment overview adopted by PRAC on	10 April 2026
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	16 April 2026
CHMP opinion	23 April 2026
The CHMP adopted a report on similarity of Inaqovi with Mylotarg, Xospata, Daurismo, Vyxeos liposomal, Rydapt and Tibsovo on	23 April 2026
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Inaqovi in comparison with existing therapies on	23 April 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

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

Claimed therapeutic indication

The proposed indication is:

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

Epidemiology

AML is the most common form of acute leukaemia in adults, with incidence increasing with age. The incidence of AML is increasing globally. Across western, central and eastern Europe the age-standardised incidence rate ranges from 1.43 to 2.79 cases per 100,000 in 2021 (Zhou 2024).

AML has the worst survival outcomes among leukaemias, with a 5-year survival of 24% (Shallis 2019).

The median age at diagnosis is 67 years. The incidence of AML is higher in males than in females.

Biologic features and aetiology

With advanced age, the relative incidence of AML with recurrent genetic abnormalities decreases, while the relative incidence of other AML categories (such as AML with myelodysplasia-related changes) or therapy related AML increases with age (ESMO Guideline 2020).

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. The effects of uncontrolled, exaggerated growth and accumulation of blasts that fail to function as normal blood cells, and the subsequent 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).

Bone marrow and blood samples are obtained for diagnosis, using immunophenotyping, cytogenetics and other molecular studies.

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).

Management

Curative therapies, including intensive chemotherapy and allogeneic stem cell transplantation, are generally applicable to the minority of AML patients who are younger.

For patients not suitable for intensive induction therapy (usually >65 years old and/or with significant co-morbidities), current recommended therapies often consist of a parenteral hypomethylating agent (HMA) combined with venetoclax (NCCN Guideline 2025, European LeukemiaNet ELN recommendations 2022, ESMO Guidelines 2020).

The indication "*Venclyxto in combination with a hypomethylating agent* (which includes decitabine) *is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy*", was approved in EU in 2021.

Furthermore, monotherapy treatments with the HMAs azacitidine (Vidaza) and decitabine (Dacogen) are approved in EU for adult patients with AML who are ineligible for standard induction chemotherapy. Both products are administered parenterally and require patients to attend hospital for treatment. Azacitidine is given subcutaneously and decitabine is given intravenously.

In addition, the tablet Inaqovi for oral use was approved as monotherapy for the treatment of adult patients with newly diagnosed AML who are ineligible for standard induction chemotherapy in 2023 (Inaqovi SmPC).

Other EU approved products for newly diagnosed AML patients not suitable for intensive induction therapy are the Hedgehog inhibitor glasdegib in combination with low-dose cytarabine, and the IDH1 inhibitor ivosidenib in combination with azacitidine.

Currently, there are no all-oral combination regimens approved in EU for the patients with AML who are not able to receive intensive induction therapy. An orally available combination of HMA Inaqovi and venetoclax would reduce the burden of chronic treatment for patients and their caregivers.

2.1.2. About the product

Inaqovi (ASTX727(INAQOVI)) is a fixed-dose combination tablet for oral administration, containing 35 mg decitabine and 100 mg cedazuridine.

Decitabine is a HMA. Hypomethylation of DNA may restore normal function to genes that are critical for the control of cellular differentiation and proliferation.

Cedazuridine (E7727), is a cytidine deaminase (CDA) 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.

Decitabine was initially approved for intravenous administration at a dose of 20 mg/m2 by intravenous infusion over 1 hour repeated daily for 5 consecutive days (i.e., a total of 5 doses per 28-day cycle).

Monotherapy with Inaqovi was approved in EU 2023, primarily based on comparable AUC of oral decitabine in combination with cedazuridine versus intravenous decitabine at the recommended dose, together with supportive single arm trial data showing efficacy and safety outcomes that were broadly consistent with those historically observed for IV decitabine alone in relevant patient populations.

The currently approved indication for Inaqovi is:

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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH sought EU scientific advice, EMA/SA/0000073001 in February 2022 regarding the clinical development plan for the Inaqovi in combination with venetoclax for the treatment of AML. The design of the single-arm Study ASTX727-07 evaluating AUC and Cmax of venetoclax with or without Inaqovi, PK of Inaqovi with venetoclax, and safety/efficacy endpoints in AML patients ineligible for intensive chemotherapy was discussed.

In relation to the proposed indication, i.e., the combination of Inaqovi plus venetoclax in AML in patients who are ineligible for intensive chemotherapy, the CHMP considered that the proposed PK endpoints were acceptable and that this single-arm study ASTX727-07 is an alternative to a direct classical parallel or cross-over PK comparison of two therapeutic regimens using the same active compounds.

The CHMP concluded that the overall clinical development plan was sufficient to support a benefit/risk assessment for the Type II extension of indication variation provided that the efficacy of Inaqovi + venetoclax is in line with the previous experience with decitabine + venetoclax combination therapy, with no new major tolerability findings.

Pre-submission interaction with the Rapporteur team

The MAH met with the Rapporteur team on September 10, 2025, and presented the topline data package of the clinical development plan agreed during scientific advice, EMA/SA/0000073001 to support the proposed extension of indication.

The Rapporteur agreed that the planned data package would allow an assessment of the proposed indication, with focus on the endpoints aiming to demonstrate pharmacokinetic aspects. In accordance with the centralised advice from 2022, it was also pointed out that efficacy results would be expected to be in line with results obtained in prior studies of hypomethylating agents in combination with venetoclax, without any new major safety concerns.

2.1.4. General comments on compliance with GCP

According to the MAH, study ASTX727-07 was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) Guidelines and applicable regulatory requirements.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

The present type II variation concerns an extension of indication to include treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy for INAQOVI in combination with venetoclax.

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

Inaqovi was previously approved for treatment of AML which is a rare condition in the EU. Inaqovi was therefore recommended orphan drug designation by the Commjttee for Orphan Medicinal Products (COMP) stating that AML was estimated to be affecting approximately 1.7 in 10,000 persons in the EU.

As the prevalence of AML is still applicable to the extension of indication, the refinement of the predicted surface water concentration (PEC_{SW}) based on prevalence of AML still applies.

Cedazuridine (CAS: 1141397-80-9) 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 prevalence (according to COMP). This is just below the 0.01 ug/L cut-off value.

Decitabine (CAS: 2353 -33-5) 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 prevalence (according to COMP) to 0.00053 µg/L.

Table 1. 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 (prevalence)	0.0094	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

Table 2. 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 (prevalence)	0.00053	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

In conclusion Cedazuridine 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 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.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application does not lead to a significant increase in environmental exposure further to the use of cedazuridine and decitabine.

Considering the above data, cedazuridine and decitabine are not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH 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

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/Safety/ Efficacy	ASTX727-07 5.3.5.2	**Phase 1**: Primary: DDI (PK) Secondary: DDI (PK), safety, clinical response, preliminary efficacy, PK	Phase 1-2, open-label, non-randomised study	ASTX727 FDC tablet (35 mg decitabine and 100 mg cedazuridine) PO Daily×5 plus venetoclax tablet PO: Cycle 1: 100 mg on Day 1, 200 mg on Day 2, and then 400 mg Days 3-28 Cycles ≥2: 400 mg Days 1-28	30	Adults (≥18 yrs) AML	Continuous	Full CSR[d] One patient ongoing treatment[d]
PK/Safety/ Efficacy	ASTX727-07 5.3.5.2	**Phase 2 Part A**: Co-primary: Clinical response, DDI (PK) Secondary: Safety, DDI (PK), composite clinical response, preliminary efficacy, PK	Phase 1-2, open-label, non-randomised study	ASTX727 FDC tablet (35 mg decitabine and 100 mg cedazuridine) PO Daily×5 plus venetoclax tablet PO: Cycle 1: 100 mg on Day 1, 200 mg on Day 2, and then 400 mg Days 3-28 Cycles ≥2: 400 mg Days 1-28	58	Adults (≥18 yrs) AML	Continuous	Full CSR[d] 9 patients ongoing treatment[d]
PK/Safety/ Efficacy	ASTX727-07 5.3.5.2	**Phase 2 Part B**: Primary: Clinical response Secondary: Safety, DDI (PK), composite clinical response, duration of response, PK	Phase 1-2, open-label, non-randomised study	ASTX727 FDC tablet (35 mg decitabine and 100 mg cedazuridine) PO Daily×5 plus venetoclax tablet PO: Cycle 1: 100 mg on Day 1, 200 mg on Day 2, and then 400 mg Days 3-28 Cycles ≥2: 400 mg Days 1-28	101	Adults (≥18 yrs) AML	Continuous	Full CSR[d] 40 patients ongoing treatment[d]

2.3.2. Pharmacokinetics

Exposure data on decitabine and cedazuridine from the clinical study ASTX727-07, submitted in this type II variation on the combination of Inaqovi with venetoclax, were analysed with non-compartmental analysis (NCA). Additionally, population pharmacokinetic (popPK) analyses were performed to quantifying covariate effects, generate individual exposure metrics for use in the ER analyses. The pop-PK model was also used to simulate PK profiles of cedazuridine and decitabine for Cycle 3 Day 3 in Study ASTX727-07 Phase 2 Part B, where only sparse sampling was conducted.

Methods

Bioanalytical methods

The bioanalytical method used to determine decitabine, cedazuridine and cedazuridine-epimer in plasma (BTM-1737) was the same method that has been used in previous applications (Inaqovi EPAR). A validated method was also used for determination of venetoclax in plasma.

Evaluation and qualification of models

Population PK analysis

A population PK analysis (THO0201-Report) was conducted to characterize the pharmacokinetic (PK) profiles of oral decitabine and cedazuridine in Subjects with Acute Myeloid Leukemia (AML).

The objectives of the analysis included:

• Updating the previous integrated semi-mechanistic population PK model of cedazuridine and oral decitabine with additional data from Study ASTX727-07 (where the combination of oral decitabine and cedazuridine with venetoclax was evaluated).

• Quantifying the impact of selected covariates on cedazuridine and decitabine disposition.

• Simulating PK profiles of cedazuridine and decitabine for Cycle 3 Day 3 in Study ASTX727-07 Phase 2 Part B.

• Generating individual exposure metrics for use in the ER analyses.

Data

The population PK analysis dataset included all AML patients in Studies ASTX727-02-EU and ASTX727-07 who received at least one dose of ASTX727(INAQOVI) and had at least one evaluable cedazuridine or decitabine concentration. All 162 subjects in Study ASTX727-07 received ASTX727(INAQOVI) (oral decitabine and cedazuridine) with concomitant venetoclax. The 87 subjects in Study ASTX727-02-EU received oral ASTX727(INAQOVI) or IV decitabine alone.

Data for cedazuridine was available in 242 subjects; they contributed 5711 observations, of which 5558 samples had quantifiable cedazuridine concentrations and 153 samples (2.7%) were BLQ (Table 3).

Data for decitabine was available in all 249 subjects, and they contributed 7149 observations, of which 5646 samples had quantifiable decitabine concentrations and 1503 samples (21%) were BLQ (Table 4).

The BLQ samples were ignored in this PK analysis. The percentage of BLQ samples in Study ASTX727-07 were about 10%. Additionally, 35 records (27 decitabine and 8 cedazuridine) were excluded from Study ASTX727-07 because of unusually high trough concentrations. For Study ASTX727-02, approximately 16 % of the samples were BLQ.

Table 3. Summary of subjects (number) and cedazuridine observations (number and percent) by study and phase

	Number			Group percent		Overall percent	
Phase	SUBJ	OBS	BLQ	OBS	BLQ	OBS	BLQ
Study: ASTX727-02							
ASTX727-02	80	1914	114	94.4	5.6	33.5	2.0
Study: ASTX727-07							
ASTX727-07 Phase 1	24	944	35	25.6	1.0	16.5	0.6
ASTX727-07 Phase 2 Part A	37	493	3	13.4	0.1	8.6	0.1
ASTX727-07 Phase 2 Part B	101	2207	1	59.9	0.0	38.6	0.0
All data	242	5558	153	—	—	97.3	2.7

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Table 4. Summary of subjects (number) and decitabine observations (number and percent) by study and phase.

	Number			Group percent		Overall percent	
Phase	SUBJ	OBS	BLQ	OBS	BLQ	OBS	BLQ
Study: ASTX727-02							
ASTX727-02	87	2682	845	76.0	24.0	37.5	11.8
Study: ASTX727-07							
ASTX727-07 Phase 1	24	806	135	22.3	3.7	11.3	1.9
ASTX727-07 Phase 2 Part A	37	416	76	11.5	2.1	5.8	1.1
ASTX727-07 Phase 2 Part B	101	1742	447	48.1	12.3	24.4	6.3
All data	249	5646	1503	—	—	79.0	21.0

The baseline covariates were comparable between Studies ASTX727-02-EU and ASTX727-07 (Table 5 and Table 6). Body size measurements (weight, height, and BSA) were highly correlated and were generally lower in females.

Table 5. Summary of baseline continuous covariates by study.

Variable	n	Mean	Median	SD	Min / Max
Study: ASTX727-02					
Age (years)	87	76.7	78.0	6.71	61.0 / 92.0
Weight (kg)	87	75.8	73.7	14.2	46.2 / 117
Height (cm)	87	167	166	9.92	143 / 196
Body surface area (m^2)	87	1.84	1.84	0.199	1.42 / 2.46
BSA-normalized creatinine clearance (mL/min/1.73m^2)	87	56.2	53.5	17.4	28.4 / 129
Bone marrow blasts (%)	87	41.8	35.0	22.3	4.00 / 95.0
Bone marrow cellularity (%)	–	–	–	–	–
White blood cell count (10^9/L)	87	4.47	2.87	4.16	0.440 / 18.9
Study: ASTX727-07					
Age (years)	162	77.2	77.5	5.46	56.0 / 91.0
Weight (kg)	162	76.3	76.0	16.3	42.5 / 138
Height (cm)	162	167	168	10.3	134 / 193
Body surface area (m^2)	162	1.86	1.87	0.230	1.36 / 2.52
BSA-normalized creatinine clearance (mL/min/1.73m^2)	162	58.3	55.1	18.8	22.6 / 128
Bone marrow blasts (%)	162	45.1	40.5	22.8	5.00 / 95.0
Bone marrow cellularity (%)	162	69.5	79.0	23.7	1.50 / 100
White blood cell count (10^9/L)	162	5.36	2.86	5.93	0.400 / 26.5
All data					
Age (years)	249	77.0	78.0	5.92	56.0 / 92.0
Weight (kg)	249	76.1	74.1	15.5	42.5 / 138
Height (cm)	249	167	167	10.1	134 / 196
Body surface area (m^2)	249	1.86	1.85	0.219	1.36 / 2.52
BSA-normalized creatinine clearance (mL/min/1.73m^2)	249	57.6	54.7	18.4	22.6 / 129
Bone marrow blasts (%)	249	44.0	40.0	22.7	4.00 / 95.0
Bone marrow cellularity (%)	162	69.5	79.0	23.7	1.50 / 100
White blood cell count (10^9/L)	249	5.05	2.87	5.39	0.400 / 26.5

Table 6. Summary of baseline categorical covariates by study.

	Study number		
	ASTX727-02 n = 87	ASTX727-07 n = 162	Summary n = 249
Sex			
Male	53 (60.9)	97 (59.9)	150 (60.2)
Female	34 (39.1)	65 (40.1)	99 (39.8)
Race			
White	0 (0.0)	130 (80.2)	130 (52.2)
Black or African American	0 (0.0)	6 (3.7)	6 (2.4)
Asian	0 (0.0)	13 (8.0)	13 (5.2)
Other	0 (0.0)	3 (1.9)	3 (1.2)
Not Reported	87 (100.0)	10 (6.2)	97 (39.0)
Venetoclax conmed			
No	87 (100.0)	0 (0.0)	87 (34.9)
Yes	0 (0.0)	162 (100.0)	162 (65.1)
Bone marrow cellularity			
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Normocellular	19 (21.8)	14 (8.6)	33 (13.3)
Hypocellular or aplastic	11 (12.6)	20 (12.3)	31 (12.4)
Hypercellular	57 (65.5)	128 (79.0)	185 (74.3)

Model

The semi-mechanistic PopPK model (Figure 1), describing the PK of cedazuridine and decitabine in subjects with AML, was previously developed and described in the initial approval (Inaqovi EPAR). A sequential modelling approach had been adopted. First the cedazuridine model was fit to cedazuridine data (1), and the predicted cedazuridine concentrations from this model were included in the decitabine analysis dataset to drive the inhibitory effect of cedazuridine on decitabine metabolism by cytidine deaminase (CDA). Then, the IV decitabine model was fit to IV decitabine data to estimate decitabine disposition parameters (2). Finally, the oral decitabine model, which included oral absorption parameters, was fit to the oral decitabine data, and population decitabine disposition parameters in the model were fixed to the estimates from the IV model (3). Model parameters were estimated using the first-order conditional estimation with η–ε interaction (FOCEI) method in NONMEM version 7.5 (ICON PLC, Ireland).

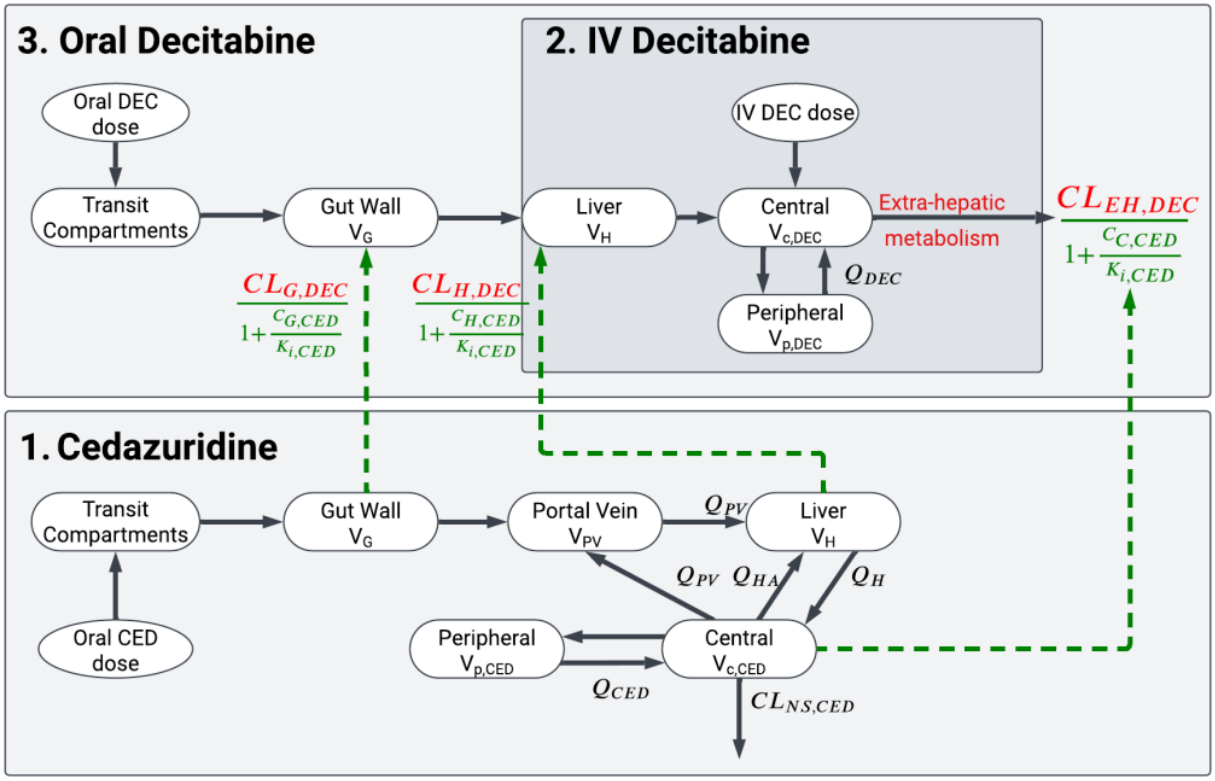


Figure 1. Semi-mechanistic population PK model schematic.

The PK model schematic of decitabine (top) and cedazuridine (bottom) shows the sequential modeling approach used herein. Vc ,D E C and Vc ,C E D are the central compartment volumes of distribution for decitabine and cedazuridine, respectively. Vp,D E C and Vp,C E D are the peripheral compartment volumes of distribution for decitabine and cedazuridine, respectively. VH and VP V are liver and portal vein volumes, respectively. QD E C and QC E D QH , QH A, QP V are the decitabine peripheral compartment cedazuridine peripheral compartment, liver, hepatic artery, and portal vein flow rates, respectively. C LN S,C E D is the nonspecific clearance of cedazuridine. C LH ,D E C , C LE H ,D E C , and C LG ,D E C are the decitabine hepatic, extra-hepatic, and gut clearance (due to CDA metabolism), respectively. CC E D,Vc , CC E D,H , and CC E D,G are cedazuridine concentrations in the central, liver, and gut compartments, respectively. Ki,C E D is the inhibition constant of cedazuridine for CDA inhibition. Physiological parameters (VH , VP V , QH , QH A, QP V) were fixed to literature values (scaled by individual baseline height).

The three models used in this sequential approach were updated with new cedazuridine and decitabine concentration data from Study ASTX727-07. Interindividual variability (IVV) model implementation was based on the prior model structure. Covariate effects were incorporated as in the previous analysis and were reevaluated. Assessment of any remaining covariate effects, including the combination with venetoclax, was conducted by graphical inspection via plots of IIV, normalized prediction distribution error (NPDE), conditional weighted residual (CWRES) versus covariates.

Results: Cedazuridine

The parameter estimates describing the PK of Cedazuridine in patients with AML, derived from the updated model including data on the combination with venetoclax, are presented in Table 7 and Table 8. The estimates were in general in line with the previous analysis in AML (Inaqovi EPAR) (data not presented here).

As in the previous analysis, the model evaluated the covariate effect of baseline CRCLN and sex. The model accounted for the body size effect via physiological parameters scaled by height. No changes in the conclusion regarding the limited clinical effect of the included covariates was identified.

Table 7. Cedazuridine: summary of fixed effect parameters.

			Estimate	95% CI
Structural model parameters				
$CL_{NS,CED}/F$ (L/h)	θ_1	Apparent non-specific clearance	39.1	36.0, 42.3
Q_{CED}/F (L/h)	θ_2	Apparent intercompartmental clearance	20.5	18.0, 22.9
$V_{c,CED}/F$ (L)	θ_3	Apparent central volume	22.5	18.5, 26.5
$V_{p,CED}/F$ (L)	θ_4	Apparent peripheral volume	213	204, 222
$k_{tr,CED}$ (/h)	θ_5	Transit rate constant	0.340	0.323, 0.357
Covariate effect parameters				
$k_{tr,CED} \sim$ Female	θ_7	Female effect on $k_{tr,CED}$	1.08	0.981, 1.18
$CL_{NS,CED}/F \sim$ CRCLN	θ_8	BSA-normalized creatinine clearance effect on $CL_{NS,CED}/F$	0.739	0.614, 0.864

CI: confidence intervals; CRCLN: BSA-normalized creatinine clearance; BSA: body surface area; SE: standard error, Confidence intervals = estimate ± 1.96 · SE

Table 8. Cedazuridine: summary of random effect parameters.

		Estimate	Shrinkage (%)	95% CI
Interindividual variance parameters				
IIV-$CL_{NS,CED}/F$	$\Omega_{(1,1)}$	0.153 [CV%=40.7]	2.33	0.123, 0.183
IIV-Q_{CED}/F	$\Omega_{(2,2)}$	0.350 [CV%=64.8]	20.4	0.209, 0.491
IIV-$V_{c,CED}/F$	$\Omega_{(3,3)}$	0.916 [CV%=122]	22.9	0.659, 1.17
IIV-$k_{tr,CED}$	$\Omega_{(5,5)}$	0.0565 [CV%=24.1]	25.9	0.0420, 0.0710
Interindividual covariance parameters				
Q_{CED}/F-$CL_{NS,CED}/F$	$\Omega_{(2,1)}$	0.125 [Corr=0.538]	-	0.0697, 0.180
Residual variance				
Proportional	$\Sigma_{(1,1)}$	0.104 [CV%=32.2]	4.95	0.102, 0.106

CI: confidence intervals; Corr: Correlation coefficient; CV: coefficient of variation; IIV: interindividual variability CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100, CV% of sigma = sqrt(estimate) · 100

Results: Decitabine

The parameter estimates describing the PK of decitabine in patients with AML, derived from the updated model including data on the combination with venetoklax, are presented in Table 9 and Table 10 (IV), Table 11 and Table 12 (oral). The estimates were in general in line with the previous analysis in AML(Inaqovi EPAR) (data not presented here).

