EMA/573983/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inaqovi

International non-proprietary name: Decitabine / Cedazuridine

Procedure No. EMEA/H/C/005823/II/02

Note

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

The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	27 Jan 2024	27 Jan 2024	☐
☐	CHMP Rapporteur Assessment Report	22 Mar 2024	25 Mar 2024	☐
☐	PRAC Rapporteur Assessment Report	27 Mar 2024	25 Mar 2024	☐
☐	PRAC members comments	03 Apr 2024	03 Apr 2024	☐
☐	Updated PRAC Rapporteur Assessment Report	04 Apr 2024	05 Apr 2024	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	11 Apr 2024	11