As in the previous analysis, the model evaluated the covariate effect of baseline weight and sex. The conclusion that there is no clinically meaningful effect of sex or body weight on the PK of decitabine persisted in the updated model analysis.

Table 9. IV decitabine: summary of fixed effect parameters.

			Estimate	95% CI
Structural model parameters				
$CL_{H,DEC}$ (L/h)	θ_1	Hepatic clearance	52.7	41.0, 64.4
$V_{c,CED}$ (L)	θ_2	Central volume	52.2	40.9, 63.4
Q_{DEC} (L/h)	θ_3	Intercompartmental clearance	11.3	7.56, 15.0
$V_{p,DEC}$ (L)	θ_4	Peripheral volume	30.7	27.4, 34.1
Covariate effect parameters				
$CL_{H,DEC} \sim$ WT	θ_{10}	Weight effect on $CL_{H,DEC}$	0.0329	-0.538, 0.604
$Q_{DEC} \sim$ WT	θ_{11}	Weight effect on Q_{DEC}	-0.123	-1.04, 0.797
$CL_{H,DEC} \sim$ Female	θ_{12}	Female effect on $CL_{H,DEC}$	0.856	0.619, 1.09
$Q_{DEC} \sim$ Female	θ_{13}	Female effect on Q_{DEC}	0.899	0.521, 1.28
$V_{c,DEC} \sim$ Female	θ_{14}	Female effect on $V_{c,DEC}$	0.784	0.579, 0.988

Table 10. IV decitabine: summary of random effect parameters.

		Estimate	Shrinkage (%)	95% CI
Interindividual variance parameters				
IIV-$CL_{H,DEC}$	$\Omega_{(1,1)}$	0.265 [CV%=55.1]	3.12	0.162, 0.369
IIV-$V_{c,DEC}$	$\Omega_{(2,2)}$	0.214 [CV%=48.8]	7.93	0.0999, 0.327
IIV-Q_{DEC}	$\Omega_{(3,3)}$	0.480 [CV%=78.5]	4.16	0.259, 0.700
Interindividual covariance parameters				
$V_{c,DEC}$-$CL_{H,DEC}$	$\Omega_{(2,1)}$	0.177 [Corr=0.742]	-	0.0829, 0.270
Q_{DEC}-$CL_{H,DEC}$	$\Omega_{(3,1)}$	0.351 [Corr=0.984]	-	0.206, 0.497
Q_{DEC}-$V_{c,DEC}$	$\Omega_{(3,2)}$	0.240 [Corr=0.750]	-	0.105, 0.375
Residual variance				
Proportional	$\Sigma_{(1,1)}$	0.184 [CV%=42.9]	4.98	0.171, 0.197

Table 11. Oral decitabine: summary of fixed effect parameters.

			Estimate	95% CI
Structural model parameters				
$k_{a,DEC}$ (/h)	θ_7	Absorption rate constant	2.22	2.07, 2.36
$N_{tr,DEC}$	θ_{15}	Number of transit compartments	2.14	1.91, 2.38
MTT_{DEC} (h)	θ_{16}	Mean transit time	0.408	0.379, 0.436
Covariate effect parameters				
$k_{a,DEC} \sim$ Female	θ_{17}	Female effect on $k_{a,DEC}$	0.894	0.825, 0.964

Table 12. Oral decitabine: summary of random effect parameters.

		Estimate	Shrinkage (%)	95% CI
Interindividual variance parameters				
IIV-$CL_{H,DEC}$	$\Omega_{(1,1)}$	0.0649 [CV%=25.9]	6.46	0.0518, 0.0779
IIV-$V_{c,DEC}$	$\Omega_{(2,2)}$	0.266 [CV%=55.2]	25.2	0.173, 0.359
IIV-Q_{DEC}	$\Omega_{(3,3)}$	0.0732 [CV%=27.6]	17.4	0.0416, 0.105
IIV-$N_{tr,DEC}$	$\Omega_{(10,10)}$	1.40 [CV%=175]	15.0	1.01, 1.78
IIV-MTT_{DEC}	$\Omega_{(11,11)}$	0.366 [CV%=66.4]	13.3	0.280, 0.451
Interindividual covariance parameters				
$V_{c,DEC}$-$CL_{H,DEC}$	$\Omega_{(2,1)}$	0.0369 [Corr=0.281]	-	0.00956, 0.0642
Q_{DEC}-$CL_{H,DEC}$	$\Omega_{(3,1)}$	0.0604 [Corr=0.877]	-	0.0420, 0.0789
Q_{DEC}-$V_{c,DEC}$	$\Omega_{(3,2)}$	0.0442 [Corr=0.317]	-	-0.0149, 0.103
Residual variance				
Proportional	$\Sigma_{(1,1)}$	0.232 [CV%=48.1]	5.73	0.224, 0.239

A model including venetoclax as a categorical covariate effect on decitabine clearance was also investigated. The resulting model predictions (not shown) were similar to the final model, and the estimated venetoclax effect was small (about 10% lower clearance with the use of venetoclax). Due to the lack of grounds for a direct DDI and the minimal impact on the model fit, venetoclax was not included as a covariate in the final decitabine model.

Visual predictive checks (VPCs) for decitabine concentration versus time following oral administration stratified by study and phase are shown in Figure 2 and Figure 3.

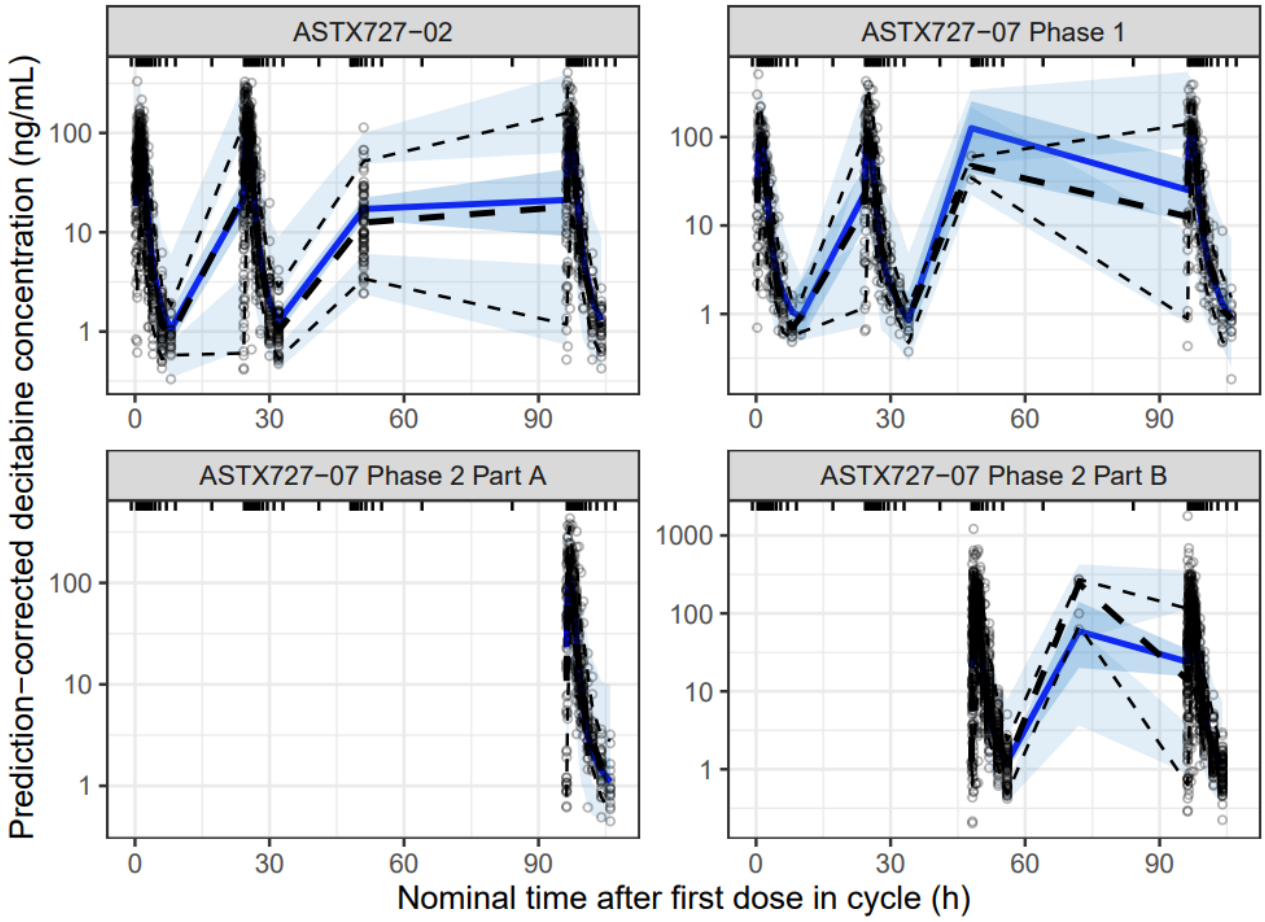


Figure 2. Oral decitabine: prediction-corrected visual predictive check of decitabine versus nominal time after first dose in cycle by study and phase.

Black dashed lines represent the median (thick) or 5th and 95th (thin) percentiles of the observed data. Shaded areas represent the 95% prediction intervals for the median (dark blue) or 5th and 95th percentiles (light blue) of the simulated data. All data and summaries have been prediction-corrected. Tick marks represent data binning.

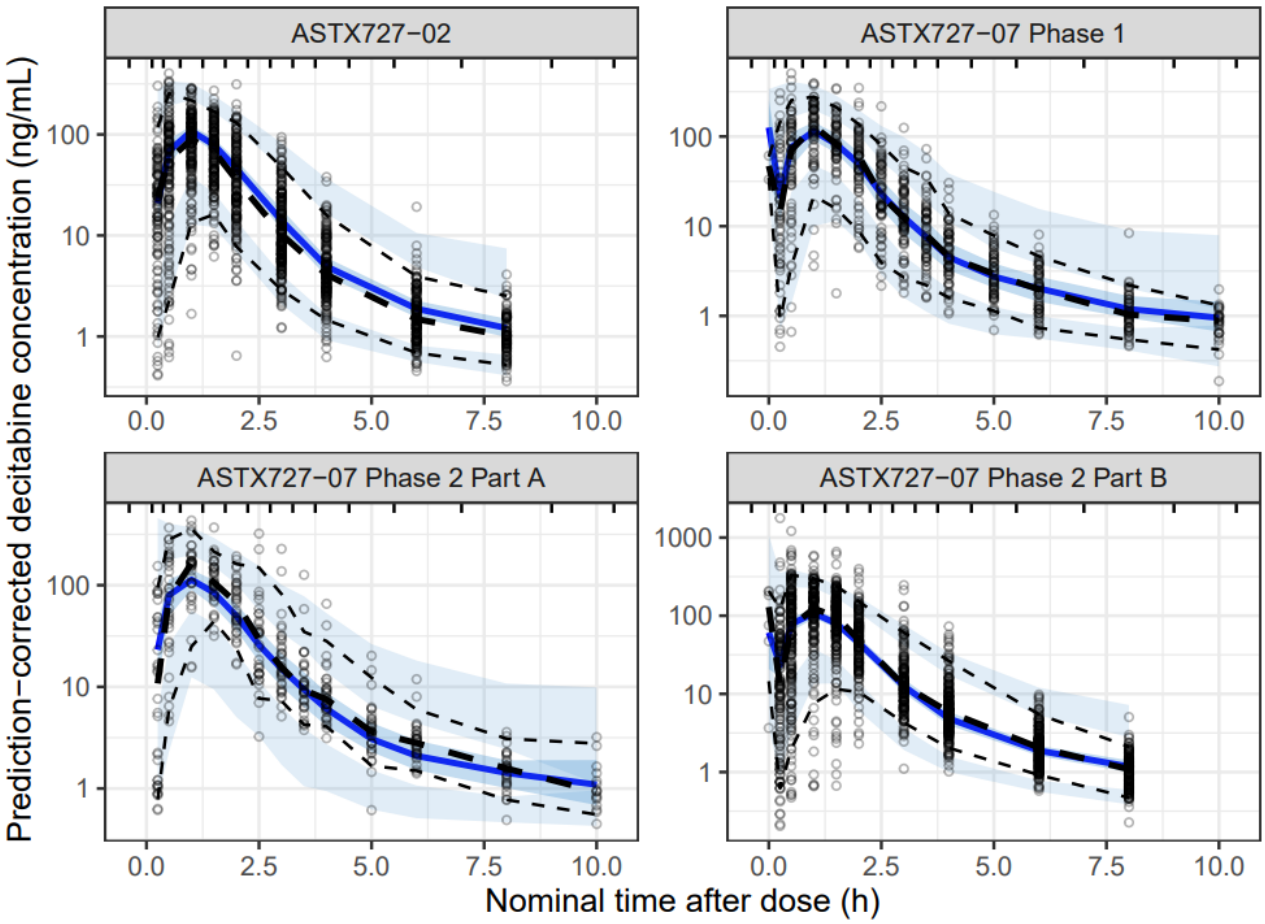


Figure 3. Oral decitabine: prediction-corrected visual predictive check of decitabine versus nominal time after dose by study and phase.

Black dashed lines represent the median (thick) or 5th and 95th (thin) percentiles of the observed data. Shaded areas represent the 95% prediction intervals for the median (dark blue) or 5th and 95th percentiles (light blue) of the simulated data. All data and summaries have been prediction-corrected. Tick marks represent data binning.

The final decitabine PK model was used to generate individual post-hoc AUC,ss for the subsequent ER-analyses of efficacy and safety.

Absorption

No new data were submitted with this variation. General information on absorption for Inaqovi can be found in the published EPAR. Results from study ASTX727-06 describing the food effect (submitted with previous variation, EMEA/H/C/005823/II/0002) are briefly summarised below.

The objective of this PK substudy was to evaluate the PK of decitabine and cedazuridine when ASTX727(INAQOVI) is given under fed (high-calorie/high-fat meal or low-calorie/low-fat meal) versus fasted conditions.

This was a Phase 2, multicenter, open-label, non-randomised, two-arm, fixed-sequence, food effect substudy within the ASTX727-06 study in subjects with higher risk MDS, CMML, and AML. A total of 18

(62.1%) male and 11 (37.9%) female subjects between 27 and 83 years of age (median age 72 years) participated in the study.

Subjects received either a high-calorie/high-fat breakfast meal (Arm A) or a low- calorie/low-fat breakfast meal (Arm B) after an overnight fast of at least 10 hours before dosing on Day 4 and continued to fast for at least 4 hours post-dose. Enrollment into Arm A and Arm B was sequential. Subjects received ASTX727(INAQOVI) once daily on Days 1 through 5 in a 28-day cycle (Cycle 1). Subjects fasted for at least 2 hours before and 2 hours after dosing on Days 1, 3, and 5; on Day 2 subjects fasted for at least 10 hours before and 4 hours after dosing. Plasma PK data of decitabine, cedazuridine and its primary metabolite, cedazuridine-epimer was evaluated on Days 2 (fasted) and 4 (fed).

Results of the statistical comparison of decitabine under fed (high-calorie/high-fat or low-calorie/low-fat) and fasted conditions (pooled fasted analysis) are presented in Table 13. The geometric mean ratio (90% CI) for decitabine AUC0-24, AUClast, AUC0 inf, and Cmax for the high-calorie/high-fat group vs. fasted from the high-calorie/high-fat group only, were 0.484 (0.302, 0.775), 0.408 (0.243, 0.686), 0.461 (0.251, 0.845), and 0.263 (0.162, 0.425). The geometric mean ratio (90% CI) for decitabine AUC0-24, AUClast, AUC0 inf, and Cmax for the low-calorie/low-fat group vs. fasted from the low-calorie/low fat group only, were 0.586 (0.494, 0.696), 0.582 (0.484, 0.700), 0.586 (0.488, 0.704), and 0.553 (0.405, 0.755). Decitabine AUCs following fasted conditions were about 25% lower in the High-Cal/High-Fat group compared to the Low-Cal/Low-Fat group. This could be due to variability and small sample size. The reduction in decitabine exposures with high-calorie/high-fat and low-calorie/low-fat meals was clinically meaningful.

Table 13. Decitabine PK Parameters equivalence assessment (all subjects)

Comparison	PK Parameter	Test Geo LSM	Reference Geo LSM	Ratio of Geo LSM	90% CI
High-Calorie/High-Fat vs. Fasted	AUC_{0-24} (h*ng/mL)	71.2 (n=13)	159 (n=28)	0.447	(0.333, 0.601)
	AUC_{last} (h*ng/mL)	59.7 (n=13)	159 (n=29)	0.376	(0.271, 0.521)
	AUC_{0-inf} (h*ng/mL)	70.4 (n=10)	157 (n=28)	0.450	(0.319, 0.634)
	C_{max} (ng/mL)	33.1 (n=13)	122 (n=29)	0.270	(0.191, 0.382)
Low-Calorie/Low-Fat vs. Fasted	AUC_{0-24} (h*ng/mL)	102 (n=15)	159 (n=28)	0.640	(0.487, 0.840)
	AUClast (h*ng/mL)	101 (n=15)	159 (n=29)	0.637	(0.468, 0.867)
	AUC_{0-inf} (h*ng/mL)	101(n=15)	157 (n=28)	0.642	(0.484, 0.853)
	C_{max} (ng/mL)	67.3 (n=15)	122 (n=29)	0.550	(0.396, 0.762)

Results of the statistical comparison of cedazuridine under fed and fasted conditions are presented in Table 14. The geometric mean ratio (90% CI) for cedazuridine AUC0-24, AUClast, AUC0 inf, and Cmax for the high-calorie/high-fat group vs. fasted from the high-calorie/high-fat group only, were 1.04 (0.807, 1.35), 0.924 (0.629, 1.36), 1.03 (0.783, 1.36), and 0.992 (0.772, 1.27). The geometric mean ratio (90% CI) for cedazuridine AUC0-24, AUClast, AUC0 inf, and Cmax for the low-calorie/low-fat group vs. fasted from the low-calorie/low-fat group only, were 0.814 (0.682, 0.970), 0.814 (0.682,

0.971), 0.794 (0.566, 1.11), and 0.760 (0.632, 0.915). Cedazuridine AUCs following fasted conditions were about 12-18% lower in the High-Cal/High-Fat group compared to the Low-Cal/Low-Fat group.

Table 14. Cedazuridine PK Parameters equivalence assessment (all subjects)

Comparison	PK Parameter	Test Geo LSM	Reference Geo LSM	Ratio of Geo LSM	90% CI
High-Calorie/High-Fat vs. Fasted	AUC_{0-24} (h*ng/mL)	3770 (n=12)	3770 (n=28)	1.00	(0.821, 1.22)
	AUC_{last} (h*ng/mL)	3560 (n=13)	3650 (n=29)	0.977	(0.795, 1.20)
	AUC_{0-inf} (h*ng/mL)	3710 (n=6)	4060 (n=21)	0.913	(0.669, 1.25)
	C_{max} (ng/mL)	341 (n=13)	353 (n=29)	0.965	(0.794, 1.17)
Low-Calorie/Low-Fat vs. Fasted	AUC_{0-24} (h*ng/mL)	3140 (n=15)	3770 (n=28)	0.834	(0.700, 0.994)
	AUC_{last} (h*ng/mL)	3080 (n=15)	3650 (n=29)	0.846	(0.697, 1.03)
	AUC_{0-inf} (h*ng/mL)	3250 (n=6)	4060 (n=21)	0.801	(0.587, 1.09)
	C_{max} (ng/mL)	274 (n=15)	353 (n=29)	0.776	(0.646, 0.932)

There was a small food effect on cedazuridine-epimer. High-calorie/high-fat meals increased cedazuridine-epimer AUC0-24 by 24%, Cmax by 18% and low-calorie/low-fat meals increased cedazuridine-epimer AUC0-24 by 12%, Cmax by 11%.

The findings from this study confirmed those from earlier food-effect study ASTX727-04 and similar effect on reduction of decitabine PK exposures was observed when ASTX727(INAQOVI) was administered with food versus fasted.

Distribution, elimination, dose proportionality and time dependencies special populations

No new data submitted. General information on absorption for inaqovi can be found in the published EPAR: https://www.ema.europa.eu/en/documents/assessment-report/inaqovi-epar-public-assessment-report_en.pdf

Pharmacokinetic interaction studies

Study ASTX727-07 (see also Clinical efficacy and Clinical safety)

Methods:

This was a Phase 1/2 single-arm, open-label, multicenter, nonrandomised interventional study to evaluate the PK, safety, and efficacy of ASTX727(INAQOVI) when given in combination with venetoclax for the treatment of newly diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. The primary purpose of the

Phase 1 part of the study was to evaluate the potential of a drug-drug interaction effect of ASTX727(INAQOVI) on the PK of venetoclax for the combination therapy. Phase 2 part A had both DDI effects (effects of ASTX727(INAQOVI) on the PK of venetoclax) and efficacy as co-primary endpoint. Phase 2 part B had efficacy as primary endpoint. In all three study parts, evaluation of effects of venetoclax on PK of ASTX727(INAQOVI) was a secondary objective. See further details in the section of clinical efficacy.

Venetoclax was administered according to the current venetoclax United States Prescribing Information (USPI) document, and ASTX727(INAQOVI) was administered according to the recommended dosing regimen (daily ×5, 28-day cycle) used in Phase 3 Study ASTX727-02. The recommended dose and regimen of ASTX727(INAQOVI) were 35 mg decitabine and 100 mg cedazuridine, which were given orally as a fixed-dose combination tablet once daily on Days 1 to 5 of each 28-day cycle.

In Cycle 1, ASTX727(INAQOVI) (35 mg decitabine and 100 mg cedazuridine) was given on Days 1 to 5 in combination with venetoclax, which was given as a ramp-up on Day 1 (100 mg) and Day 2 (200 mg), followed by venetoclax 400 mg daily on Days 3 to 28. From Cycle 2 onwards, ASTX727(INAQOVI) was administered on Days 1 to 5 and venetoclax (400 mg daily) was administered on Days 1 to 28. In all cycles, ASTX727(INAQOVI) was given on an empty stomach and venetoclax was given at least 2 hours later with breakfast. In Cycle 2, PK sampling was performed on Day 5 (venetoclax with ASTX727(INAQOVI)) to ensure steady state venetoclax levels when given in combination with ASTX727(INAQOVI), and on Day 15 (venetoclax alone). The primary PK endpoints for venetoclax were the Cycle 2 Day 5 (venetoclax with ASTX727(INAQOVI)) and Day 15 (venetoclax alone) AUC_{0-24} and $C_{max.}$ The 90% CIs for the ratios of venetoclax AUC_{0-24} and C_{max} when given with ASTX727(INAQOVI) relative to when given alone (intra-patient) were calculated using ln-transformed data. Data for decitabine and cedazuridine from cycle 2 were compared to historical data from Study ASTX727-02 (AML).

In Cycle 3 and beyond, subjects continued to receive ASTX727(INAQOVI) and venetoclax in combination on Days 1 to 5 and venetoclax alone on Days 6 to 28 unless they had been dose reduced.

Phase 2 Part A followed the same overall design and dosing schedule as Phase 1. Rich PK sampling occurred on day 5 and 15 in cycle 2.

Phase 2 Part B followed the same overall design and dosing schedule as Phase 1 except for changes in PK collections (rich sampling on day 5 in cycle 1 and day 3 in cycle 2 plus sparse sampling on day 3 in cycle 3). Decitabine AUC_{0-24} and C_{max} values obtained from C1D5 were compared with historical data from study ASTX727-02 (AML). Pharmacokinetic data from C3D3 sparse samples was used for model-based derivation of exposure data to compare with C1 and C2. Phase 2 Part B also included ASTX727(INAQOVI) and venetoclax dose modification recommendations to manage drug toxicities after subjects had achieved clearance of marrow blasts.

In Phase 1, Phase 2 Part A, and Phase 2 Part B, 30, 58, and 101 subjects were enrolled and treated, respectively. Plasma PK data for venetoclax, decitabine, cedazuridine, and cedazuridine-epimer when ASTX727(INAQOVI) is given in coadministration with venetoclax were available in a total of 24 subjects in Phase 1, 37 subjects in Phase 2 Part A, and 101 subjects in Phase 2 Part B.

Results

Venetoclax

Phase 1 and Phase 2 Part A PK data showed that C_{max} and AUC_{0-24} exposures of venetoclax were unaffected by coadministration with ASTX727(INAQOVI). The percentage ratio of the geometric LSMs was close to 100% for both parameters and the 90% CIs fell within the range of 80% to 125%. Overall, these data indicated that there was no ASTX727(INAQOVI) effect on venetoclax PK.

Table 15. Plasma Venetoclax DDI Assessment Between ASTX727 + Venetoclax and Venetoclax Alone – Combined Phase 1 and Phase 2 Part A (Study ASTX727-07)

PK Parameter	Units	Test Geo LSM (N = 54)	Reference Geo LSM (N = 49)	Ratio of Geo LSM (%)	90% CI
AUC_{0-24}	h*ng/mL	25800[a]	25670[b]	100.5	(84.88, 119.0)
C_{max}	ng/mL	1859	1930	96.30	(84.13, 110.2)

AUC_{0-24}=area under the plasma concentration-time curve from time zero to 24 hours; CI=confidence interval; C_{max}=maximum plasma concentration; DDI=drug-drug interaction; Geo LSM=geometric least square means; PK=pharmacokinetic(s).

[a] n=46

[b] n=45

Notes: Reference treatment = Venetoclax Alone (Cycle 2 Day 15). Test treatment = ASTX727 + Venetoclax (Cycle 2 Day 5).

Decitabine

In Phase 1 and Phase 2 Part A (compared to data without venetoxlax from study ASTX727-02), the C_{max} and AUC_{0-24} exposures of decitabine were increased when ASTX727(INAQOVI) was coadministered with venetoclax. The percentage ratios of the geometric LSMs were 125% and 142%, respectively, for C_{max} and AUC_{0-24}. Although the 90% CIs were above the standard bioequivalence range of 80% to 125%, the differences were <1.5-fold.

Table 16. Plasma Decitabine DDI Assessment Between ASTX727 + Venetoclax and ASTX727 Alone – Combined Phase 1 and Phase 2 Part A (Study ASTX727 07)

PK Parameter	Units	Test Geo LSM (N = 55)	Reference Geo LSM (N = 76)	Ratio of Geo LSM (%)	90% CI
AUC_{0-24}	h*ng/mL	264.00[a]	186.50[b]	141.6	(121.9, 164.3)
C_{max}	ng/mL	173.80	138.80	125.2	(106.9, 146.7)

AML=acute myeloid leukemia; AUC_{0-24}=area under the plasma concentration-time curve from time zero to 24 hours; CI=confidence interval; C_{max}=maximum plasma concentration; DDI=drug-drug interaction; EU=European Union; Geo LSM=geometric least square means; PK=pharmacokinetic(s).

[a] n=52

[b] n=75

Notes: Reference treatment = ASTX727 Alone (data from ASTX727-02 EU [AML] from Cycle 1 Day 5 and Cycle 2 Day 5). Test treatment = ASTX727 + Venetoclax (Cycle 2 Day 5).

The Phase 2 Part B results of the statistical comparison of decitabine drug-drug interaction (DDI) assessment between ASTX727(INAQOVI) in combination with venetoclax for Cycle 1 Day 5 and ASTX727(INAQOVI) alone from Study ASTX727-02 EU (AML) are presented below (Table 17, Figure 4). The C_{max} and the AUC_{0-24} were both close to 100% and, although the 90% CI for C_{max} extended slightly below the 80% to 125% range, there was no meaningful effect of venetoclax coadministration on decitabine PK.

On cycle 1 day 5, the geometric mean (geometric CV%) for decitabine was 200 h*ng/mL (61.3) for AUC_{0-24} and 131 ng/mL (88.4) for C_{max}.

In addition, comparison of decitabine exposure on Cycle 1 Day 5 with exposure on Cycle 2 Day 3 and simulated exposure on Cycle 3 Day3 showed that decitabine exposures did not increase in later cycles (Table 18).

Table 17. Plasma Decitabine DDI Assessment Between ASTX727 + Venetoclax and ASTX727 Alone – Phase 2 Part B (Study ASTX727-07)

PK Parameter	Units	Test Geo LSM (N = 94)	Reference Geo LSM (N = 76)	Ratio of Geo LSM (%)	90% CI
AUC_{0-24}	h*ng/mL	200.10[a]	186.50[b]	107.3	(93.11, 123.7)
C_{max}	ng/mL	131.30	138.80	94.59	(79.45, 112.6)

AML=acute myeloid leukemia; AUC_{0-24}=area under the plasma concentration-time curve from time zero to 24 hours; CI=confidence interval; C_{max}=maximum plasma concentration; DDI=drug-drug interaction; EU=European Union; Geo LSM=geometric least square means; PK=pharmacokinetic(s).

[a] n=92

[b] n=75

Notes: Reference treatment = ASTX727 Alone (data from ASTX727-02 EU [AML] from Cycle 1 Day 5 and Cycle 2 Day 5). Test treatment = ASTX727 + Venetoclax (Cycle 1 Day 5).

Table 18. Plasma Decitabine DDI Assessment Between Cycle 2 Day 3 or Simulated Cycle 3 Day 3 Versus Cycle 1 Day 5 – Phase 2 Part B (Study ASTX727-07)

Test Treatment Visit	PK Parameter	Units	Test Geo LSM (N = 72)	Reference Geo LSM (N = 94)	Ratio of Geo LSM (%)	90% CI
Cycle 2 Day 3	AUC_{0-24}	h*ng/mL	231.80[a]	199.30[b]	116.3	(107.00, 126.40)
	C_{max}	ng/mL	153.40	132.20	116.1	(103.20, 130.60)
Test Treatment Visit	**PK Parameter**	**Units**	**Test Geo LSM (N = 100)**	**Reference Geo LSM (N = 94)**	**Ratio of Geo LSM (%)**	**90% CI**
Cycle 3 Day 3[c]	AUC_{0-24}	h*ng/mL	227.90	199.30[b]	114.3	(106.20, 123.10)
	C_{max}	ng/mL	133.60	132.20	101.1	(90.92, 112.40)

AUC_{0-24}=area under the plasma concentration-time curve from time zero to 24 hours; CI=confidence interval; C_{max}=maximum plasma concentration; CV=coefficient of variation; DDI=drug-drug interaction; Geo LSM=geometric least square mean; PK=pharmacokinetic(s); PopPK=population pharmacokinetic(s).

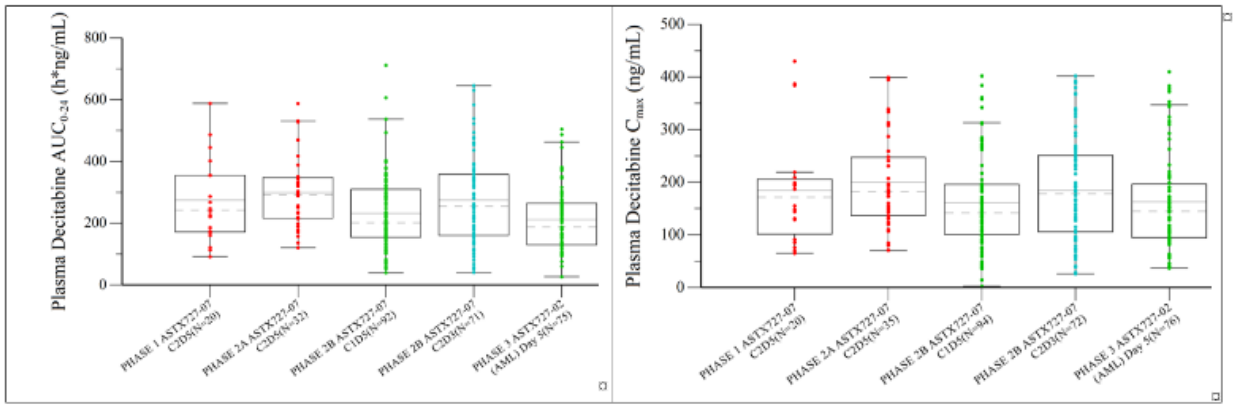
[a] n=71

[b] n=92

[c] Simulated data using the PopPK model and sparse PK sampling.

Notes: Reference treatment = ASTX727-07 Cycle 1 Day 5. Test treatment = ASTX727-07 Cycle 2 Day 3 or simulated Cycle 3 Day 3.

Figure 4. Drug-Drug Interaction Box Plots of Plasma Decitabine Parameters (AUC0-24 and Cmax) – Study Overall



Abbreviations: AUC_{0-24}= AUC from 0 to 24 hours; C=cycle; C_{max}=maximum concentration; D=day; N=number of patients.

Cedazuridine

In Phase 1 and Phase 2 Part A, the C_{max} and AUC exposures of cedazuridine were increased when ASTX727(INAQOVI) was coadministered with venetoclax. The percentage ratios of the geometric LSMs were 120% and 114%, respectively, for C_{max} and AUC_{0-24} on Day 2 of Cycles 1 and 2 (Table 19). The percentage ratios of the geometric LSMs were 118% and 120%, respectively, for C_{max} and AUC_{08} on Day 5 of Cycles 1 and 2. Although the 90% CIs were above the standard bioequivalence range of 80% to 125%, the differences were <1.5-fold.

Table 19. Plasma Cedazuridine DDI Assessment Between ASTX727 + Venetoclax and ASTX727 Alone – Combined Phase 1 and Phase 2 Part A (Study ASTX72707)

Reference Treatment Visit	PK Parameter	Units	Test Geo LSM (N = 55)	Reference Geo LSM (N = 78)	Ratio of Geo LSM (%)	90% CI
Cycle 1 Day 2 and Cycle 2 Day 2	AUC_{0-24}	h*ng/mL	4088[a]	3600	113.5	(99.35, 129.8)
	AUC_{0-8}	h*ng/mL	2313	1902	121.6	(107.2, 138.0)
	AUC_{0-inf}	h*ng/mL	4428[b]	4060[c]	109.1	(93.48, 127.2)
	C_{max}	ng/mL	412.3	342.6	120.3	(106.4, 136.1)
Reference Treatment Visit	**PK Parameter**	**Units**	**Test Geo LSM (N = 55)**	**Reference Geo LSM (N = 77)**	**Ratio of Geo LSM (%)**	**90% CI**
Cycle 1 Day 5 and Cycle 2 Day 5	AUC_{0-8}	h*ng/mL	2313	1925[d]	120.1	(105.9, 136.2)
	C_{max}	ng/mL	412.3	350.3	117.7	(104.1, 133.0)

AML=acute myeloid leukemia; AUC_{0-8}=area under the plasma concentration-time curve from time zero to 8 hours; AUC_{0-24}=area under the plasma concentration-time curve from time zero to 24 hours; AUC_{0-inf}=area under the plasma concentration-time curve from time zero extrapolated to infinity; CI=confidence interval; C_{max}=maximum plasma concentration; DDI=drug-drug interaction; EU=European Union; Geo LSM=geometric least square means; PK=pharmacokinetic(s).

[a] n=53

[b] n=39

[c] n=56

[d] n=76

Notes: Reference treatment = ASTX727 Alone (data from ASTX727-02 EU [AML] from Cycle 1/2 Day 2 and Cycle 1/2 Day 5). Test treatment = ASTX727 + Venetoclax (Cycle 2 Day 5).

The Phase 2 Part B results of the statistical comparison of cedazuridine DDI assessment between ASTX727(INAQOVI) in combination with venetoclax for Cycle 1 Day 5 and ASTX727(INAQOVI) alone from Study ASTX727-02 EU (AML) are presented in Table 20. Cedazuridine exposure was slightly lower when ASTX727(INAQOVI) was coadministered with venetoclax compared with ASTX727(INAQOVI) alone in Study ASTX727-02 EU (AML). When ASTX727(INAQOVI) was coadministered with venetoclax, the cedazuridine C_{max} and the AUC_{0-24} were both 87% of the historical data for ASTX727(INAQOVI) alone and the 90% CI for cedazuridine exposures extended slightly below the 80% to 125% range (except AUC_{0-8}). However, the effect of venetoclax coadministration on cedazuridine PK was slight and not clinically meaningful.

In addition, comparison of cedazuridine exposure on Cycle 1 Day 5 with exposure on Cycle 2 Day 3 and simulated exposure on Cycle 3 Day3 showed that cedazuridine exposures did not increase in later cycles.

Table 20. Plasma Cedazuridine DDI Assessment Between ASTX727 + Venetoclax and ASTX727 Alone – Phase 2 Part B (Study ASTX72707)

PK Parameter	Units	Test Geo LSM (N = 95)	Reference Geo LSM (N = 78)	Ratio of Geo LSM (%)	90% CI
AUC_{0-24}	h*ng/mL	3136[a]	3600	87.09	(76.93, 98.60)
AUC_{0-8}	h*ng/mL	1768	1902	92.97	(81.99, 105.40)
AUC_{0-inf}	h*ng/mL	3330[b]	4060[c]	82.02	(71.84, 93.65)
C_{max}	ng/mL	299.0	342.6	87.26	(77.66, 98.05)

AML=acute myeloid leukemia; AUC_{0-8}=area under the plasma concentration-time curve from time zero to 8 hours; AUC_{0-24}=area under the plasma concentration-time curve from time zero to 24 hours; AUC_{0-inf}=area under the plasma concentration-time curve from time zero extrapolated to infinity; CI=confidence interval; C_{max}=maximum plasma concentration; DDI=drug-drug interaction; EU=European Union; Geo LSM=geometric least square means; PK=pharmacokinetic(s).

[a] n=93

[b] n=76

[c] n=56

Notes: Reference treatment = ASTX727 Alone (data from ASTX727-02 EU [AML] from Cycle 1 Day 2 and Cycle 2 Day 2). Test treatment = ASTX727 + Venetoclax (Cycle 1 Day 5).

Cedazuridine-epimer

The C_{max} and AUC exposures of cedazuridine were slightly increased when ASTX727(INAQOVI) was coadministered with venetoclax. The percentage ratios of the geometric LSMs were 121% and 114%, respectively, for C_{max} and AUC_{0-24} on Day 2 of Cycles 1 and 2. The percentage ratios of the geometric LSMs were 130% each, for C_{max} and AUC_{08} on Day 5 of Cycles 1 and 2. Although the 90% CIs were above the standard bioequivalence range of 80% to 125%, the differences were <1.5-fold.

Pharmacokinetics using human biomaterials

The purpose of this study was to determine the direct inhibition potential of venetoclax on cytidine deaminase (CDA) using recombinant enzyme and cytidine as substrate. In this study, recombinant CDA (10 ng/mL) was incubated for 5 minutes at 37°C with cytidine (25 µM) alone or in the presence of venetoclax (prepared in DMSO) at concentrations ranging from 0 to 100 µM. Additional incubations were performed with CDA in the presence of cytidine (25 µM) and the positive control inhibitor

tetrahydrouridine (0 to 10 μM) or the positive control inhibitor zebularine (0 to 100 μM). In all cases, metabolism of cytidine to uridine was determined by LC-MS/MS.

Venetoclax did not inhibit CDA activity within the range of tested concentrations and an IC50 value was not generated. In contrast, the positive control inhibitors generated mean IC50 values of 1.02 μM (tetrahydrouridine) and 3.78 μM (zebularine).

2.3.3. Pharmacodynamics

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.

Cytidine deaminase, cedazuridine, (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.

Primary and secondary pharmacology

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

As assessed and discussed in the initial Inaqovi submission (EMA/CHMP/402324/2023), the MAH has provided supportive PD data where the PD endpoint, i.e., the maximum percent LINE-1 demethylation, was not significantly different between Inaqovi and IV decitabine in the Phase 3 Study ASTX727-02 in AML or in MDS/CMML patients.

2.3.4. PK/PD modelling

Exposure-Response Analysis

Exploratory Exposure-Response (E-R) model analysis was conducted to characterize E-R for efficacy and safety outcomes for Study ASTX727-07 Phase 1, Phase 2 Part A, and Phase 2 Part B.

Efficacy outcomes included three time-to-event (TTE) outcomes (overall survival (OS), progression-free survival (PFS), and duration of complete response (CR)) and two binary outcomes (CR and any response).

Primary safety outcomes were grade 3+ neutropenia, grade 3+ thrombocytopenia, any grade febrile neutropenia, and any-grade gastrointestinal adverse event (AE). Secondary safety endpoints were any grade neutropenia, any grade thrombocytopenia, and any grade 3+ AE.

The analysis population included participants in Study ASTX727-07 who had both evaluable PK data (n= 162) and an efficacy or safety endpoint measurements. 162 subjects had evaluable PK data of which all had safety data and TTE data, and 155 subjects had disease response data.

The exposure metric used for the E-R analysis was the model-predicted daily decitabine AUC0-24 at steady-state, calculated using empirical Bayes estimates (EBEs) from the pop-PK model analysis presented in Section 9.2.

Exploratory data analysis (EDA) was performed for each efficacy and safety endpoint. Tables were constructed with descriptions of survival times (for TTE outcomes) or event rates (for binary outcomes) by various subgroups including study phase and baseline disease severity. Kaplan-Meier (KM) plots were constructed for TTE outcomes, and LOESS smooths and bar charts were constructed for binary outcomes, including overall and subgroup-faceted populations.

Results indicated that subjects with higher daily decitabine (DEC) AUC0-24 at steady-state generally had longer OS, PFS, and duration of CR, along with higher probabilities of CR (Figure 5) and any response. However, the safety ER analysis indicated that several examined AEs were more common in subjects with higher daily DEC AUC0-24 at steady-state, including grade 3+ and any grade neutropenia, grade 3+ and any grade thrombocyteopenia (Figure 6).

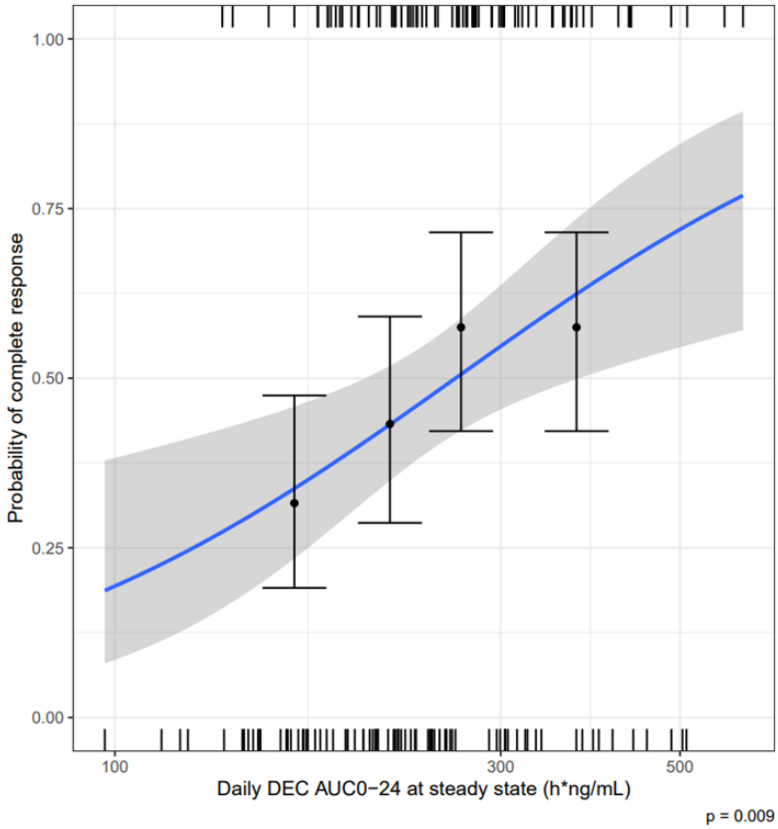


Figure 5. Efficacy: Relationship between the probability of complete response and daily DEC AUC0-24 at steady-state for all study parts with overlaid exposure quartiles.

Solid blue line represents a LOESS smooth of original data (tick marks along the x-axes), and the gray region indicates a 95% CI for the smooth. Error bars represent the 95% CIs of probability at the Cycle

2 Day-5 decitabine AUC exposure quartiles for subject subgroups. AUC: area under the curve; CI: confidence interval.

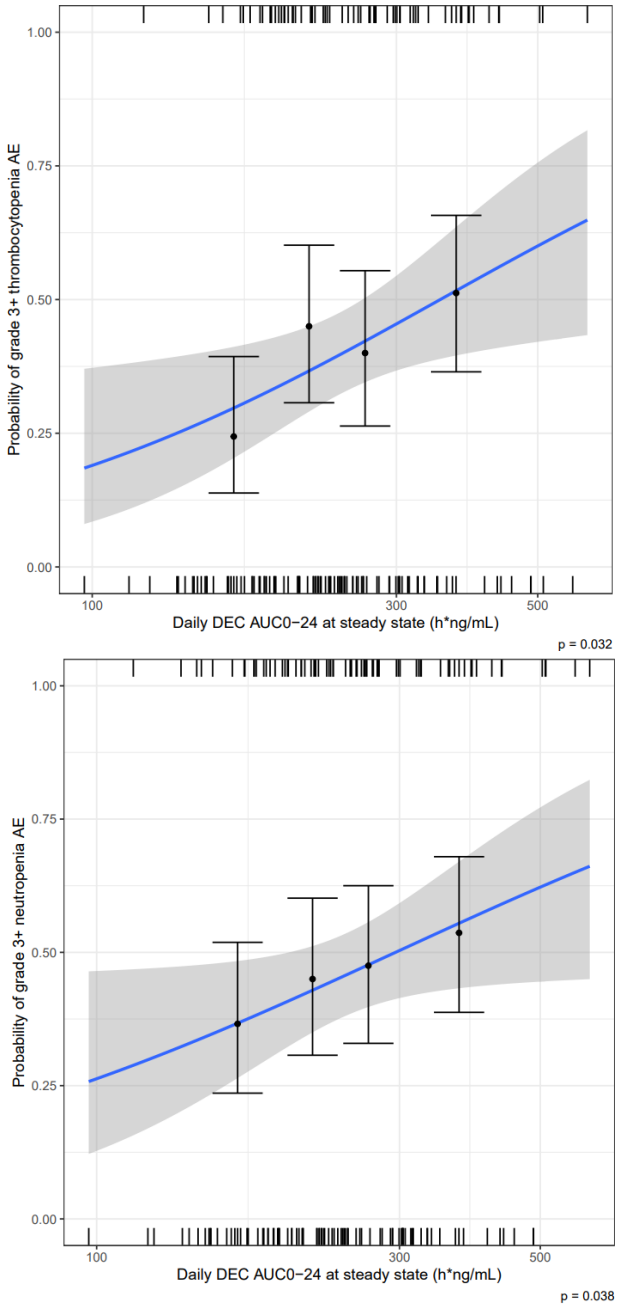


Figure 6. Relationship between the probability of grade 3+ thrombocytopenia/neutropenia adverse event and daily DEC AUC0-24 at steady-state for all study parts with overlaid exposure quartiles.

2.3.5. Discussion on clinical pharmacology

Inaqovi was originally approved based on a PK bridge between the orally administered decitabine in Inaqovi (ASTX727(INAQOVI)) (1 tablet daily x 5) and previous efficacy and safety data for i.v. decitabine (20 mg/m^2 daily×5) based on equivalent decitabine exposure (total AUC over the 5-day

cycle). Bioequivalence for 5-Day AUC_{0-24} between oral and i.v. decitabine could be concluded for both the AML (ASTX727-02 EU, pivotal) and the MDS/CMML (ASTX727-02 NA, supportive) population as well as for pooled data from the two studies in the initial application.

The purpose of the current application is to extend the use of ASTX727(INAQOVI) to include combination therapy with venetoclax. Overall, the application relies upon the PK similarity between Inaqovi at the relevant dose, and i.v. decitabine at the dose given based on the available clinical experience in combination with venetoclax. The main objective is to present PK data demonstrating absence of interactions between venetoclax and decitabine and cedazuridine when given orally rather than i.v.

Methods

The bioanalytical method used to determine decitabine, cedazuridine and cedazuridine-epimer was the one used in the original application which was considered adequately validated. A new validated method for venetoclax was also used. A bioanalytical report was submitted for study ASTX727-07, indicating adequate performance of the analytical methods. Samples were analysed within established stability and ISR was performed with acceptable results.

Evaluation and qualification of models

The previous developed semi-mechanistic popPK model was updated with data from the ASTX727-07-study. The model described both cedazuridine and decitabine data adequately well. Parameter estimates were in general similar with the previous analysis including patients with AML (ASTX727-02-EU). Covariates, including sex, creatinine clearance and weight, were re-evaluated and no changes in the conclusions regarding the clinical effect of the covariates were identified. Individual post-hoc PK parameter estimates were derived from the model to be used in the exploratory ER-analysis. Additionally, PK profiles of cedazuridine and decitabine were simulated for Cycle 3 Day 3 in Study ASTX727-07 Phase 2 Part B, where only sparse sampling was available. Exposure metrics (Cmax and AUC_{0-24}, Cycle 1 Day 5) in the SmPC section 5.2 were derived from non compartmental analysis (as for previous indication). This is acceptable.

Co-treatment with venetoclax was additionally tested as a covariate on the exposure of cedazuridine and decitabine. The observed exposure of decitabine in Study ASTX727-07 Cycle 2 appeared to be slightly higher than in Study ASTX727-02 (where data from cycle 1 and 2 were presented together). Of note, since data with and without venetoclax were not available from the same study, it is however not possible to separate a potential venetoclax effect from a study-covariate. From the model analysis, a trend toward lower ETAs on both CL and Q was observed in the venetoclax group. A separate model including venetoclax as a categorical covariate effect on decitabine clearance had been investigated and had resulted in only limited venetoclax effect (about 10% lower clearance) and similar parameter estimates. The detailed results from this model were however not submitted in this application. The assessment of the possible effect of venetoclax on decitabine PK is further discussed in the drug-drug interaction section. Based on the intended use of the model, and ability of the current model to describe the observed data adequately, the omission of venetoclax as a covariate in the pop-PK analysis is yet accepted.

Absorption

A post-approval food effect study (ASTX727-06 food effect sub-study) was previously submitted as part of variation EMEA/H/C/005823/II/0002. This food effect study was a post-marketing commitment with FDA, already ongoing at the time of the initial European MAA and investigated both the effect of a high-fat and a low-fat meal, while the original food effect study (ASTX727-04) only investigated the effect of a high-fat meal. It is currently recommended (section 4.2 of the SmPC) that Inaqovi should be administered in the fasted state, on an empty stomach with no food intake 2 hours before and following

administration of the Inaqovi tablet. No changes were proposed by the Applicant due to the results of ASTX27-06. As in the initial MAA the Applicant argues that the lower exposure of decitabine may lead to reduced efficacy, and that this was the recommendation used also in the phase-3 studies. This is acceptable,

Since the previous variation EMEA/H/C/005823/II/0002 was withdrawn, data from the new food effect study was not included in the SmPC, but has now been included as part of the current variation.

Drug-drug interactions

The *in vitro* study A2001052 was submitted with the original MAA but was not assessed as it was not relevant for that application. This study demonstrated that venetoclax is not a direct inhibitor of cytidine deaminase (CDA), the enzyme that metabolizes decitabine to an inactive deaminated form, at concentrations up to 100 µM and therefore venetoclax is not likely to alter metabolism of decitabine and as such, no drug-drug interactions are expected when venetoclax will be dosed in combination with ASTX727(INAQOVI).

Study ASTX727-07 investigated potential interactions between venetoclax and decitabine/cedazuridine. Venetoclax and decitabine/cedazuridine have different SmPC recommendations regarding administration in relation to food and were given in accordance with their respective SmPC recommendations.

For venetoclax, data on exposure with and without decitabine/cedazuridine was available from the same study. It has been well characterized that there was no effect of decitabine/cedazuridine on venetoclax, since results were within conventional BE criteria. However, decitabine/cedazuridine was not given without venetoclax in study ASTX727-07.

Instead, the investigation of interaction effect is based on a between-study comparison to historical data for decitabine/cedazuridine from study ASTX727-02 EU (AML). This is not optimal as already discussed by the Applicant, due to differences in e.g. study population and study design, and thus this potential interaction is less well characterized.

Based on data from Phase 1 and Phase 2 Part A (cycle 2 data), decitabine C_{max} and AUC when given with venetoclax were 25% and 42% higher, respectively, compared to those observed for decitabine without venetoclax in Study ASTX727-02 EU (AML). The applicant discusses that the higher exposures were driven by several subjects with very low bone marrow cellularity in Cycle 2 and that the dual myelosuppressive therapy could have led to rapid reduction of these cells that produce CDA, resulting in higher levels of decitabine in some individual patients until their cellularity has recovered. This hypothesis is noted but it cannot be concluded based on current data whether this is the explanation or if the higher observed exposure could be explained by the weaknesses of the between-study comparison. Also, in case this hypothesis is true, this would be a systemic effect that would be present also when combining venetoclax with i.v. decitabine.

On the other hand, based on data from phase 2 part B (cycle 1 data), decitabine C_{max} and AUC when given with venetoclax were within or almost within BE acceptance criteria compared to those observed for decitabine without venetoclax in Study ASTX727-02 EU (AML). In cycle 2 and 3 of phase 2 part B, AUC was approximately 15% higher compared to cycle 1 data. It was originally planned to use cycle 2 data for the PK comparisons, since venetoclax dosage was up-titrated during cycle 1. On the other hand, use of cycle 1 data generally means less effects of dose reductions that may occur in later cycles.

There were a number of protocol deviations related to dosage of decitabine, where Inaqovi was either dosed in the fed state instead of in the fasted state (which could lead to a decrease in decitabine exposure) or where there were less than 2 hours between Inaqovi and venetoclax administration,

indicating that there was less than the recommended 2 hours between intake of Inaqovi and food intake, which could also lead to a decrease in decitabine exposure. However, considering that such deviations in most cases occurred on only one occasion per patient, the effect on the decitabine exposure following multiple-dose administration is expected to be limited.

For cedazuridine, exposure data from Phase 1 and Phase 2 Part A were slightly higher and exposure data from phase 2 part B were slightly lower compared to data from Study ASTX727-02 EU (AML). Any differences in cedazuridine exposure are not expected to be relevant as such, since decitabine is the active substance. Thus, the focus is on the effects on decitabine exposure.

As discussed above, potential effects of venetoclax on decitabine exposure are less well characterised due to the between-study comparison and results vary somewhat based on which cycle and study part of study ASTX727-07 is compared to the historical data from study ASTX727-02 EU (AML), with an observed worst-case 1.4-fold increase in AUC based on phase 1 and phase 2 part A data but with comparable exposure compared to historical data based on phase 2 part B data. Based on theoretical considerations, no pharmacokinetic interactions between venetoclax and decitabine are expected. It is thus questioned whether existing differences in exposure between study ASTX727-07 and ASTX727-02 can be attributed to an actual DDI effect or other between study differences. Given the limited magnitude of any potential DDI a substantial impact on clinical safety is deemed unlikely (moreover any impact of venetoclax on the systemic clearance of decitabine would likely be relevant also for i.v. decitabine).

Decitabine exposure when Inaqovi was coadministered with venetoclax (Study ASTX727-07 phase 2 part B) was comparable to Inaqovi monotherapy (study ASTX727-02 EU (AML)), which demonstrated bioequivalence for 5-Day AUC_{0-24} compared to IV decitabine.

Exposure-Response analysis

The analysis was exploratory and of limited impact, including data from only one dose and one study.

Briefly, E-R analysis including endpoints for both efficacy and safety were performed, with individual decitabine exposure measures (daily decitabine AUC0-24 at steady-state) derived from the pop-PK model.

Trends indicating longer OS, PFS, and duration of CR, along with higher probabilities of CR and any response for subjects with higher decitabine exposure (AUC0-24) were observed. Higher decitabine exposure was however also correlated with more AEs.

2.3.6. Conclusions on clinical pharmacology

The purpose of the current application is to extend the use of ASTX727(INAQOVI) to include combination therapy with venetoclax. Overall, the application relies upon the PK similarity between Inaqovi at the proposed dose, and i.v. decitabine at the dose given based on available clinical experience in combination with venetoclax. The main objective was to present PK data demonstrating absence of interactions between venetoclax and decitabine and cedazuridine when given orally rather than i.v..

It has been well characterized that there was no effect of decitabine/cedazuridine on venetoclax exposure. The potential effect of venetoclax on decitabine/cedazuridine is less well characterised since it is based on a comparison to historical data from a different study, with an observed worst-case 1.4-fold increase in AUC based on a between-study comparison (phase 1 and phase 2 part A data) but with comparable exposure compared to historical data based on phase 2 part B data. Based on theoretical

considerations, no pharmacokinetic interactions between venetoclax and decitabine are expected. Given the magnitude of any potential DDI a substantial impact on clinical safety is deemed unlikely.

Decitabine exposure when Inaqovi was coadministered with venetoclax (Study ASTX727-07 phase 2 part B) was comparable to Inaqovi monotherapy (study ASTX727-02 EU (AML)), which demonstrated bioequivalence for 5-Day AUC_{0-24} compared to i.v. decitabine.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response study has been performed for the sought indication.

The PK parameters of decitabine and cedazuridine have previously been studied following administration of Inaqovi at the recommended dose in patients with myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML), and AML (Inaqovi EPAR). Decitabine AUC exposure equivalent to those achieved with intravenous infusion of decitabine at 20 mg/m2 was reached with the recommended dose of monotherapy Inaqovi which is 1 tablet once daily on Days 1 through 5 of each 28 day cycle (Inaqovi SmPC). The recommended dose of Inaqovi remains unchanged in the present application.

2.4.2. Main study

Title of Study

A Single-Arm, Open-Label Pharmacokinetic, Safety, and Efficacy Study of ASTX727(INAQOVI) in Combination with Venetoclax in Adult Patients with Acute Myeloid Leukemia

Study ASTX727-07 is a Phase 1/2 single arm, open-label, multicentre, non-randomised interventional study designed to evaluate the PK, safety, and efficacy of oral decitabine and cedazuridine when given in combination with venetoclax to AML patients who are not eligible for intensive induction chemotherapy.

Phase 2 Part B is the pivotal portion of Study ASTX727-07 for the efficacy analysis. Supportive efficacy data are derived from Phase 1 and Phase 2 Part A.

Treatment schedules were the same for all parts of the study. The differences among Phase 1, Phase 2 Part A, and Phase 2 Part B involved the timing of PK sampling, prophylactic azole antifungal treatment, and dose modifications.

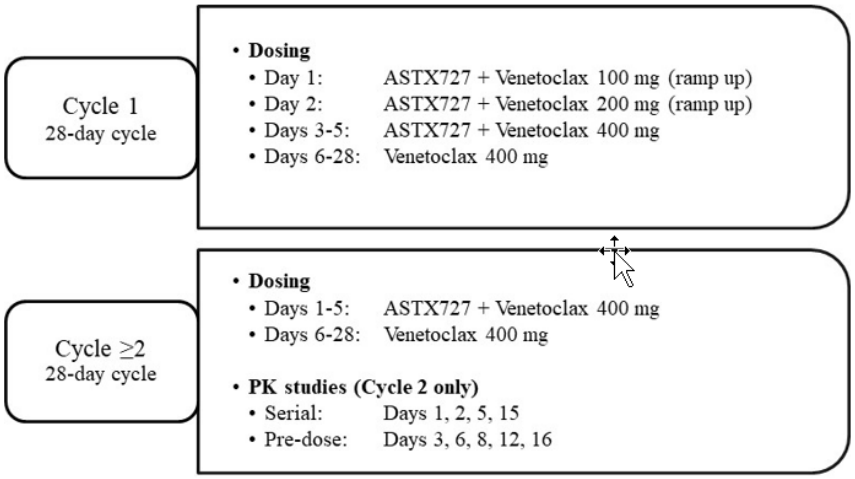


Figure 7. Study Schema – Phase 1

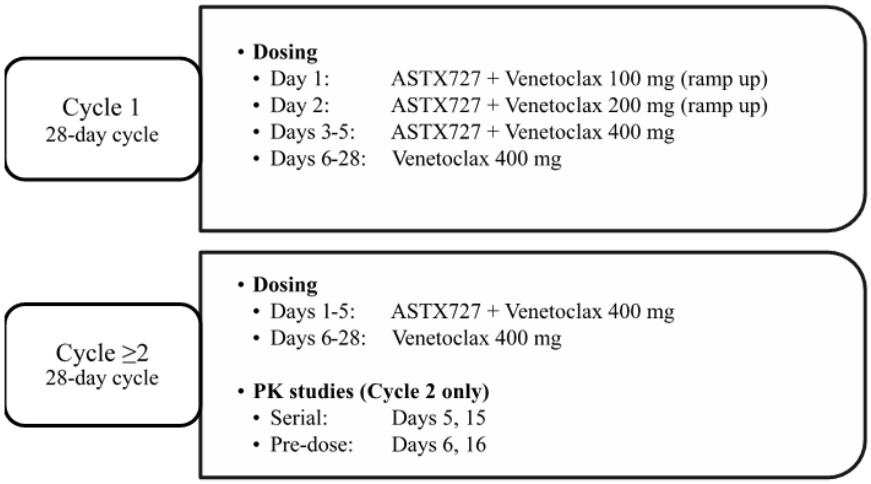


Figure 8. Study Schema – Phase 2 Part A

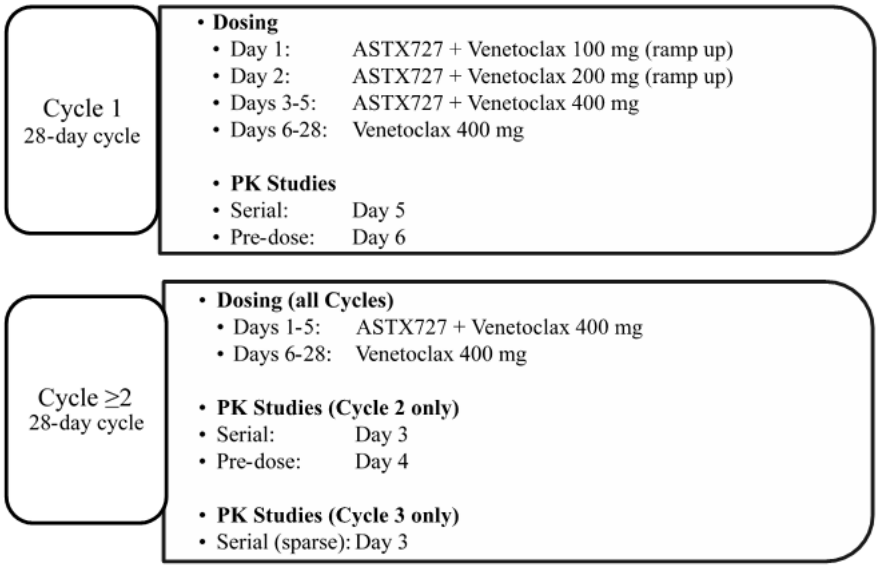


Figure 9. Study Schema – Phase 2 Part B

Methods

Study participants

Key inclusion criteria

- ≥ 18 years of age.
- Histological confirmation of newly diagnosed AML by WHO 2016 criteria.
- Ineligible for intensive induction chemotherapy defined by the following:
  a. Age 75 years or older, or
  b. Age 18 to 74 years with at least one of the following comorbidities: Severe cardiac disorder, Severe pulmonary disorder, Creatinine clearance ≥30 mL/min to <45 mL/min, Moderate hepatic impairment with total bilirubin >1.5 to ≤3.0 × upper limit of normal (ULN), Performance Status ≥ 2.
- Phase 1: Performance Status 0-2. Phase 2 Part A and Phase 2 Part B: Performance Status 0-3.

Key exclusion criteria

- History of myeloproliferative neoplasm.
- Known active central nervous system involvement from AML.
- Severe hepatic impairment.
- Severe renal impairment.
- Cardiovascular disability status of New York Heart Association Class >2.
- Clinically significant uncontrolled systemic infection requiring therapy.
- WBC count >25,000/μL (hydroxyurea treatment was permitted to meet this criterion.)
- Prior/concomitant therapy with azacitidine or decitabine or venetoclax, CAR-T cell therapy, or investigational therapies for MDS or AML.

Treatments

Treatment schedules were the same for all parts of Study ASTX727-07.

Each treatment cycle was 28 days.

- Inaqovi tablets (35 mg decitabine and 100 mg cedazuridine) were administered orally once daily on Days 1-5 of each cycle.
- Venetoclax tablets were administered orally once daily as follows: 100 mg on Cycle 1 Day 1 (C1D1), 200 mg on Cycle 1 Day 2, 400 mg on Cycle 1 Days 3-28, and 400 mg on Cycles ≥2 Days 1-28.

During days 1-5, Inaqovi should be taken on an empty stomach (morning before breakfast) with no food for 2 hours before and at least 2 hours after administration, and, venetoclax should be taken with breakfast at least 2 hours after Inaqovi. During days 6-28, venetoclax should be taken with breakfast at the same time each day.

According to the protocol, alternative options for Inaqovi and venetoclax administration on days 1-5 were allowed, as shown in table below.

Table 21. Alternative ASTX727 and Venetoclax Dose Timing with Meals

Venetoclax	ASTX727	Last meal (≥2 hours BEFORE taking ASTX727)	Next meal (≥2 hours AFTER taking ASTX727)
with breakfast	between breakfast and lunch	breakfast	lunch
with breakfast	between lunch and dinner	lunch	dinner
with breakfast	at bedtime	dinner	breakfast (next day)

Phase 1 and Phase 2 Part A

Dose reductions for hematologic toxicity required consultation with the medical monitor, and in general were not allowed until completion of PK sampling. Prophylactic azole antifungal therapy was prohibited during the time that could affect the PK measurements (7 days or 5 half-lives, whichever was greater, prior to C1D1 through C2D16).

Phase 2 Part B

Dose modifications for hematologic toxicity were permitted after the end of Cycle 1, at the investigator's discretion. Azole antifungals were restricted for a shorter period than in Phase 1 and Phase 2 Part A (7 days or 5 half-lives, whichever was greater, prior to C1D1 through C1D6).

Objectives

Table 22. Phase 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the potential of drug-drug interaction: effect of ASTX727 on PK of venetoclax	Venetoclax AUC_{0-24} and C_{max} on Day 5 with ASTX727 and Day 15 without ASTX727 in Cycle 2
Secondary	
To evaluate the potential of drug-drug interactions: effect of venetoclax on PK of ASTX727	Decitabine and cedazuridine AUC_{0-24} and C_{max} on Day 5 with venetoclax; cedazuridine AUC_{0-8} on Day 5 with venetoclax in Cycle 2
To evaluate the safety of ASTX727 and venetoclax combination therapy	Incidence and severity of adverse events (AEs) as well as other safety assessments
To evaluate clinical response[a] with ASTX727 and venetoclax combination therapy	CR rate CR+CRh rate CR+CRi rate
To evaluate preliminary efficacy as determined by time-to-event endpoints with ASTX727 and venetoclax combination therapy	Time to CR or CRh Duration of CR or CRh Overall survival
To evaluate secondary PK parameters of venetoclax, decitabine, and cedazuridine	5-day cumulative decitabine AUC in Cycle 2. Decitabine AUC_{0-24} and C_{max} on Days 1 and 2 in Cycle 2 Cedazuridine AUC_{0-8} on Days 1, 2, and 5 in Cycle 2; AUC_{0-24}, AUC_{0-inf}, and C_{max} on Days 1, 2, and 5 in Cycle 2 C_{max}, C_{min}, T_{max}, $T_{½}$ and other secondary PK parameters

Abbreviations: AE=adverse event; AUC=area under the curve; AUC_{0-24}=area under the curve from time 0 to 24 hours; C_{max}=maximum observed concentration; C_{min}=minimum observed concentration at steady state; CR=complete response; CRh=complete response with partial hematologic recovery; CRi=complete response with incomplete hematologic recovery; PK=pharmacokinetic; T½=apparent elimination half-life; T_{max}=time to maximum observed concentration.

Table 23. Phase 2 Part A Objectives and Endpoints

Objectives	Endpoints
Co-Primary	
To evaluate clinical response[a] with ASTX727 and venetoclax combination therapy	CR rate
To evaluate the potential of drug-drug interactions: effect of ASTX727 on PK of venetoclax	Venetoclax AUC_{0-24} and C_{max} on Day 5 with ASTX727 and Day 15 without ASTX727 in Cycle 2
Secondary	
To evaluate the safety of ASTX727 and venetoclax combination therapy	Incidence and severity of adverse events (AEs) as well as other safety assessments
To evaluate the potential of drug-drug interactions: effect of venetoclax on PK of ASTX727	Decitabine and cedazuridine AUC_{0-24}, C_{max}, AUC_{0-8}, and AUC_{0-inf} on Day 5 with venetoclax in Cycle 2
To evaluate composite clinical response rates[a] with ASTX727 and venetoclax combination therapy	CR+CRh rate CR+CRi rate
To evaluate preliminary efficacy as determined by time-to-event endpoints with ASTX727 and venetoclax combination therapy	Time to CR or CRh Duration of CR or CRh Overall survival
To evaluate secondary PK parameters of venetoclax, decitabine, and cedazuridine	C_{max}, C_{min}, T_{max}, $T_{½}$, and other secondary PK parameters

Abbreviations: AE=adverse event; AUC=area under the curve; AUC_{0-24}=area under the curve from time 0 to 24 hours; C_{max}=maximum observed concentration; C_{min}=minimum observed concentration at steady state; CR=complete response; CRh=complete response with partial hematologic recovery; CRi=complete response with incomplete hematologic recovery; PK=pharmacokinetic; T½=apparent elimination half-life; T_{max}=time to maximum observed concentration.

Phase 2 Part A was added with the implementation of Protocol Amendment 2.0 (dated 09 July 2021) to further evaluate safety and efficacy with CR rate and also DDI effect of venetoclax on the pharmacokinetics of ASTX727(INAQOVI) as the co-primary efficacy endpoints.

Table 24. Phase 2 Part B Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate clinical response[a] with ASTX727 and venetoclax combination therapy	CR rate
Secondary	
To evaluate the safety of ASTX727 and venetoclax combination therapy.	Incidence and severity of adverse events (AEs) as well as other safety assessments
To evaluate the potential of drug-drug interactions: effect of venetoclax on PK of ASTX727	Decitabine and cedazuridine AUC_{0-24}, C_{max}, AUC_{0-8}, and AUC_{0-inf} on Day 5 with venetoclax in Cycle 1
To evaluate composite clinical response rates[a] with ASTX727 and venetoclax combination therapy	CR+CRh rate CR+CRi rate
To evaluate time to response, duration of response, and overall survival for patients receiving ASTX727 and venetoclax combination therapy	Time to CR or CRh Duration of CR or CRh Overall survival
To evaluate secondary PK parameters of venetoclax, decitabine, and cedazuridine	C_{max}, C_{min}, T_{max}, $T_{½}$, and other secondary PK parameters

Abbreviations: AE=adverse event; AUC=area under the curve; AUC_{0-8}=area under the curve from time 0 to 8 hours; AUC_{0-24}=area under the curve from time 0 to 24 hours; AUC_{0-inf}=area under the curve from time 0 to infinity hours; C_{max}=maximum observed concentration; C_{min}=minimum observed concentration at steady state; CR=complete response; CRh=complete response with partial hematologic recovery; CR_{MRD-}= complete response without minimal residual disease; CRh_{MRD-}=complete response with partial hematologic recovery without minimal residual disease; CRi_{MRD-}= complete response with incomplete hematologic recovery and without minimal residual disease; CRi=complete response with incomplete hematologic recovery; MRD=minimal residual disease; PK=pharmacokinetic; T½=apparent elimination half-life; Tmax=time to maximum observed concentration.

Phase 2 Part B was added with the implementation of Protocol Amendment 3.0 (dated 05 January 2023) with CR as the primary endpoint. In this part of the study, modifications regarding PK sampling

were incorporated and Investigators were permitted to initiate dose modifications (of ASTX727(INAQOVI), venetoclax, or both) for patients who achieved complete remission to decrease the occurrence of bone marrow toxicity. The modified timepoints for pharmacokinetic sampling enabled an earlier initiation of prophylactic treatment with azole antifungals than was allowed in Phase 1 and Phase 2 Part A.

Outcomes/endpoints

Efficacy endpoints in the pivotal Phase 2 Part B were assessed by the investigator.

European LeukemiaNet (ELN) response criteria from 2017 was used to identify CR, CR with incomplete hematologic recovery (CRi), or partial remission (Döhner et al 2017).

The ELN recommendations were initially based on the International Working Group response criteria by Cheson et al in 2003, to which molecular genetics and MRD assessment have been incorporated (Döhner et al 2010, Döhner et al 2017).

Table 25. Definition of response categories CR, CRi, and PR according to ELN 2017

Response	Peripheral Blood (PB)[a]	Bone Marrow (BM)
Complete Remission (CR)	Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count (ANC) >1.0 × 10^9/L (1000/µL); platelet count >100 × 10^9/L (100 000/µL); Applies regardless of minimal residual disease (MRD) status.	<5% leukemic blasts
CR with incomplete hematologic recovery (CRi)	All CR criteria except for residual neutropenia (≤1.0 × 10^9/L [1000/µL]) or thrombocytopenia (≤100 × 10^9 /L [100 000/µL])	<5% leukemic blasts
Partial remission	All hematologic criteria of CR	Decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%

CR with partial hematologic recovery (CRh) was defined as morphologic CR in blood and bone marrow according to ELN criteria except the ANC and platelet count criteria are not met but there is partial hematologic recovery defined as ANC (>0.5×10 ^{9} /L [500/µL]) and platelet (>50×10^9/L [50,000/µL]) according to Kantarjian et al 2017.

After achieving a confirmed CR or CRh, BM evaluation was to be performed at least every 3 cycles for the first year, then as clinically indicated, to monitor duration of response (DOR).

According to protocol amendment 5, responses may be assessed and adjudicated by the Sponsor and/or an external committee.

Sample size

Phase 1

A sample size of up to 24 evaluable patients (with a minimum of 18) was planned. Assuming that the coefficient of variation for the PK assessment for venetoclax was 0.48, a correlation between the paired time points for venetoclax with or without ASTX727(INAQOVI) was 0.725, the true ratio of geometric means was 1.0, the 90% CI equivalence limits for the ratio of geometric means were 0.8 and 1.25, up

to 24 evaluable patients included in the two one-sided equivalence tests would provide 75% to 89% power at a 5% significance level.

Phase 2 Part A

A sample size of approximately 98 to 100 patients was planned. As of Amendment 3.0 (dated 05 January 2023), enrolment in Phase 2 Part A stopped with 58 patients enrolled and treated.

With CR rates assumed to be 31.0%-36.7%, 98 or 100 subjects was expected to yield a 95% CI width of less than 20% and a lower limit of at least 22% to exclude a clinically relevant response rate of the monotherapy IV decitabine. The CR response rates were based on previous studies on decitabine single therapy (Kantarjian et al 2012) and the combination therapy of azacitidine plus venetoclax in the AML population (DiNardo et al, 2020).

Phase 2 Part B

The target sample size was the same as for Phase 2 Part A.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

Statistical analyses were performed separately for each study phase (Phase 1, Phase 2 Part A, and Phase 2 Part B).

In both parts of Phase 2, the primary efficacy population included all patients who received at least one dose of study drug (the 'all treated population').

Rates of CR, CR+CRh, and CR+CRi were defined as the number of patients whose best response was CR, CR or CRh, and CR or CRi; divided by the total number of patients. Each patient was counted once according to their best response. Best overall responses were based on clinical response as assessed by the Investigator performed at different visits. 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method. The protocol stated that efficacy should be considered established if the 95% confidence interval for CR exceeds 22%. This threshold was lowered to 17.9% in the statistical analysis plan.

For binary endpoints, missing data were considered to indicate non-response. Intercurrent events, such as administration of growth factors, were handled using a treatment policy strategy.

Overall survival (OS) time was estimated using the Kaplan-Meier method. Median OS (mOS) and two-sided 95% CI were provided. The OS rate at 3, 6, 9, 12, and 24 months (and in subsequent 6-month increments if there were participants still at risk) were estimated with corresponding two-sided 95% CIs. For patients not known to have died, OS was censored on the date they were last known to be alive.

Results

Participant flow

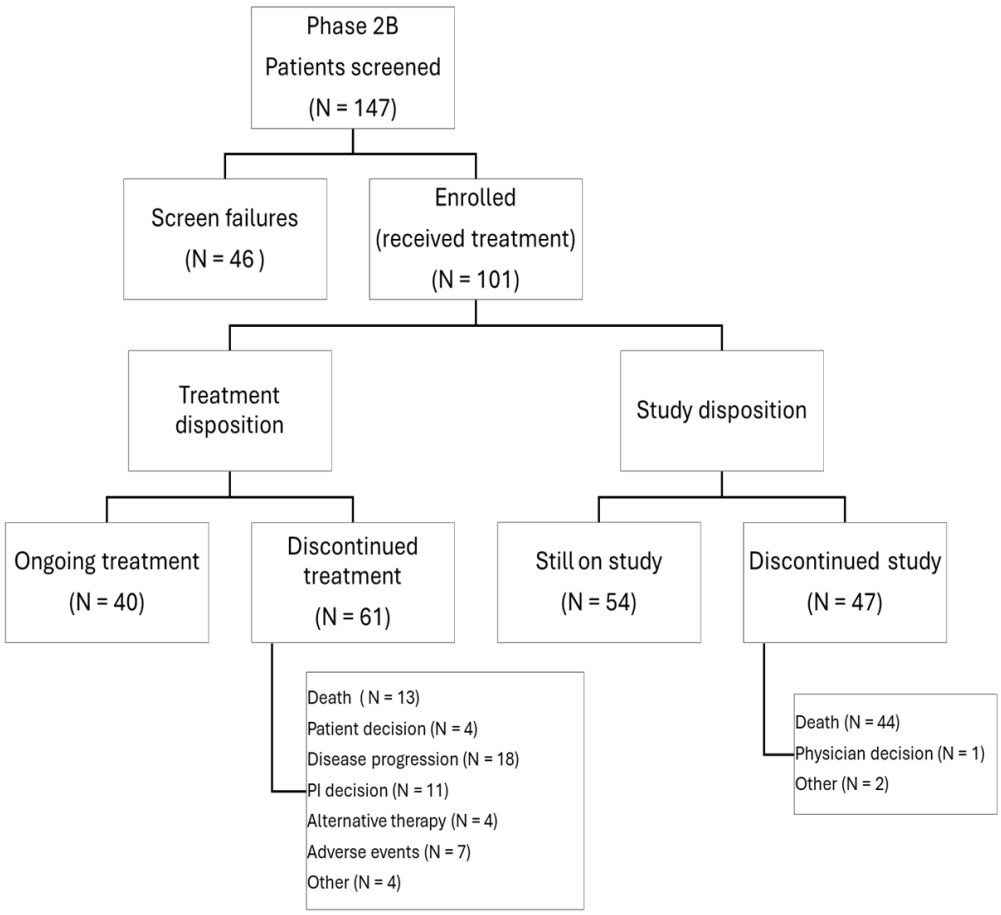


Figure 10. Patient Disposition for Phase 2 Part B

Beginning 3 months after the 30-day Safety Follow-up visit (for subjects who permanently discontinued treatment), subjects were to be followed in long-term follow up for health status information, which was to be gathered every 3 months until death, subject withdrawal of consent, loss to follow up, or the study ended, whichever occurred first.

Recruitment

First subject enrolled in Phase 1: 09 February 2021.

First subject enrolled in Phase 2 Part A: 04 November 2021

First subject enrolled in Phase 2 Part B: 10 April 2023

Last Patient Visit: Not Applicable (study ongoing).

As of protocol amendment 3 (dated 05 January 2023), when the Phase 2 Part B was added, enrollment in Phase 1 was completed with 30 subjects treated, and enrollment in Phase 2 Part A was stopped with 58 patients enrolled and treated.

Data cutoff date was 17 July 2024 for Phase 1 and 30 Sep 2024 for Phase 2 Part A and Part B.

This study was conducted at 50 sites that enrolled patients in North America and Europe.

Conduct of the study

Protocol amendments

The original protocol was dated 06 August 2020 and was amended 5 times.

Amendment 1 (16 March 2021): The main purpose was to add ECOG performance status 2 as a qualifying comorbidity inclusion criteria for subjects <75 years old, to expand the subject population eligible for study participation.

Amendment 2 (09 July 2021). The main purpose was to add a Phase 2 portion to the study, with largely the same study design as Phase 1 except for two co-primary objectives in the Phase 2 portion, i.e., to evaluate both efficacy and potential drug-drug interaction effect of ASTX727(INAQOVI) on venetoclax.

Amendment 3 (05 January 2023): The main purpose was to rename the existing Phase 2 portion to Phase 2 Part A, and also to add the Phase 2 Part B. For Phase 2 Part B, changes affecting PK sampling, supportive care recommendations, and dose modification recommendations after achieved clearance of marrow blasts were introduced. Per the 'Dear Investigator Letter" issued on 12 September 2022, these changes were expected to help with the number of evaluable subjects for the PK objectives and help subjects stay on treatment longer by minimizing treatment toxicity.

Amendment 4 (04 August 2023): Minor modifications were done, including the addition of exploratory MRD endpoints.

Amendment 5 (08 May 2024): Modifications related to change of sponsor from Astex to Taiho Oncology were made.

Protocol deviations

Table 26. Important Protocol Deviations - Phase 1

Table 14.1.2
Important Protocol Deviations - Phase 1
All Treated Population

	Total (N=30) n (%)
Patients with at least One Important Protocol Deviation	21 (70.0)
IP ADMINISTRATION	4 (13.3)
LABORATORY ASSESSMENT	8 (26.7)
PK/PD	4 (13.3)
SAFETY	1 (3.3)
SOURCE DOCUMENT CRITERIA	1 (3.3)
STUDY PROCEDURES	10 (33.3)
SUBJECT IP COMPLIANCE	11 (36.7)
VISIT SCHEDULE	4 (13.3)

IP = investigational products

Table 27. Important Protocol Deviations - Phase 2

Table 14.1.2.p2
Important Protocol Deviations - Phase 2
All Treated Population

	Part A (N=58) n (%)	Part B (N=101) n (%)
Patients with at least One Important Protocol Deviation	48 (82.8)	74 (73.3)
ADMINISTRATIVE	1 (1.7)	0
CONCOMITANT MEDICATION	2 (3.4)	4 (4.0)
EFFICACY	0	1 (1.0)
INFORMED CONSENT AND PROCESS	10 (17.2)	18 (17.8)
IP ADMINISTRATION	18 (31.0)	29 (28.7)
LABORATORY ASSESSMENT	16 (27.6)	12 (11.9)
PATIENT REPORTED OUTCOMES	1 (1.7)	0
PK/PD	13 (22.4)	26 (25.7)
SAFETY	6 (10.3)	7 (6.9)
STUDY PROCEDURES	17 (29.3)	20 (19.8)
SUBJECT IP COMPLIANCE	25 (43.1)	34 (33.7)
VISIT SCHEDULE	2 (3.4)	2 (2.0)

IP = investigational products

Baseline data

Table 28. Selected Demographics and Baseline Characteristics

	Phase 1 (N=30)	**Phase 2 Part A (N=58)**	**Phase 2 Part B (N=101)**
Age (years)			
Median (Min, Max)	78.0 (66, 87)	75.0 (56, 91)	78.0 (63, 88)
Sex, n (%)			
Male	16 (53.3)	33 (56.9)	61 (60.4)
ECOG Performance Status, n (%)			
0	1 (3.3)	3 (5.2)	27 (26.7)
1	18 (60.0)	24 (41.4)	51 (50.5)
2	11 (36.7)	28 (48.3)	19 (18.8)
>2	0	3 (5.2)	3 (3.0)
Missing	N/A	0	1 (1.0)
Baseline Bone Marrow Blast (%)			
n	28	58	100
Median (Min, Max)	40.00 (13.0, 90.0)	49.00 (5.0, 97.0)	40.00 (7.0, 95.0)
Missing	2 (6.7)	0	1 (1.0)
Cytogenic Classification (%)			
n	30	58	101
Favorable	6 (20.0)	12 (20.7)	32 (31.7)
Intermediate	14 (46.7)	24 (41.4)	34 (33.7)
Adverse	9 (30.0)	18 (31.0)	30 (29.7)
Test Failed	0	3 (5.2)	4 (4.0)

	Phase 1 (N=30)	Phase 2 Part A (N=58)	Phase 2 Part B (N=101)
Missing	1 (3.3)	1 (1.7)	1 (1.0)
Baseline Hemoglobin (g/L)	-		
n	30	58	101
Mean (SD)	83.13 (10.689)	81.12 (11.411)	85.81 (12.531)
Median	82.00	79.50	85.00
Min, Max	67.0, 106.0	66.0, 120.0	67.0, 133.0
Baseline Absolute Neutrophils (10^9/L)			
n	28	57	98
Mean (SD)	1.84 (2.105)	0.93 (1.376)	1.49 (2.550)
Median	0.94	0.37	0.54
Min, Max	0.1, 8.2	0.0, 6.3	0.0, 14.9
Missing	2 (6.7)	1 (1.7)	3 (3.0)
Baseline Platelets (10^9/L)			
n	30	58	101
Mean (SD)	59.43 (49.568)	47.86 (41.425)	66.77 (60.797)
Median	38.00	37.50	48.00
Min, Max	10.0, 207.0	3.0, 238.0	3.0, 312.0

Table 29. Diagnosis at baseline

	Phase 1 (N=30)	Phase 2 Part A (N=58)	Phase 2 Part B (N=101)
Diagnosis, n (%)			
AML with recurrent genetic abnormalities	1 (3.3)	6 (10.3)	14 (13.9)
AML with myelodysplasia-related changes	12 (40.0)	25 (43.1)	57 (56.4)
AML, therapy-related	1 (3.3)	3 (5.2)	7 (6.9)
AML, NOS	16 (53.3)	24 (41.4)	23 (22.8)

Table 30. Prior Systemic Anti-Cancer

	Phase 1 n (%)	Phase 2 Part A n (%)	Phase 2 Part B n (%)
Number of Prior Anti-Cancer Therapies			
No prior anti-cancer therapies reported	23 (76.7)	52 (89.7)	86 (85.1)
1	5 (16.7)	4 (6.9)	13 (12.9)
2	1 (3.3)	2 (3.4)	1 (1.0)
3	0	0	0
≥4	1 (3.3)	0	1 (1.0)
Best Response to the Last Therapy, n (%)			
CR	3 (10.0)	3 (5.2)	3 (3.0)
PR	0	0	0
SD	0	0	0
PD	0	0	2 (2.0)
Unknown	4 (13.3)	3 (5.2)	10 (9.9)

Abbreviations: CR=complete response; PD=progressive disease; SD=stable disease; max=maximum; min=minimum; n=number of patients; PR=partial response.

The median (min, max) duration of treatment with ASTX727(INAQOVI) in the pivotal Phase 2 Part B was 5.5 months (0.2, 17.2 months), and 5.5 months (0.2, 17.2 months) with venetoclax, both for a median of 4.0 cycles (1, 15 cycles). Please refer to section Patient exposure in the safety assessment for further details on the extent of exposure.

Numbers analysed

The primary efficacy analysis of response in the pivotal Phase 2 Part B is based on the "All Treated Population", defined as all patients who received at least one dose of study drug, using the investigator assessment, N=101.

Supportive efficacy data are based on the "All Treated Populations" in Phase 1 (N=30) and Phase 2 Part A (N=58).

Outcomes and estimation

Pivotal Phase 2 Part B

Phase 2 Part B was the pivotal portion of the efficacy analyses for Study ASTX727-07, with median follow-up time 11.2 months (min, max: 0.3, 17.5) at the data cutoff date 30 Sep 2024.

Primary and secondary endpoints

Primary endpoint CR by investigator

Table 31. Response by Investigator – Phase 2 Part B (All Treated Population)

	Part B (N=101)
Best overall response, n (%)	
Complete response (CR) (95% CI)	47 (46.5) (36.5, 56.7)
Complete response with incomplete hematologic recovery (CRi) or Partial hematologic recovery (CRh)	17 (16.8)
Complete response with incomplete hematologic recovery (CRi)	17 (16.8)
Complete response with partial hematologic recovery (CRh)	5 (5.0)
Partial response (PR)	4 (4.0)
Stable disease (SD)	21 (20.8)
Progressive disease (PD)	3 (3.0)
Not evaluable (NE)	2 (2.0)
Unknown (UNK)	7 (6.9)

Abbreviations: CI=confidence interval; n=number of patients in a specific subgroup; N=total number of patients
Note: The exact 95% confidence intervals of the rate are two-sided and calculated using the Clopper–Pearson method.

CR by Independent Review Committee

Table 32. Response by IRC – Phase 2 Part B (All Treated Population)

	Part B (N=101)
Best overall response, n (%)	
Complete response (CR) (95% CI)	38 (37.6) (28.2, 47.8)
Complete response with incomplete hematologic recovery (CRi) or partial hematologic recovery (CRh)	25 (24.8)
Complete response with incomplete hematologic recovery (CRi)	22 (21.8)
Complete response with partial hematologic recovery (CRh)	13 (12.9)
Partial response (PR)	0
Stable disease (SD)	33 (32.7)
Progressive disease (PD)	2 (2.0)
Not evaluable (NE)	3 (3.0)
Unknown (UNK)	0

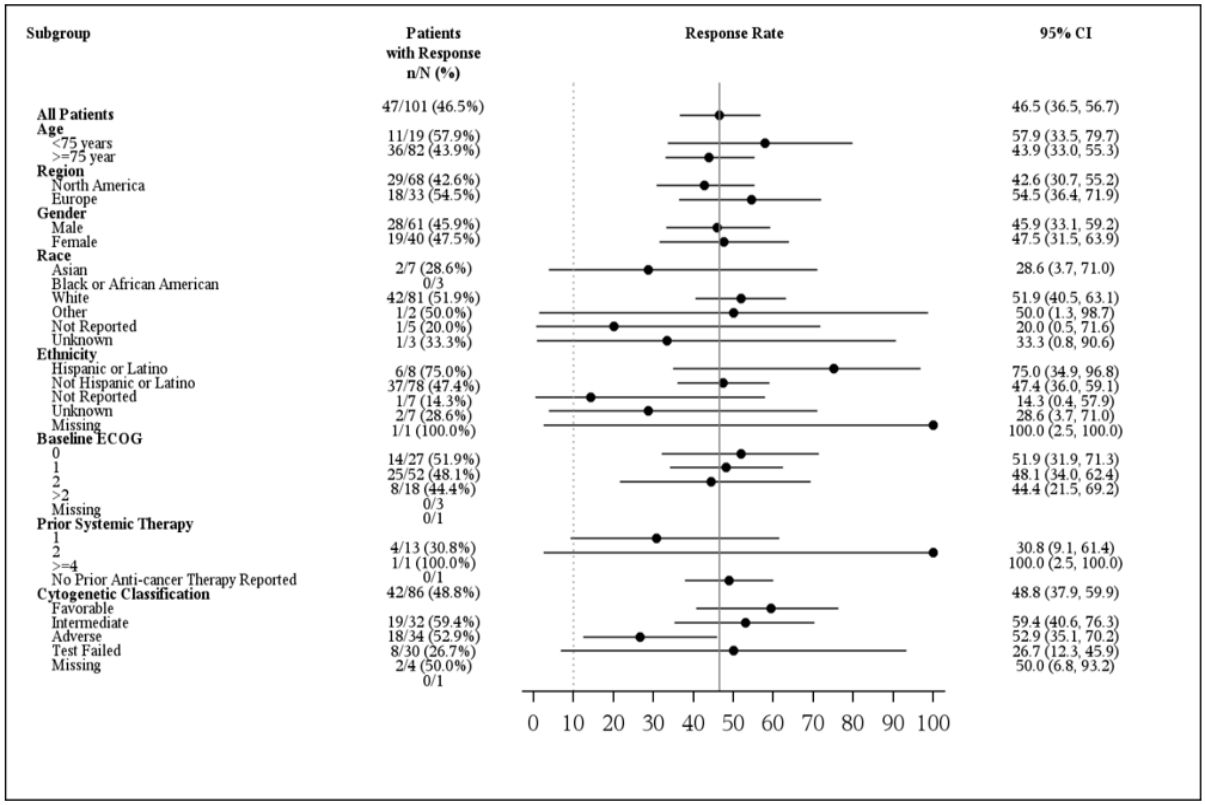
Abbreviations: CI=confidence interval; n=number of patients in a specific subgroup; N=total number of patientsSource:

Table 33. Concordance in CR per Investigator and IRC – Phase 2 Part B (All Treated Population)

Phase 2 Part B (N=101)		
IRC Assessment, n (%)	Investigator Assessment, n (%)	
	Responders (CR)	Non-responders
Responders (CR)	36 (35.6)	2 (2.0)
Non-responders	11 (10.9)	52 (51.5)

Abbreviations: CR=complete response; IRC=Independent Review Committee; n=number of patients per specific subgroup; N=total number of patients

Subgroup analysis for CR



Abbreviations: CI=confidence interval; ECOG= Eastern Cooperative Oncology Group; n=number of patients per specific subgroup; N=total number of patients

Figure 11. Forest Plot of CR by Investigator -Phase 2 Part B (All Treated Population)

Duration of response and Time to response

Table 34. Duration of Response and Time to Response by Inv – Phase 2 Part B (All Responders)

	Phase 2 Part B	
	CR (N=47)	**CR or CRh (N=52)**
Kaplan-Meier estimate of duration of response (months)		
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
1st quartile (95% CI)	NE (3.3, NE)	7.4 (3.8, NE)
3rd quartile (95% CI)	NE (NE, NE)	NE (NE, NE)
Time to response (months)		
Mean (standard deviation)	3.66 (3.321)	2.84 (2.477)
Median	2.37	2.10
Min, Max	0.7, 15.3	0.7, 10.7

PFS

Table 35. Progression Free Survival by Investigators - Phase 2 Part B (All Treated Population)

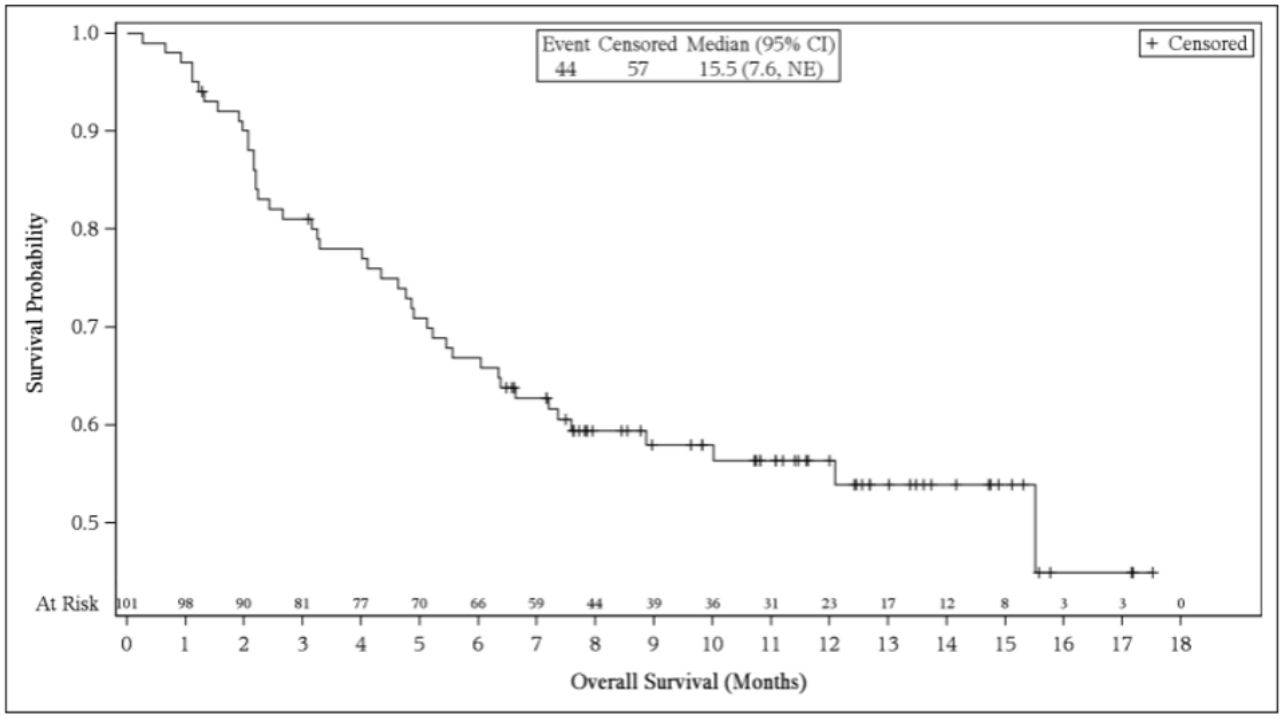
	Part B (N=101)
Event, n (%)	
Progressive disease (PD)	12 (11.9)
Death	22 (21.8)
Censored patients, n (%)	
Death or progression after more than one missed visit	12 (11.9)
Incomplete or no baseline cancer assessments	5 (5.0)
No progression	38 (37.6)
Treatment discontinuation for toxicity or other reasons	4 (4.0)
Treatment discontinuation without documented progression	8 (7.9)
PFS (months)	
Median (95% CI)	NE (11.30, NE)
Min, Max	0.03, 17.51

OS

Table 36. Overall Survival - Phase 2 Part B (All Treated Population)

	Part B (N=101)
Death, n (%)	44 (43.6)
Censored patients, n (%)	
Withdrawn from study	3 (3.0)
Alive at data cutoff	54 (53.5)
Overall survival (months)	
Median (95% CI)	15.51 (7.59, NE)
Min, Max	0.26, 17.51
Overall survival rate (%) (95% CI)	
At 3 months	81.1 (71.9, 87.5)
At 6 months	66.9 (56.7, 75.2)
At 9 months	58.0 (47.5, 67.1)
At 12 months	56.4 (45.7, 65.8)

Abbreviations: CI=confidence interval; Max=maximum; Min=minimum; n= number of patients; N=total number of patients
Note: OS is estimated using the KM product-limit method



Abbreviations: CI=confidence interval; NE=not evaluable

Figure 12. Kaplan-Meier Estimate of Overall Survival- Phase 2 Part B (All Treated Population)

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37. Summary of efficacy for trial ASTX727-07, phase 2 Part B, the pivotal portion of study ASTX727-07

Title: A Single-Arm, Open-Label Pharmacokinetic, Safety, and Efficacy Study of ASTX727(INAQOVI) in Combination with Venetoclax in Adult Patients with Acute Myeloid Leukemia		
Study identifier	ASTX727-07, EudraCT Number: 2020-004772-18, EU CT Number: 2024-516294-78	
Design	A non-randomized, open-label, single-arm, multicenter study to evaluate clinical response with ASTX727(INAQOVI) and venetoclax combination therapy.	
	Duration of main phase:	The study consisted of a 21-day Screening Period, a Treatment Period, and a 30-day Follow-up period. The duration of patient participation in this study was not fixed. Treatment continued until disease progression or unacceptable toxicity, or until the patient was
Hypothesis	The lower bound of the 95% confidence interval (CI) for the complete response rate of combination therapy of ASTX727(INAQOVI) and venetoclax was expected to exceed the pre-specified clinically relevant response rate of monotherapy IV decitabine. The efficacy threshold was based on the lower limit of the 95% CI to exceed a clinically relevant critical value of a 22% CR rate.	
Treatments groups	Phase 2 Part B	Each cycle was 28 days. In Cycle 1, ASTX727(INAQOVI) was administered on Days 1 to 5 in combination with venetoclax, which was given as a ramp-up on Day 1 (100 mg) and Day 2 (200 mg), followed by 400 mg daily on Days 3 to 28. From Cycle 2 onwards, ASTX727(INAQOVI) was administered on Days 1-5 and venetoclax (400 mg) was administered on Days 1-28.
		Number planned: N= 100 Number Treated: N= 101

Endpoints and definitions	CR rate	Complete Response Rate	The proportion of subjects who achieve CR. Response was assessed by the investigator using the 2017 European LeukemiaNet (ELN) response criteria (Döhner et al 2017) to identify CR, CRi, or PR, and the 2022 ELN update (Döhner et al 2022) to include MRD response categories, CR_{MRD-}, CRh_{MRD-}, and CRi_{MRD-}. Additionally, CRh was assessed as described in Kantarjian et al 2017
	CRi rate	Complete response with incomplete blood count recovery rate	The proportion of subjects who achieve CRi
	CRh rate	Complete response with partial hematologic recovery rate	The proportion of subjects who achieve CRh
	DoR	Duration of Response	DoR was calculated among responders from the date of initial documentation of a response to the date of first documented evidence of disease progression or death due to any
	TTR	Time to Response	Time to response is defined as time between treatment (first dose date) to the first documented response
	OS	Overall Survival	OS is defined as the time from the date of first dose until death due to any cause.
Database lock	Data cut-off date: 30 September 2024		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	All Treated Population using the Investigator's Assessment. All Treated Population is defined as All patients who received at least one dose of study drug. Data cut-off: 30 September 2024		
	Treatment group	ASTX727(INAQOVI) + Venetoclax N=101	
	CR	47 (46.5 %)	
	95% CI	(36.5, 56.7)	

Analysis description	Secondary analysis	
	Best Response	
	CRi	17 (16.8%)
	CRh	5 (5.0%)
	CR + CRi	64 (63.4% [95% CI: 53.2, 72.7])
	CR + CRh	52 (51.5 [95% CI:41.3, 61.6])
	Duration of Response (months)	
	CR, median (95% CI)	NE (NE, NE)
	CR or CRh, median (95% CI)	NE (NE, NE)
	Time to Response (months)	
	CR, median (min, max)	2.37 (0.7, 15.3)
	OS, median (months)	15.5 (95% CI: 7.59, NE)

NE=not evaluable/not reached

Supportive study(ies)

Data cutoff date was 17 July 2024 for Phase 1 (median follow-up time 34.3 months, min, max: 1.0, 41.1) and 30 Sep 2024 for Phase 2 Part A (median follow-up time 26.0 months, min, max:0.7, 34.8).

Phase 1

In Phase 1, 12 out of 30 (40.0%) patients achieved CR (95% CI: 22.7, 59.4) by investigator assessment. The median DoR was 17.5 months (95% CI: 2.6, NE) for CR. The median time to CR was 1.87 months (min, max: 0.9, 9.6). Median OS was 6.8 months (95% CI: 4.3, 19.5).

Phase 2 Part A

In Phase 2 Part A, 22 out of 58 (37.9%) patients achieved CR (95% CI 25.5, 51.6) by investigator assessment. Median DoR for CR was NE (95% CI: 9.6, NE). The median time to CR was 2.43 months (min, max: 0.8, 12.2). At the time of data cutoff, the median OS was 14.5 months (95% CI: 8.11, 18.20).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The purpose of the current application is to extend the use of Inaqovi to include combination therapy with venetoclax. Overall, the application relies upon the PK similarity between Inaqovi at the relevant dose, and i.v. decitabine at the dose given based on the available clinical experience in combination with venetoclax. Given absence of clinically significant interactions between venetoclax and decitabine when given orally rather than i.v., efficacy for Inaqovi in combination with venetoclax is inferred based on bridging to the results of study M14-358 of IV decitabine with venetoclax (see Venclyxto SmPC section 5.1.)

Thus, clinical efficacy data from Study ASTX727-07 are descriptive rather than inferential.

Study ASTX727-07 is a Phase 1/2 single arm, open-label, multicentre, non-randomised interventional study designed to evaluate the PK, safety, and efficacy of oral decitabine and cedazuridine when given in combination with venetoclax to AML patients who are not eligible for intensive induction chemotherapy.

Phase 2 Part B is the pivotal portion of Study ASTX727-07 for the efficacy descriptive analysis. Supportive efficacy data are derived from Phase 1 and Phase 2 Part A.

Study population

The eligibility criteria are acceptable and allow selection of a study population that is in line with the proposed target population. The inclusion/exclusion criteria are also in line with the eligibility criteria used in previous studies supporting registration of products for newly diagnosed AML patients who are not eligible for intensive induction chemotherapy.

Treatment

Inaqovi was given in the same dose that is recommended for monotherapy Inaqovi, i.e., 1 tablet once daily on Days 1 through 5 of each 28 day cycle (Inaqovi SmPC). Venetoclax was given as recommended in the venetoclax SmPC for AML on Days 1 through 28 of each 28 day cycle.

No food was to be taken 2 hours before and 2 hours after administration of Inaqovi. In contrast, venetoclax was to be given with food. Thus, the patients needed to plan the intake of these two products in relation to each other and in relation to food during days 1-5.

In line with the monotherapy recommendation and as per guidelines (ESMO guidance), treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) not eligible for standard chemotherapy with Inaqovi in combination with venetoclax or not, is recommended to be continued for a minimum of 4 cycles until disease progression or unacceptable toxicity.

Objectives and Endpoints

For the pivotal Phase 2 Part B, the primary objective was to evaluate efficacy (CR) by investigator. The European LeukemiaNet (ELN) response criteria from 2017 was used to identify CR (Döhner et al 2017), which is acceptable. The ELN recommendations are widely accepted in the management of AML according to international guidelines (ESMO GL 2020, NCCN GL 2025).

The primary objective for Phase 1 was to evaluate PK interactions. The co-primary objectives of Phase 2 Part A were to evaluate efficacy (CR) and potential drug-drug interactions of ASTX727(INAQOVI) and venetoclax.

Statistical considerations

The three parts of study ASTX727-07 (phase 1, phase 2 part A, and phase 2 part B) can be seen as three independent studies. Each participant was included in only one of the three parts.

The pivotal part of the study for the efficacy analysis (phase 2 part B) met the target sample size of approximately 100 patients. All treated patients were included in the primary efficacy analysis.

In the analysis of the primary efficacy endpoint (CR), missing data were handled using non-response imputation. This method is appropriate because it is a conservative in a single-arm trial.

The protocol stated that efficacy should be considered established if the 95% confidence interval for CR exceeds 22%. This threshold was lowered to 17.9% in the statistical analysis plan. The lower threshold cannot be considered fully pre-specified because the statistical analysis plan was issued after the start of phase 2 Part B (version 1.0 was dated 02 April 2024). Nevertheless, the trial met both thresholds.

The CR thresholds are acceptable for sample-size planning, but they are not necessary for demonstrating the efficacy of the combination therapy. As explained above, efficacy can be inferred based on comparable drug exposure as for i.v. decitabine, which is approved for the presently proposed use in combination with venetoclax.

Study conduct

The original protocol was dated 06 August 2020 and was amended 5 times. The Phase 2 portion, with co-primary endpoints for both efficacy and drug-drug interaction, was added in protocol amendment 2. The Phase 2 Part B was added in protocol amendment 3, with changes affecting PK sampling, supportive care recommendations, and dose modifications.

Important protocol deviations with regard to the administration of the two investigational products (IP) administration were reported for 31.0% of patients in Phase II and 28.7% of patients in Phase IIB. These protocol deviations included administration of ASTX727(INAQOVI) and venetoclax with less than 2 hours between intake of the two products, missed dose reductions of venetoclax during concomitant antifungal therapy, intake of venetoclax without food, and intake of ASTX727(INAQOVI) without fasting. These protocol deviations on IP administration are not considered to have a major impact on the clinical outcome.

Efficacy data and additional analyses

Study population

A total of 189 patients were treated on Study ASTX727-07: 30 patients in Phase 1, 58 patients in Phase 2 Part A, and 101 patients in Phase 2 Part B. Fifteen patients (15%) in Phase 2 Part B had received prior systemic anti-cancer medicine with best response to last therapy reported as CR in 3 patients (3%) and unknown in 10 patients (10%). However, none of the patients in Phase 2 Part B were in CR at baseline.

Overall, baseline characteristics in Phase 2 Part B adequately reflect the intended target population for the sought indication, and they are roughly similar to the patient populations studied in trial M15-656 (VIALE-A) and study M14-358 in which venetoclax and hypomethylating agents were given in the same setting (DiNardo et al 2020, DiNardo et al 2019).

Patient demographics were generally similar across Phase 1, Phase 2 Part A, and Phase 2 Part B.

Outcome in the pivotal Phase 2 Part B

The primary endpoint, CR by investigator assessment, was achieved by 47 patients in Phase 2 Part B resulting in a CR rate of 46.5% (95% CI: 36.5, 56.7). As a sensitivity analysis, CR was also assessed

by an Independent Review Committee (IRC). CR by IRC was achieved by 38 patients in Phase 2 Part B resulting in a CR rate of 37.6% (95% CI: 28.2, 47.8). Eighty-eight patients (87.1%) had concordant results for CR assessment, demonstrating acceptable agreement between the investigator assessment and IRC assessment.

Although noticeably hampered by limited sample size and exploratory nature, subgroup results suggest overall consistency of the CR results, including age, gender, and performance status.

The median time to CR by investigator assessment were 2.37 months (min, max: 0.7, 15.3).

At the time of data cutoff, the median DoR for CR was not reached.

The median PFS was not reached with a 95% CI of (11.30, NE) at the time of data cutoff. At the data cutoff, 44 (43.6%) patients had died, and 57 (56.4%) patients were censored of which 54 patients were alive at data cutoff. The median OS was 15.51 months (95% CI: 7.59, not evaluable [NE]). No patients had been lost to follow-up as of the data cutoff. However, time-to-event endpoints from a single-arm study are difficult to interpret.

Of note, CHMP has previously concluded that results from study M15-656 (VIALE-A), in which a prolongation of OS was shown when venetoclax was combined with azacitidine, are relevant regardless of which HMA used in patients with AML who are ineligible for intensive chemotherapy (Venclyxto EPAR EMEA/H/C/004106/II/0030, DiNardo et al. N Engl J Med. 2020;383:617, DiNardo et al. Blood. 2019;133:7). Thus, the use of i.v. decitabine at a dose which yields similar AUC as the presently proposed use of Inaqovi, has been agreed to have a positive B/R when used in combination with venetoclax for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy. Consequently, with the present application, Inaqovi in combination with venetoclax as an oral regimen is shown to have comparable efficacy and safety profile to venetoclax in combination with azacitidine or i.v. decitabine.

Efficacy data from Phase 1 and Phase 2 Part A overall support the efficacy results from Phase 2 Part B.

2.4.4. Conclusions on the clinical efficacy

Results from study ASTX727-07 are in line with results obtained in study M14-358, in which venetoclax was combined with either azacitidine or IV decitabine in the same setting (DiNardo 2019, Venclyxto SmPC). This is anticipated given the equivalent decitabine exposure following Inaqovi administration, and the i.v. dose of decitabine given in study M14-358. Thus, efficacy is inferred through PK equivalence, and described by the rate of CR. Furthermore, in support, the efficacy results for Inaqovi in combination with venetoclax appears to be numerically higher than results seen with monotherapy Inaqovi that is already approved in the same setting in EU (Inaqovi EPAR).

2.5. Clinical safety

Introduction

This application concerns venetoclax in combination with ASTX727(INAQOVI), a fixed-dose combination of decitabine, and the cytidine deaminase (CDA) inhibitor cedazuridine.

In the EU, ASTX727(INAQOVI) is approved as monotherapy for the treatment of adult patients with newly diagnosed AML who are ineligible for standard induction chemotherapy.

Venetoclax (Venclyxto), in combination with a hypomethylating agent, is approved for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive induction chemotherapy.

The safety assessment is based on study ASTX727-07 in which 189 subjects were treated with ASTX727(INAQOVI) and venetoclax combination therapy. The existing experience of iv decitabine is extensive and PK-similarity between ASTX727(INAQOVI) and iv decitabine was previously established (EMEA/H/C/005823/0000). The safety profile of venetoclax is also well established.

Patient exposure

The safety of ASTX727(INAQOVI) (oral decitabine and cedazuridine) and venetoclax combination therapy was evaluated in Study ASTX727-07. A total of 189 patients across two phases were treated with ASTX727(INAQOVI) and venetoclax combination therapy.

All patients in Phase 1 and Phase 2 (N=189) received at least 1 dose of both ASTX727(INAQOVI) and venetoclax. (Table 38).

Table 38. Study Treatment Extent of Exposure for ASTX727 and Venetoclax – Phase 2 Part A, Phase 2 Part B, and Phase 1 and Phase 2 (All Treated Population)

	Phase 2 Part A (ASTX727 + venetoclax)		Phase 2 Part B (ASTX727 + venetoclax)		Phase 1 and Phase 2 (ASTX727 + venetoclax)	
	ASTX727 (N=58) n (%)	venetoclax (N=58) n (%)	ASTX727 (N=101) n (%)	venetoclax (N=101) n (%)	ASTX727 (N=189) n (%)	venetoclax (N=189) n (%)
Duration of treatment (months)						
n	58	58	101	101	189	189
Mean (SD)	8.798 (8.802)	9.172 (8.694)	5.783 (4.731)	6.027 (4.557)	6.965 (7.1589)	7.265 (7.0349)
Median	4.96	5.52	5.45	5.52	4.90	5.22
Min, Max	0.16, 27.96	0.26, 28.02	0.16, 17.18	0.20, 17.18	0.16, 39.10	0.20, 39.13
Number of patients with treatment duration, n (%)						
< 3 months	21 (36.2)	21 (36.2)	38 (37.6)	35 (34.7)	71 (37.6)	68 (36.0)
3 – 6 months	11 (19.0)	9 (15.5)	19 (18.8)	19 (18.8)	38 (20.1)	36 (19.0)
≥6 months	26 (44.8)	28 (48.3)	44 (43.6)	47 (46.5)	80 (42.3)	85 (45.0)
6 – 9 months	5 (8.6)	7 (12.1)	14 (13.9)	18 (17.8)	20 (10.6)	26 (13.8)
9 – 12 months	3 (5.2)	3 (5.2)	16 (15.8)	15 (14.9)	21 (11.1)	20 (10.6)
> 12 months	18 (31.0)	18 (31.0)	14 (13.9)	14 (13.9)	39 (20.6)	39 (20.6)
Number of Cycles Treated						
n	58	58	101	101	189	189
Mean (SD)	7.4 (6.97)	7.4 (6.99)	5.3 (3.72)	5.2 (3.69)	6.1 (5.72)	6.1 (5.72)
Median	5.0	5.0	4.0	4.0	4.0	4.0
Min, Max	1, 26	1, 26	1, 15	1, 15	1, 33	1, 33

Number of doses received						
n	58	58	101	101	189	189
Mean (SD)	28.1 (23.48)	116.4 (103.73)	22.5 (15.39)	83.1 (56.61)	25.0 (20.89)	95.3 (78.23)
Median	19.5	91.0	20.0	76.0	20.0	77.0
Min, Max	5, 105	8, 547	5, 65	5, 282	5, 141	5, 547
Relative dose intensity (%)						
n	58	58	101	101	189	189
Mean (SD)	88.38 (15.118)	75.65 (24.665)	92.88 (11.344)	71.94 (25.915)	91.61 (12.818)	74.30 (25.445)
Median	100.00	76.80	100.00	75.06	100.00	80.00
Min, Max	52.2, 100.0	26.3, 102.4[a]	54.8, 100.0	17.6, 105.5[a]	52.2, 100.0	17.6, 105.5[a]

Abbreviations: n=number of patients; SD=standard deviation
[a] One patient in Phase 2 Part A, and 2 patients in Phase 2 Part B, and 4 patients in Phase 1 and Phase 2 had a relative dose intensity >100% due to the investigator's special notation practice in the context of a cycle delay.
Note: ASTX727 is a Fixed Dose Combination (FDC) and the fixed daily dose is 135 mg.
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Subject disposition

Table 39. Patient Disposition and Reason for Discontinuation from Study Treatment

	Phase 1 (N=30) n (%)	**Phase 2 Part A (N=58) n (%)**	**Phase 2 Part (N=101) n (%)**
Treatment Ongoing at Data Cutoff	1 (3.3)	9 (15.5)	40 (39.6)
Discontinued Treatment	29 (96.7)	49 (84.5)	61 (60.4)
Primary Reason for End of Study Participation			
Death	2 (6.7)	5 (8.6)	13 (12.9)
Patient Decision to Permanently Stop Treatment	4 (13.3)	3 (5.2)	4 (4.0)
Lost to Follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Disease Progression	14 (46.7)	22 (37.9)	18 (17.8)
PI Decision	7 (23.3)	4 (6.9)	11 (10.9)
Alternative Therapy	1 (3.3)	3 (5.2)	4 (4.0)
Adverse Events	0 (0.0)	6 (10.3)	7 (6.9)
Other	1 (3.3)	6 (10.3)	4 (4.0)

Abbreviations: PI= Principal Investigator; n=number of patients in a specific subgroup; N=total number of patients.
Note: Phase 1 data cutoff date: 17 Jul 2024, Phase 2 (Part A and Part B) data cutoff date: 30 Sep 2024.

Demographic and Other Baseline Characteristics

Of the 189 patients who received study treatment, 58% were male. The majority of patients were elderly, 72% were ≥75 years. Please also refer to Table 28 in the efficacy section.

Adverse events

Treatment-emergent adverse events (TEAEs) were defined as events that first occur or worsen on or after the date of the first study treatment (C1D1) until 30 days after the last dose of study treatment, or the start of an alternative anticancer treatment, whichever occurred first. Serious adverse events (SAEs) that occur with an onset >30 days from last study treatment and determined to be related to study treatment by the Investigator were also included as TEAEs.

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

Table 40. Overview of Adverse Events – Phase 1 and Phase 2 (All-Treated Population)

	Phase 1 and Phase 2 (N=189) n (%)
Adverse Events (AEs)	188 (99.5)
Grade≥3 AEs	178 (94.2)
AEs with Outcome of Death	26 (13.8)
Treatment Related AEs - Any Drug	145 (76.7)
Treatment Related AEs - Both Drugs	136 (72.0)
Treatment Related AEs - ASTX727	39 (20.6)
Treatment Related AEs - Venetoclax	41 (21.7)
Grade ≥3 Treatment Related AEs - Any Drug	129 (68.3)
Grade ≥3 Treatment Related AEs - Both Drugs	126 (66.7)
Grade ≥3 Treatment Related AEs - ASTX727	11 (5.8)
Grade ≥3 Treatment Related AEs - Venetoclax	22 (11.6)
Serious Adverse Events (SAEs)	149 (78.8)
Treatment Related SAEs - Any Drug	59 (31.2)
Treatment Related SAEs - Both Drugs	54 (28.6)
Treatment Related SAEs - ASTX727	2 (1.1)
Treatment Related SAEs - Venetoclax	5 (2.6)

	Phase 1 and Phase 2 (N=189) n (%)
Action Taken due to AE	
Dose Reduced - Any Drug	26 (13.8)
Dose Reduced - Both Drugs	2 (1.1)
Dose Reduced - ASTX727	8 (4.2)
Dose Reduced - Venetoclax	17 (9.0)
Drug Interrupted - Any Drug	121 (64.0)
Drug Interrupted - Both Drugs	96 (50.8)
Drug Interrupted - ASTX727	9 (4.8)
Drug Interrupted - Venetoclax	55 (29.1)
Drug Withdrawn - Any Drug	15 (7.9)
Drug Withdrawn- Both Drugs	13 (6.9)
Drug Withdrawn- ASTX727	1 (0.5)
Drug Withdrawn- Venetoclax	1 (0.5)

Abbreviations: N=total number of patients; n=number of patients.
Note: MedDRA Version 27.0; Treatment-emergent adverse events are defined as events that first occur or worsen on or after the date of the first study treatment (C1D1) until 30 days after the last dose of study treatment.

Common adverse events

Table 41. Adverse Events in ⩾ 10% of Patients by Preferred Term and Worst CTCAE Grade - Phase 1 and Phase 2 (All Treated Population)

	Phase 1 and Phase 2 N =189 n (%)	
Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**
Patients with at least 1 TEAE	188 (99.5)	152 (80.4)
Febrile neutropenia	87 (46.0)	87 (46.0)
Diarrhoea	79 (41.8)	7 (3.7)
Anaemia	72 (38.1)	64 (33.9)
Constipation	72 (38.1)	2 (1.1)
Hypokalaemia	72 (38.1)	12 (6.3)
Neutrophil count decreased	64 (33.9)	62 (32.8)
Nausea	60 (31.7)	0
Platelet count decreased	60 (31.7)	58 (30.7)
Decreased appetite	59 (31.2)	6 (3.2)
Neutropenia	53 (28.0)	53 (28.0)
Fatigue	52 (27.5)	12 (6.3)

	Phase 1 and Phase 2 N =189 n (%)	
Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**
Oedema peripheral	49 (25.9)	2 (1.1)
White blood cell count decreased	49 (25.9)	49 (25.9)
Stomatitis	42 (22.2)	5 (2.6)
Thrombocytopenia	41 (21.7)	38 (20.1)
Hyponatraemia	39 (20.6)	3 (1.6)
Hypotension	36 (19.0)	11 (5.8)
Vomiting	36 (19.0)	0
Hypomagnesaemia	35 (18.5)	0
Arthralgia	34 (18.0)	3 (1.6)
Fall	34 (18.0)	1 (0.5)
Blood creatinine increased	33 (17.5)	4 (2.1)
Cough	33 (17.5)	0
Pneumonia	32 (16.9)	25 (13.2)
Pyrexia	32 (16.9)	1 (0.5)
Hyperphosphataemia	31 (16.4)	0
Hypophosphataemia	30 (15.9)	3 (1.6)
Insomnia	30 (15.9)	0
Blood bilirubin increased	28 (14.8)	5 (2.6)
Sepsis	28 (14.8)	20 (10.6)
Abdominal pain	27 (14.3)	2 (1.1)
Alanine aminotransferase increased	27 (14.3)	6 (3.2)
Aspartate aminotransferase increased	27 (14.3)	7 (3.7)
Dyspnoea	27 (14.3)	4 (2.1)
Dizziness	26 (13.8)	2 (1.1)
Epistaxis	26 (13.8)	2 (1.1)
Muscular weakness	25 (13.2)	7 (3.7)
Pain in extremity	24 (12.7)	2 (1.1)
Back pain	22 (11.6)	2 (1.1)
Blood alkaline phosphatase increased	22 (11.6)	1 (0.5)
Headache	22 (11.6)	0
Hypocalcaemia	22 (11.6)	0
Asthenia	21 (11.1)	3 (1.6)
Weight decreased	21 (11.1)	2 (1.1)
Anxiety	20 (10.6)	0

	Phase 1 and Phase 2 N =189 n (%)	
Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**
Chills	20 (10.6)	0
Covid-19	20 (10.6)	3 (1.6)
Hyperuricaemia	19 (10.1)	3 (1.6)
Hypoalbuminaemia	19 (10.1)	2 (1.1)
Pruritus	19 (10.1)	0
Urinary tract infection	19 (10.1)	6 (3.2)

Abbreviations: N=total number of patients; n=number of patients; TEAE=treatment-emergent adverse event.
Note: AEs were evaluated based on CTCAE v5.0, MedDRA v27.0.
Note: Includes events reported between the first dose and 30 days after the last dose of study treatment.

Treatment-related adverse events

Table 42. Treatment-Related Adverse Events in ⩾ 10% of Patients by Preferred Term and Worst CTCAE Grade - Phase 1 and Phase 2 (All Treated Population)

	Phase 1 and Phase 2 N =189 n(%)	
Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**
Patients with at least 1 TRAE	145 (76.7)	123 (65.1)
Platelet count decreased	55 (29.1)	53 (28.0)
Anaemia	54 (28.6)	49 (25.9)
Neutrophil count decreased	53 (28.0)	52 (27.5)
Neutropenia	40 (21.2)	40 (21.2)
Febrile neutropenia	39 (20.6)	39 (20.6)
White blood cell count decreased	37 (19.6)	37 (19.6)
Nausea	36 (19.0)	0
Decreased appetite	31 (16.4)	1 (0.5)
Thrombocytopenia	30 (15.9)	27 (14.3)
Stomatitis	26 (13.8)	3 (1.6)
Constipation	24 (12.7)	1 (0.5)
Diarrhoea	23 (12.2)	0
Fatigue	23 (12.2)	3 (1.6)
Vomiting	19 (10.1)	0

Abbreviations: N=total number of patients; n=number of patients; TEAE=treatment-emergent adverse event.
Note: AEs were evaluated based on CTCAE v5.0, MedDRA v27.0.
Note: Includes events reported between the first dose and 30 days after the last dose of study treatment.

Serious adverse event/deaths/other significant events

Deaths

Table 43 summarizes deaths that occurred within 30 days, between 30 and 60 days, and >60 days of last dose of study treatment for Study ASTX727-07.

For all phases, 35 (18.5%) patients died within 30 days of last dose of study treatment, of which 11 (5.8%) died from disease progression.

Table 43. Overview of Cause of Deaths

	Phase 1 (N=30) n (%)	**Phase 2 Part A (N=58) n (%)**	**Phase 2 Part B (N=101) n (%)**
All deaths	25 (83.3)	38 (65.5)	44 (43.6)
Within 30 days of last dose of study treatment			
Deaths	7 (23.3)	10 (17.2)	18 (17.8)
Cause of death			
adverse event	2 (6.7)	6 (10.3)	15 (14.9)
disease progression	4 (13.3)	4 (6.9)	3 (3.0)
other	1 (3.3)	-	-
Between 30-60 days of last dose of study treatment			
Deaths	4 (13.3)	4 (6.9)	14 (13.9)
Cause of death			
adverse event	1 (3.3)	0	2 (2.0)
disease progression	1 (3.3)	2 (3.4)	7 (6.9)
other	2 (6.7)	2 (3.4)	5 (5.0)
Greater than 60 days of last dose of study treatment			
Death	14 (46.7)	24 (41.4)	12 (11.9)
Cause of death			
adverse event	0	1 (1.7)	2 (2.0)
disease progression	8 (26.7%)	16 (27.6)	7 (6.9)
other	6 (20.0%)	7 (12.1)	3 (3.0)

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Overall, AEs with the outcome of death are reported in Table 44.

Seven patients had AEs with an outcome of death considered treatment-related by the investigator: sepsis (4 patients), bacteroides infection (1 patient), bacteraemia (1 patient) and TLS (1 patient). The 2 cases of sepsis and the case of TLS have been considered as related to study treatment.

Table 44. Adverse Events with Outcome of Death by Preferred Term – Phase 1, Phase 2 Part A, Phase 2 Part B and Phase 1 and Phase 2 (All Treated Population)

	Phase 1 (N=30)	Phase 2 Part A (N=58)	Phase 2 Part B (N=101)	Phase 1 and Phase 2 (N=189)
Preferred Term	**Grade 5 n(%)**	**Grade 5 n(%)**	**Grade 5 n(%)**	**Grade 5 n(%)**
Patients with at least 1 AE	3 (10.0)	7 (12.1)	16 (15.8)	26 (13.8)
Cardiac arrest	0	1 (1.7)	2 (2.0)	3 (1.6)
Myocardial infarction	0	1 (1.7)	0	1 (0.5)
Multiple organ dysfunction syndrome	0	1 (1.7)	0	1 (0.5)
Sepsis	2 (6.7)	0	5 (5.0)	7 (3.7)
Pneumonia	0	1 (1.7)	1 (1.0)	2 (1.1)
Bacteraemia	0	0	1 (1.0)	1 (0.5)
Bacteroides infection	0	1 (1.7)	0	1 (0.5)
Bronchopulmonary aspergillosis	1 (3.3)	0	0	1 (0.5)
Escherichia bacteraemia	0	0	1 (1.0)	1 (0.5)
Septic shock	0	0	1 (1.0)	1 (0.5)
Tumour lysis syndrome	0	0	1 (1.0)	1 (0.5)
Haemorrhage intracranial	0	0	3 (3.0)	3 (1.6)
Respiratory failure	0	1 (1.7)	1 (1.0)	2 (1.1)
Acute respiratory failure	0	1 (1.7)	0	1 (0.5)

Note: AEs were evaluated based on CTCAE v5.0, MedDRA v27.0.
Note: CTCAE v5.0, MedDRA v27.0.
Note: Includes events reported between the first a dose and 30 days after the last dose of study treatment.
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Other Serious Adverse Events

Table 45. Phase 1 and Phase 2 – Serious Adverse Events in ⩾2% of Patients by Preferred Term and Worst CTCAE Grade (All Treated Population)

Preferred Term	**Phase 1 and Phase 2 N=189**	
	Any Grade n (%)	**Grade 3-4 n (%)**
Patients with at least 1 SAE	149 (78.8)	118 (62.4)
Febrile neutropenia	53 (28.0)	53 (28.0)
Sepsis	24 (12.7)	17 (9.0)
Pneumonia	19 (10.1)	16 (8.5)
Anaemia	7 (3.7)	6 (3.2)
Bacteraemia	6 (3.2)	2 (1.1)
Cellulitis	6 (3.2)	5 (2.6)

Preferred Term	Phase 1 and Phase 2 N=189	
	Any Grade n (%)	Grade 3-4 n (%)
Fatigue	5 (2.6)	4 (2.1)
Hypotension	5 (2.6)	5 (2.6)
Pneumonia fungal	5 (2.6)	5 (2.6)
Respiratory failure	5 (2.6)	3 (1.6)
Cardiac arrest	4 (2.1)	1 (0.5)
Covid-19	4 (2.1)	3 (1.6)
Escherichia bacteraemia	4 (2.1)	2 (1.1)
Septic shock	4 (2.1)	3 (1.6)
Syncope	4 (2.1)	4 (2.1)

Note: AEs were evaluated based on CTCAE v5.0, MedDRA v27.0.
Note: Includes events reported between the first dose and 30 days after the last dose of the study treatment.

Table 46. Treatment-related Serious Adverse Events Reported for ⩾2% of Patients by Preferred Term – Phase 1 and Phase 2 (All Treated Population)

Preferred Term	Phase 1 and Phase 2 N=189	
	Any Grade n (%)	Grade 3-4 n (%)
Patients with at least 1 treatment-related SAE	59 (31.2)	51 (27.0)
Febrile neutropenia	22 (11.6)	22 (11.6)
Pneumonia	9 (4.8)	9 (4.8)
Sepsis	9 (4.8)	6 (3.2)

Abbreviations: N=total number of patients; n=number of patients; SAE=serious adverse event.
Note: AEs were evaluated based on CTCAE v5.0, MedDRA v27.0.
Note: Includes events reported between the first dose and 30 days after the last dose of the study treatment.

Other Clinically Relevant Adverse Events

Two (1.1%) patients had a AE of acute febrile neutrophilic dermatosis. Both events were assessed by investigator as not treatment related.

Four patients (2.1%) had AEs of tumor lysis syndrome (TLS). Grade 3-4 events occurred in 2 (1.1%) patients, a Grade 2 event occurred in 1 (0.5%) patient, and 1 (0.5%) patient had an SAE resulting in death (Grade 5). The 4 TEAEs were assessed by investigator as related to study treatment.

Laboratory findings

Laboratory data for ASTX727(INAQOVI) was not unexpected. Worsening to any grade of liver function markers and increased creatinine were very common. However, worsening of these parameters to grade 3 or 4 was generally seen in < 10% of AML patients,

There were no cases of liver test abnormalities meeting Hy's Law criteria on the study.

Safety in special populations

Age

Of the 189 patients who received study treatment, 72% were ≥75 years.

For Phase 1 and Phase 2 (N=189), the most frequently reported AEs with differences ≥5% in incidence for Any Grade that occurred in patients <75 years versus ≥75 years included vomiting (30.2% versus 14.7%), nausea (43.4% versus 27.2%), and abdominal distension (15.1% versus 3.7%). The most frequently reported TEAEs of Grade 3-4 with differences ≥5% in incidence were anemia (28.3% versus 36.0%) and febrile neutropenia (50.9% versus 44.1%).

The most frequently reported TRAEs with differences ≥5% in incidence for Any Grade in patients <75 years versus those ≥75 years old included nausea (28.3% versus 15.4%), vomiting (18.9% versus 6.6%), and anemia (22.6% versus 30.9%). The most frequently reported TRAEs of Grade 3-4 with differences ≥5% in incidence were anemia (18.9% versus 28.7%), febrile neutropenia (15.1% versus 22.8%), and thrombocytopenia (9.4% versus 16.2%).

The most frequently reported SAEs with differences ≥5% in incidence for Any Grade in patients <75 years versus those ≥75 years old was febrile neutropenia (32.1% versus 26.5%). The most frequently reported SAEs of Grade 3-4 with differences ≥5% in incidence was febrile neutropenia (32.1% versus 26.5%).

No overall differences in safety were observed between patients age <75 years old and ≥75 years. Of note, patients <75 years old were only allowed to enroll in the study if they had significant cardiac, pulmonary, renal, or hepatic comorbidities which may have contributed to differences seen in the incidence of most frequently reported adverse events.

Table 47. Overview of Adverse Events by <75 and ⩾75 Years of Age - Phase 1 and Phase 2 (All Treated Population)

Category	Phase 1 and Phase 2 (N=189)			
	Any Grade		Grade 3-4	
	Age <75 (N=53) n (%)	Age ≥75 years (N=136) n (%)	Age <75 (N=53) n (%)	Age ≥75 years (N=136) n (%)
Patients with at least 1 TEAE	53 (100)	135 (99.3)	43 (81.1)	109 (80.1)
Patients with at least 1 TRAE	42 (79.2)	103 (75.7)	34 (64.2)	89 (65.4)
Patients with at Least 1 SAE	40 (75.5)	109 (80.1)	32 (60.4)	86 (63.2)

Abbreviations: SAE=serious adverse event, TEAE=treatment=emergent adverse event, TRAE=treatment-related adverse event.

Adverse Events by Sex

Of the 189 patients who received study treatment, 110 (58%) were male and 79 (42%) patients were female. The most frequently reported AEs with differences ≥5% in incidence for Any Grade in male patients versus female patients were urinary tract infection (4.5% versus 17.7%), diarrhea (36.4% versus 49.4%), and arthralgia (12.7% versus 25.3%).

The most frequently reported Grade 3-4 AEs with differences ≥5% in incidence anemia (29.1% versus 40.5%), thrombocytopenia (16.4% versus 25.3%), neutropenia (25.5% versus 31.6%) and febrile neutropenia (48.2% versus 43.0%).

The most frequently reported TRAEs with differences ≥5% in incidence for Any Grade in male patients versus female patients were anemia (24.5% versus 34.2%), neutropenia (17.3% versus 26.6%), and thrombocytopenia (12.7% versus 20.3%). The most frequently reported TRAEs of Grade 3-4 with differences ≥5% in incidence were neutropenia (17.3% versus 26.6%), thrombocytopenia (10.9% versus 19.0%), anemia (22.7% versus 30.4%).

SAEs with differences ≥5% in incidence for Any Grade in male patients versus female patients was pneumonia (12.7% versus 6.3%); and SAEs for Grade 3-4 for male patients versus female patients was pneumonia (11.8% versus 3.8%).

In summary, for patients receiving study treatment, incidences of AEs, TRAEs, and SAEs for Any Grade and Grade 3-4 were similar in male patients versus female patients.

Table 48. Overview of Adverse Events by Sex in Patients - Phase 1 and Phase 2 (All Treated Population)

Category	Phase 1 and Phase 2 (N=189)			
	Any Grade		Grade 3-4	
	Male (N=110) n (%)	Female (N=79) n (%)	Male (N=110) n (%)	Female (N=79) n (%)
Patients with at least 1 TEAE	109 (99.1)	79 (100)	85 (77.3)	67 (84.8)
Patients with at least 1 TRAE	79 (71.8)	66 (83.5)	68 (61.8)	55 (69.6)
Patients with at Least 1 SAE	86 (78.2)	63 (79.7)	66 (60.0)	52 (65.8)

Abbreviations: SAE=serious adverse event, TEAE=treatment=emergent adverse event, TRAE=treatment-related adverse event.

Adverse Events by Patient Race

Table 49. Overview of Adverse Events by Race - Phase 1 and Phase 2 (All Treated Population)

Category	Phase 1 and Phase 2 (N=189)			
	White (N=151) n (%)	Black (N=6) n (%)	Asian (N=15) n (%)	Other/ Unknown (N=17) n (%)
Patients with at least 1 TEAE	151 (100)	6 (100)	15 (100)	16 (94.1)
Patients with at least 1 Grade 3-4 TEAE	122 (80.8)	4 (66.7)	14 (93.3)	12 (70.6)
Patients with at least 1 TRAE	118 (78.1)	3 (50.0)	12 (80.0)	12 (70.6)
Patients with at least 1 Grade 3-4 TRAE	97 (64.2)	3 (50.0)	12 (80.0)	11 (64.7)

Category	Phase 1 and Phase 2 (N=189)			
	White (N=151) n (%)	Black (N=6) n (%)	Asian (N=15) n (%)	Other/ Unknown (N=17) n (%)
Patients with at Least 1 SAE	120 (79.5)	5 (83.3)	12 (80.0)	12 (70.6)
Patients with at Least 1 Grade 3-4 SAE	97 (64.2)	4 (66.7)	10 (66.7)	7 (41.2)

Abbreviations: SAE=serious adverse event, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event.

Adverse Events by Geography

Of the 189 patients who received study treatment, there were more patients who received study treatment in North America (147 [77.8%]) versus Europe (46 [22.2%]). Overall, the incidences of TEAEs and AEs by Any Grade and Grade 3-4 occurred at similar frequencies for both regions. SAEs by Any Grade and Grade 3-4 occurred at a slightly higher frequency in Europe versus North America.

The most commonly reported AEs by Consolidated Term ≥5% difference by region for Europe versus North America were Cough (0% versus 27.2% [includes grouped preferred terms cough, productive cough, and upper airway cough syndrome), Stomatitis (4.8% versus 29.9% [includes grouped preferred terms aphthous ulcer, oral blood blister, stomatitis, and tongue ulceration]), and Rash (2.4% versus 25.2% [includes grouped preferred terms eczema, rash, rash erythematous, rash macular, rash maculopapular, rash pruritic, skin lesion, and stasis dermatitis]).

The most commonly reported TRAEs by Consolidated Term ≥5% difference by region for Europe versus North America were Stomatitis (24% versus 18.4% [includes grouped preferred terms aphthous ulcer, oral blood blister, stomatitis, and tongue ulceration]), Anemia (19.0% versus 31.3% [includes anemia only]), and Vomiting (2.4% versus 12.2% [includes vomiting only]).

The most commonly reported SAEs by Consolidated Term ≥5% difference by region for Europe versus North America were Sepsis (45.2% versus 15.0% [includes grouped preferred terms bacteremia, bacteroides infection, Enterobacter bacteremia, Escherichia bacteremia, micrococcal sepsis, sepsis, septic shock, staphylococcal bacteremia, and streptococcal bacteremia]), Pneumonia (21.4% versus 12.2% [includes grouped preferred terms bronchopulmonary aspergillosis, pneumonia, pneumonia fungal, and pneumonia proteus]), and Fatigue (0% versus 5.4% [includes grouped preferred terms asthenia and fatigue]).

Table 50. Overview of Adverse Events by Geographic Region - Phase 1 and Phase 2 (All Treated Population)

Category	Phase 1 and Phase 2 (N=189)			
	Any Grade		Grade 3-4	
	Europe (N=42) n (%)	North America (N=147) n (%)	Europe (N=42) n (%)	North America (N=47) n (%)
Patients with at least 1 TEAE	42 (100)	146 (99.3)	33 (78.6)	119 (81.0)
Patients with at least 1 TRAE	31 (73.8)	114 (77.6)	25 (59.5)	98 (66.7)

Category	Phase 1 and Phase 2 (N=189)			
	Any Grade		Grade 3-4	
	Europe (N=42) n (%)	North America (N=147) n (%)	Europe (N=42) n (%)	North America (N=47) n (%)
Patients with at Least 1 SAE	40 (95.2)	109 (74.1)	30 (71.4)	88 (59.9)

Abbreviations: SAE=serious adverse event, TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.

Safety related to drug-drug interactions and other interactions

No drug-drug interactions were observed between ASTX727(INAQOVI) and venetoclax in Study ASTX727-07.

Discontinuation due to adverse events

In Phase 1 and Phase 2 (N=189), permanent discontinuation of study treatment due to a TEAE pertaining to study treatment by Any Grade occurred in 15 (7.9%) patients and included atrial fibrillation, cardiac failure, myocardial infarction, large intestinal hemorrhage, asthenia, fatigue, multiple organ dysfunction syndrome, pulmonary mucormycosis, sepsis, white blood cell count decreased, failure to thrive, tumor lysis syndrome, hemorrhage intracranial, acute kidney injury, respiratory disorder, and Steven-Johnson Syndrome (1 [0.5%] each).

Permanent discontinuation of study treatment due to a AE of Grades 3-4 occurred in 10 (5.3%) patients and included cardiac failure, large intestinal hemorrhage, fatigue, pulmonary mucormycosis, sepsis, white blood cell count decreased, failure to thrive, hemorrhage intracranial, acute kidney injury, respiratory disorder, and Steven-Johnson Syndrome (1 [0.5%] each).

Permanent discontinuation of study treatment due to a TRAE by Any Grade occurred in 6 (3.2%) patients and were asthenia, fatigue, pulmonary mucormycosis, white blood cell count decreased, tumor lysis syndrome, and acute kidney injury. TRAEs by Grades 3-4 leading to permanent study treatment discontinuation occurred in were 4 (2.1%) patients and were fatigue, pulmonary mucormycosis, white blood cell count decreased, and acute kidney injury (1 [0.5%]).

Overall, 3 patients who permanently discontinued study treatment died from TEAEs of tumor lysis syndrome, myocardial infarction, and multiple organ dysfunction syndrome.

Dose modifications due to adverse events

For Phase 1 and Phase 2 (N=189), 26 (13.8%) patients had a dose reduction due to AEs. The most common AEs by Any Grade that led to study treatment reduction in patients were neutrophil count decreased (9 [4.8%]), febrile neutropenia (5 [2.6%]), and neutropenia (4 [2.1%]).

For Phase 1 and Phase 2 (N=189), 121 (64.0%) patients had study treatment interruptions due to a AEs. AEs that led to dose interruptions in ≥ 5% of patients who received study treatment included neutrophil count decreased (36 [19.0%]), neutropenia (36 [19.0%]), febrile neutropenia (29 [15%]), and thrombocytopenia (12 [6.3%]).

Table 51. Adverse Events leading to Study Treatment Interruption by Preferred Term in ⩾ 2% of Patients – Phase 1 and Phase 2 – (All Treated Population)

System Organ Class Preferred Term	Phase 1 and Phase 2 N=189	
	Any Grade n (%)	Grade 3-4 (%)
Patients with at least 1 dose interruption/delay	121 (64.0)	113 (59.8)
Neutropenia	36 (19.0)	36 (19.0)
Neutrophil count decreased	36 (19.0)	36 (19.0)
Febrile neutropenia	29 (15.3)	28 (14.8)
Thrombocytopenia	12 (6.3)	11 (5.8)
Anaemia	4 (2.1)	3 (1.6)
Pneumonia	7 (3.7)	7 (3.7)
Covid-19	6 (3.2)	1 (0.5)
Sepsis	6 (3.2)	5 (2.6)
Platelet count decreased	5 (2.6)	5 (2.6)

Note: CTCAE v5.0, MedDRA v27.0.

In combination with venetoclax

Blood cell counts have to be monitored frequently through resolution of cytopenias. Dose modification and interruptions for cytopenias are dependent on remission status. Day 1 of Inaqovi dosing cycles should be matched with that used for venetoclax dosing. For Cycle 1, bone marrow assessment for response may be performed as early as Day 22. In the absence of remission (bone marrow blasts < 5%), Inaqovi dosing schedule should not be delayed.

Haematologic adverse reactions

Complete blood cell counts have to be obtained prior to initiating Inaqovi and before each cycle and have to be monitored until neutrophils and platelet counts have recovered to Grade 1 or 2 (see section 4.4 and section 4.2 for dose modifications).

- If haematological recovery occurs (ANC at least 1.0 × 109/L and platelets at least 50 × 109/L) within 2 weeks of the last treatment cycle, treatment is to be continued at the same dose.
- If haematological recovery does not occur (ANC at least 1.0 × 109/L and platelets at least 50 × 109/L) within 2 weeks of achieving remission, treatment with Inaqovi must be delayed for up to 2 additional weeks and reduction of the number of days of Inaqovi per cycle is to be considered according to Table 52.

Table 52. Recommended Inaqovi dose reductions for adverse reactions

Dose reduction	Dose
First	1 tablet once daily on Days 1 through 3
Second	1 tablet once daily on Days 1, 3 and 5

Third	1 tablet once daily on Days 1 and 3

Persistent severe neutropaenia and febrile neutropaenia have to be managed with supportive treatment including, administration of prophylactic antibiotics and/or growth factor support (e.g., G CSF) for neutropaenia according to institutional guidelines.

Dose modifications for haematologic adverse reactions associated with venetoclax must follow the instructions in the venetoclax SmPC.

Non-Haematologic Adverse Reactions

For Cycle 3 onwards, dose reductions of Inaqovi for non-haematologic adverse reactions are provided in Table 52.

Dose modifications for non-haematologic adverse reactions associated with venetoclax must follow the instructions in the venetoclax SmPC.

Post marketing experience

The combination of oral decitabine and cedazuridine in combination with venetoclax is not currently approved for the treatment of AML in any region.

Adverse drug reactions for the label

The ADR table in section 4.8 of the SmPC is based on previous clinical experience with Dacogen (IV decitabine), the group of 80 AML patients included in study ASTX727-02 EU that received oral ASTX727(INAQOVI) or IV decitabine alone and 189 AML patients included in study ASTX727-07.

Adverse drug reactions (ADRs) were selected after an assessment of the available data from the clinical trials for a suspected causal relationship between AEs and the medicinal product.

Depending on the information available for individual TEAEs the assessments included:

- Frequencies of TEAEs
- Temporal relationship between TEAEs and exposure to investigational medicinal products (IMPs)
- Evaluation of the extent to which the TEAE was consistent with the pharmacology of the IMPs
- Consistency of the pattern of symptoms across other studies/indications.
- Biologic plausibility based on mechanism of action and known effects of the IMPs
- Event or laboratory test abnormality, with plausible time relationship to IMP intake
- De-challenge/re-challenge information: evidenced based and frequently occurring with reasonable causality and likelihood related to IMP
- Evaluation whether a TEAE is related to the underlying medical condition or whether it is a symptom of an already known adverse reaction

Based on the analysis of data for the monotherapy pool and combination therapy, no new ADRs are identified. No new or unexpected safety signals emerged, and the safety findings aligned with

previously reported data for decitabine and cedazuridine, as well as for venetoclax in similar patient populations.

ADRs for INAQOVI Combination Therapy

The ADR selection for INAQOVI in combination with venetoclax is based on Study ASTX727-07 (ASTX727(INAQOVI) in combination with venetoclax).

The ADR profile of ASTX727(INAQOVI) in combination with venetoclax in patients with newly diagnosed AML is consistent with that for INAQOVI monotherapy with no clinically important differences observed between the monotherapy pools and the combination study.

The most common ADRs (reported at a frequency ≥20%) with ASTX727(INAQOVI) in combination with venetoclax by Any Grade and Grade ≥3, respectively, for the Phase 1 and Phase 2 combined population are platelet count decreased (29.1% and 28.0%), anemia (28.6% and 25.9%), neutrophil count decreased (28.0% and 27.5%), neutropenia (21.2% and 21.2%), and febrile neutropenia (20.6% and 20.6%).

Across Phase 1 and Phase 2, the most frequently reported TEAEs include hematologic toxicities (e.g., febrile neutropenia, anemia, and neutrophil count decreased) and gastrointestinal events (e.g., nausea and diarrhea).

If the grouped frequency of an ADR in the combination therapy is the same or lower in comparison to INAQOVI and Venclyxto monotherapies for all CTCAE grades and CTCAE grades 3-4, it would be considered that the ADR is sufficiently covered by the current labels, and no changes is required to the ADR Section of the EU SmPC of INAQOVI.

If the grouped frequency of an ADR would be higher in the combination therapy than INAQOVI monotherapy, but lower than the ones reflected in the EU SmPC of Venclyxto, it would be considered that the ADR be sufficiently covered by the current label of the latter product, thus not requiring modifications to the EU SmPC of INAQOVI either.

Finally, if the grouped frequency of an ADR would be higher in the combination therapy when compared to INAQOVI and Venclyxto monotherapies, the EU SmPC for INAQOVI is updated accordingly to reflect the additional risk of using venetoclax in combination with INAQOVI, unless an explanation is provided.

Further to this, the Applicant also conducted an analysis of all the safety data, including the TEAEs reported in CSR of study ASTX727-07, to identify any potential additional effects or risks of the combination therapy not sufficiently covered by the current EU SmPC of INAQOVI or Venclyxto; including, but not limited to, new ADRs, changes in severity or outcomes.

No new or unexpected safety signals emerged, and the frequency of safety findings align with previously reported data for decitabine and cedazuridine, as well as for venetoclax in similar patient populations.

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

Table 53. Adverse drug reactions observed with Inaqovi, Inaqovi combined with venetoclax or with intravenous decitabine therapy in AML patients

MedDRA SOC	MedDRA Term [a]	AML monotherapy (N=80), AML combination therapy (N=189) and IV decitabine	
		All CTCAE Grades Frequency	CTCAE Grade 3-4 Frequency
Infections and infestations	All other infections (viral, bacterial, fungal) [b]	Very common	Very common
	Pneumonia	Very common	Very common
	Sepsis [c]	Very common	Common
	Urinary tract infection [d]	Very common	Common
	Sinusitis (including fungal and bacterial [e])	Common[e]	Common[e]
Blood and lymphatic system disorders	Leukopenia [f]	Very common	Very common
	Thrombocytopaenia [f,g]	Very common	Very common
	Anaemia [f]	Very common	Very common
	Neutropaenia [f]	Very common	Very common
	Febrile neutropaenia	Very common	Very common
	Pancytopaenia [h]	Uncommon [h]	Uncommon [h]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Differentiation syndrome [i]	Not known	Not known
Metabolism and nutrition disorders	Hyperglycaemia [f]	Very common	Common
Nervous system disorders	Headache	Common	Common
Cardiac disorders	Cardiomyopathy [j]	Uncommon[j]	Uncommon[j]
Respiratory, thoracic and mediastinal disorders	Epistaxis	Common	Common
	Interstitial lung disease	Not known	Not known
Gastrointestinal disorders	Stomatitis [k]	Very common	Common
	Nausea	Very common	Uncommon
	Diarrhoea [l]	Very common	Common[l]
	Vomiting [l]	Very common	Common[l]
	Neutropaenic colitis [m]	Common	Common
Hepatobiliary disorders	Aspartate aminotransferase increased [f]	Very common	Common

MedDRA SOC	MedDRA Term [a]	AML monotherapy (N=80), AML combination therapy (N=189) and IV decitabine	
		All CTCAE Grades Frequency	CTCAE Grade 3-4 Frequency
	Alanine aminotransferase increased [f]	Very common	Common
	Alkaline phosphatase increased [f]	Very common	Not applicable
	Bilirubin increased [f]	Very common	Uncommon
Skin and subcutaneous tissue disorders	Acute febrile neutrophilic dermatosis (Sweet's syndrome) [n]	Uncommon [n]	Not applicable [o]
General disorders and administration site conditions	Pyrexia	Very common	Common

[a] The corresponding frequency category for each adverse drug reaction is based on the CIOMS III convention
[b] The most commonly observed include anal abscess, anorectal infection, bacteraemia, cellulitis, herpes virus infection, candidiasis, skin infection, varicella zoster virus infection
[c] The most commonly observed include sepsis, septic shock, systemic candidiasis, urosepsis
[d] The most commonly observed include bacteriuria, cystitis, urinary tract infection
[e] 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
[f] Based on laboratory values
[g] Thrombocytopaenia may lead to bleeding and haemorrhagic reactions that may be fatal
[h] Pancytopaenia, 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
[i] 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
[j] 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
[k] The most commonly observed include aphthous ulcer, glossitis, stomatitis, tongue ulceration
[l] 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
[m] 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
[n] 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
[o] 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

CTCAE= Common Terminology Criteria for Adverse Events

In the footnote to the adverse reaction table, the listing of all terms encompassed by a grouped term has been replaced with "The most commonly observed".

In study ASTX727-07, four patients (2.1%) had AEs of tumor lysis syndrome (TLS). All cases of TLS were assessed by investigator as related to study treatment. This is mentioned in sections 4.2 and 4.4; specifically, the MAH has included a sentence regarding TLS in section 4.4 in the SmPC: "For patients taking venetoclax, due to the increased risk of tumour lysis syndrome (TLS), refer to the venetoclax SmPC sections 4.2, 4.4 and 4.8 for additional information." The AE TLS was not added to the ADR-table since TLS is a well-known safety concern for venetoclax and there was no increase in the incidence or severity of TLS beyond what is expected for venetoclax based regimens when compared with the combination therapy with ASTX727(INAQOVI).

2.5.1. Discussion on clinical safety

The safety assessment is based on study ASTX727-07 (all phases) in which 189 subjects were treated with ASTX727(INAQOVI) and venetoclax combination therapy. The existing experience of iv decitabine is extensive. Moreover, PK-similarity between ASTX727(INAQOVI) and iv decitabine was previously established (EMEA/H/C/005823/0000). The safety profile of venetoclax is also well established.

Study conduct

In Phase 1 and Phase 2 Part A, dose reductions for haematologic toxicity required consultation with the medical monitor, and in general were not allowed until completion of PK sampling. Prophylactic azole antifungal therapy was prohibited during the time that could affect the PK measurements (7 days or 5 half-lives, whichever was greater, prior to C1D1 through C2D16).

In Phase 2 Part B dose modifications for hematologic toxicity were permitted after the end of Cycle 1, at the investigator's discretion. Azole antifungals were restricted for a shorter period than in Phase 1 and Phase 2 Part A (7 days or 5 half-lives, whichever was greater, prior to C1D1 through C1D6).

In accordance with the above, per protocol amendment 3, stipulations were changed and the phase 2 part of the study started de novo (now termed Phase 2 Part B). The relevant protocol changes affect PK sampling, supportive care recommendations, and ASTX727(INAQOVI) dose modification recommendations after subjects have achieved clearance of marrow blasts. The applicant states that these changes were expected to help with the number of evaluable subjects for the PK objectives and help subjects stay on treatment longer.

For ASTX727(INAQOVI), subjects received a median of 4 treatment cycles. Eighty (42.3%) patients received ASTX727(INAQOVI) for 6 months or longer. The median relative dose intensity of ASTX727(INAQOVI) was 100%.

For venetoclax, subjects received a median of 4 treatment cycles. Eighy-five (45.0%) patients received venetoclax for 6 months or longer. The median relative dose intensity was 80% for venetoclax.

Adverse events

More than half of the patients were older than 75 years, which is representative of a large part of the target population. Median baseline neutrophils were below $1x10^9$/L. The baseline condition should be taken into account assessing safety of ASTX727(INAQOVI) and venetoclax in combination.

The overall safety profile observed in the ASTX727-07 trial could be expected for this treatment modality and in this patient population. Thus, haematologic suppression and gastrointestinal (GI) disorders were very commonly reported, as were different types of infections. Haematological toxicity and infections were the most commonly reported AEs of Grade 3 or higher.

In study ASTX727-07, four patients (2.1%) had AEs of tumor lysis syndrome (TLS). All cases of TLS were assessed by investigator as related to study treatment. TLS is a well-recognized adverse effect of venetoclax. It is more common in chronic lymphocytic leukemia (CLL), where the initial clinical development showed several early cases of both laboratory and clinical TLS. TLS is less frequent in AML, but it still occurs and requires careful monitoring. The incidence of TLS has been reported as high as 18% in clinical practice, compared to just 1% in the VIALE-A trial (Wei 2025). Section 4.4 of the SmPC contains a cross-reference to the venetoclax SmPC, specifically with regards to the risk of TLS.

Considering the oral route of administration of decitabine and venetoclax in combination, it is of particular interest to look at the GI adverse events for potential local toxicity. Importantly, the GI adverse events appear to have been tolerated in the ASTX727-07 study, as they did not lead to dose

modification or treatment discontinuations, except in one case of constipation and one case of dysphagia.

Serious adverse events

Overall, SAEs occurred in 149 (78.8%) patients who received the combination treatment of ASTX727(INAQOVI) and venetoclax. SAEs (assessed as unrelated or related) were most commonly reported within SOCs Infections and infestations (febrile neutropenia [28.0%], sepsis [12.7%], and pneumonia [10.1%]).

AEs with the outcome of death

AEs with the outcome of death occurred in 26 (13.8%) patients. Fatal AEs were sepsis (7 [3.7%]), cardiac arrest and intracranial hemorrhage (3 [1.6%] each), pneumonia and respiratory failure (2 [1.1%] each), and acute respiratory failure, bacteremia, bacteroides infection, bronchopulmonary aspergillosis, escherichia bacteremia, myocardial infarction, multiple organ dysfunction syndrome, septic shock, and tumor lysis syndrome (1 [0.5%] each).

Seven patients had AEs with an outcome of death considered treatment-related by the investigator: sepsis (4 patients), bacteroides infection (1 patient), bacteraemia (1 patient) and tumor lysis syndrome (1 patient). The MAH considered 2 cases of sepsis and the case of tumor lysis syndrome as related to study treatment.

The pattern of fatal AEs may be considered as expected for the patient population.

Adverse events leading to treatment discontinuation or dose modification

Fifteen subjects (7.9%) permanently discontinued treatment due to AEs. Six subjects (3.2%) had discontinuation AEs considered related to treatment by the investigator.

Dose modifications for Phase 2 Part B were allowed for both ASTX727(INAQOVI) and for venetoclax after the patient achieved a complete remission. Dose modification could be made either by reducing the number of treatment days in a cycle or by delaying the next cycle.

Dose reduction due to an AE occurred in 13.8% of patients. The most common AE that led to study treatment reduction were neutrophil count decreased (4.8%), febrile neutropenia (2.6%), and neutropenia (2.1%) Drug interruption due to an AE occurred in 64.0% of patients. The most common AEs that led to dose interruptions included neutrophil count decreased (19.0%), neutropenia (19.0%), febrile neutropenia (15%), and thrombocytopenia (6.3%).

Overall, the reasons for treatment discontinuation and dose modification do not lead to concerns for ASTX727(INAQOVI) in combination with venetoclax.

SmPC

The ADR table in section 4.8 of the SmPC is proposed based on previous experience with Dacogen (I.V. decitabine), the group of 80 AML patients included in study ASTX727-02 EU who received oral or IV decitabine and 189 AML patients included in study ASTX727-07 and is acceptable. ADRs were selected after an assessment of the available data from the clinical trials for a suspected causal relationship between AEs and the medicinal product.

2.5.2. Conclusions on clinical safety

The purpose of the current application is to extend the use of ASTX727(INAQOVI) to include combination therapy with venetoclax. Overall, the application relies upon the PK similarity between

ASTX727(INAQOVI) at the relevant dose, and i.v. decitabine at the dose given based on available clinical experience in combination with venetoclax.

The safety profile of ASTX727(INAQOVI) in combination with venetoclax in patients with newly diagnosed AML was generally consistent with that for ASTX727(INAQOVI) monotherapy, as well as the added toxicity that would be anticipated from venetoclax. No unexpected safety signals emerged. The safety profile is deemed acceptable for the proposed use.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

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] III-IV])

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
None	None	None	None	None

Risk minimisation measures

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

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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4,8, 5,1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Belgium, Luxemburg and Iceland.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Inaqovi (decitabine/cedazuridine). The bridging report submitted by the MAH was found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The currently proposed extension of indication is:

- *Inaqovi in combination with venetoclax 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

For AML patients not eligible for intensive induction therapy, current recommended therapies typically consist of a parenteral hypomethylating agent (HMA) combined with venetoclax (NCCN Guideline 2025, European LeukemiaNet ELN recommendations 2022, ESMO Guidelines 2020), in line with the EU-approved use of Venclyxto.

Monotherapy treatment with the HMAs azacitidine and decitabine are also approved in EU for AML patients who are not candidates for intensive induction therapy. Azacitidine is given subcutaneously and decitabine is given intravenously. Thus, these products require recurring hospital visits for the patient.

Other EU approved products for AML patients not suitable for intensive induction therapy are the hedgehog inhibitor glasdegib in combination with low-dose cytarabine, and the IDH1 inhibitor ivosidenib in combination with azacitidine.

Currently, there are no all-oral combination regimens approved in EU for the patients with AML. An orally available combination of HMA Inaqovi and venetoclax would reduce the burden of chronic treatment for patients and their caregivers.

3.1.3. Main clinical studies

Previously, the PK equivalence between Inaqovi and i.v. decitabine was established in study ASTX727-02 EU, which supported the monotherapy indication for Inaqovi in AML.

New data to support the proposed indication are derived from Study ASTX727-07. This is a Phase 1/2 single arm, multicenter, non-randomized study designed to evaluate the PK, safety, and efficacy of oral decitabine and cedazuridine when given in combination with venetoclax to AML patients who are not eligible for intensive induction chemotherapy.

Inaqovi was given at the same dose that is recommended for AML monotherapy with Inaqovi, i.e., 1 tablet once daily on Days 1 through 5 of each 28 day cycle (Inaqovi SmPC). Venetoclax was given as recommended in the venetoclax SmPC for AML on Days 1 through 28 of each cycle.

- Phase 2 Part B is the pivotal portion of Study ASTX727-07 for the efficacy analysis, with CR by investigator as primary endpoint according to ELN 2017 criteria.
- Supportive efficacy data are derived from Phase 1 and Phase 2 Part A. The primary objective for Phase 1 was to evaluate PK interactions. The co-primary objectives of Phase 2 Part A were to evaluate efficacy and potential drug-drug interactions of ASTX727(INAQOVI) and venetoclax.

The treatment schedules were the same in all parts of the study, but there were differences regarding the timing of PK sampling, prophylactic antifungal treatment, and dose modifications.

A total of 189 patients were treated on Study ASTX727-07: 30 patients in Phase 1, 58 patients in Phase 2 Part A, and 101 patients in Phase 2 Part B.

Scientifically, this application relies on the PK similarity between Inaqovi at the relevant dose, and i.v. decitabine at the dose given in the available regimen in combination with venetoclax. Given the absence of clinically significant interactions between venetoclax and decitabine when given orally rather than i.v., efficacy is inferred based on bridging to the M14-358 study (see Venclyxto SmPC section 5.1.).

3.2. Favourable effects

Pharmacokinetics

Results of study ASTX727-07 convincingly showed that there was no effect of decitabine/cedazuridine on venetoclax exposure.

Decitabine exposure when Inaqovi was co-administered with venetoclax (Study ASTX727-07 phase 2 part B) was comparable to Inaqovi monotherapy (study ASTX727-02 EU (AML)), which demonstrated bioequivalence for 5-Day AUC_{0-24} compared to IV decitabine (20 mg/m^2 daily×5).

Efficacy (as descriptive)

The primary endpoint in Study ASTX727-07 Phase 2 Part B, CR by investigator assessment, was achieved by 47 patients resulting in a CR rate of 46.5% (95% CI: 36.5, 56.7).

At the time of data cutoff, with a median follow-up time in Phase 2 Part B of 11.2 months (min, max: 0.3, 17.5), the median DoR for CR was not reached.

3.3. Uncertainties and limitations about favourable effects

The potential effect of venetoclax on decitabine/cedazuridine exposure is less well characterised than the effect of decitabine/cedazuridine on venetoclax exposure since itis based on a comparison to historical data from a different study, with an observed worst-case of 1.4-fold increase in AUC based on a between-study comparison (phase 1 and phase 2 part A data) but with comparable exposure compared to historical data based on phase 2 part B data.

In general, though, no significant uncertainties, that have a major impact on the B/R balance, remain.

3.4. Unfavourable effects

The safety assessment is based on study ASTX727-07 in which 189 subjects were treated with ASTX727(INAQOVI) and venetoclax combination therapy. The existing clinical experience of iv decitabine is extensive and PK-similarity between ASTX727(INAQOVI) and iv decitabine was previously established (EMEA/H/C/005823/0000). The safety profile of venetoclax is also well established. The addition of venetoclax to ASTX727(INAQOVI) caused an expected and overall manageable increase in toxicity.

Considering the oral route of administration of decitabine and venetoclax in combination, it is of particular interest to look at the GI adverse events for potential local toxicity. Importantly, the GI adverse events appear to have been tolerated in the ASTX727-07 study, as they did not lead to dose

modification or treatment discontinuations, except in one case of constipation and one case of dysphagia.

SAEs (assessed as unrelated or related) were most commonly reported within SOCs Infections and infestations. AEs with the outcome of death occurred in 26 (13.8%) patients. AEs leading to death was most commonly reported within SOC infections and infestations (n=14; 7.4% of the total study population). Seven patients had AEs with an outcome of death considered treatment-related by the investigator: sepsis (4 patients), bacteroides infection (1 patient), bacteraemia (1 patient) and tumor lysis syndrome (1 patient). The pattern of fatal AEs may be considered as expected for the patient population.

Fifteen subjects (7.9%) permanently discontinued treatment due to AEs. Six subjects (3.2%) had discontinuation AEs considered related to treatment by the investigator.

Dose reduction/treatment interruption due to an AE occurred in 13.8% and 64% of patients. The most common reasons were haematological toxicity or infections.

In study ASTX727-07, four patients (2.1%) had AEs of tumor lysis syndrome (TLS). All cases of TLS were assessed by investigator as related to study treatment. TLS is a well-recognized adverse effect of venetoclax. Section 4.4 of the SmPC is updated accordingly.

The overall safety profile observed in the ASTX727-07 trial could be expected for this treatment modality and in this patient population. Thus, haematologic suppression and gastrointestinal (GI) disorders were very commonly reported, as were different types of infections. Haematological toxicity and infections were the most commonly reported AEs of Grade 3 or higher.

3.5. Uncertainties and limitations about unfavourable effects

The abovementioned cross-study comparison (section 3.3) of the potential impact of venetoclax on decitabine results in some uncertainty. Based on theoretical considerations, no pharmacokinetic interactions between venetoclax and decitabine are expected. Given the limited magnitude of any potential DDI a substantial impact on clinical safety is deemed unlikely (moreover any impact of venetoclax on the systemic clearance of decitabine would likely be relevant also for i.v. decitabine).

3.6. Effects Table

Table 54. Effects Table for Inaqovi (ASTX727(INAQOVI)) in the combination with Venclyxto (venetoclax) (data cut-off dates: Phase 1, 17 July 2024, Phase 2, 30 September 2024)

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Favourable Effects (from Phase 2 Part B of study ASTX727-07, n=101)					
Complete response (CR)		N(%) (95% CI)	47(46.5) (36.5, 56.7)	Efficacy data are descriptive only but efficacy is inferred through PK equivalence, (as described by the rate of CR).	Study ASTX727-07, Phase 2 Part B

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Median duration of CR		Months (95% CI)	NE (NE, NE)	Median follow-up time 11.2 months (min, max: 0.3, 17.5).	Study ASTX727-07, Phase 2 Part B

Unfavourable Effects (from Phase 1 and 2 of study ASTX727-07, n=189)

Effect	Description	Subjects with AE (%)	Treatment	Uncertainties/Strength of evidence	References
Haema-tologic toxicity		76.7%	ASTX727(INAQOVI) (35 mg decitabine + 100 mg cedazuridine) x 5 days per 28-day cycle + venetoclax 400 mg once daily (after ramp-up)	Small dataset (n=189) No control arm	Study ASTX727-07
Infections		61.4%	"	"	"
Gastroin-testinal disorders		70.9%	"	"	"

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Treatment-related Grade ≥3 AEs	Treatment-relatedness as assessed by investigator	68.3%	"	"	"
Treatment-related SAEs	Treatment-relatedness as assessed by investigator	31.2%	"	"	"
Discon-tinuation due to treatment-related AE	Treatment-relatedness as assessed by investigator	3.2%	"	"	"
Fatal treatment-related AE	Treatment-relatedness as assessed by investigator	3.7%	"	"	"

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The combination of parenteral HMAs and venetoclax tablets is considered the standard of care for the majority of AML patients who are not eligible for intensive induction therapy. This is in line with the EU-approved use of venetoclax combined with a hypomethylating agent (e.g. either azacitidine or decitabine).

In the current application, the MAH seeks approval for Inaqovi, oral decitabine with cedazuridine, in combination with venetoclax. The efficacy of Inaqovi in combination with venetoclax is inferred based on PK results from Study ASTX727-07 and ASTX727-02 EU, which allows for a PK bridge to the clinical experience with parenteral HMA's in combination with venetoclax. Therefore, it is endorsed that Inaqovi in combination with venetoclax as an oral regimen has been shown to have comparable efficacy and safety profile to venetoclax in combination with IV decitabine (M14-358); see also Venclyxto SmPC section 5.1.

Additional supportive data are provided from efficacy results from the Phase 2 Part B of Study ASTX727-07 as descriptive. These show a CR rate of 46.5%, with a median DoR not reached after a median follow-up of 11.2 months, and are supportive of similar efficacy as when i.v. decitabine is given with venetoclax.

In addition, CHMP previously concluded that results from study M15-656 (VIALE-A), in which a prolongation of OS was shown when venetoclax was combined with azacitidine, are relevant regardless of which HMA used in patients with AML who are ineligible for intensive chemotherapy (Venclyxto EPAR 2021 EMEA/H/C/004106/II/0030, DiNardo 2020). Thus, these results are relevant for venetoclax in combination with decitabine.

The safety profile of INAQOVI in combination with venetoclax in patients with newly diagnosed AML was generally consistent with that for INAQOVI monotherapy, as well as the added toxicity that would be anticipated from venetoclax. No unexpected safety signals emerged.

3.7.2. Balance of benefits and risks

The benefit/risk balance for the oral regimen of Inaqovi in combination with venetoclax in the proposed target population is positive.

3.8. Conclusions

The overall B/R of Inaqovi in the combination with Venclyxto is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

Extension of indication to include treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy for INAQOVI in combination with venetoclax, based on interim results from study ASTX727-07; this is a single-arm, open-label pharmacokinetic, safety, and efficacy study of ASTX727(INAQOVI) in combination with venetoclax in adult patients with acute myeloid leukemia; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.3 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives for Belgium, Luxemburg and Iceland in the Package Leaflet and bring editorial changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

The variation leads to amendments to the annexes I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Inaqovi is not similar to Mylotarg, Xospata, Daurismo, Vyxeos liposomal, Rydapt and Tibsovo within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers, that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

5. EPAR changes

The EPAR will be updated following Commission Decision for variation. In particular the "EPAR- Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMA/VR/0000304730.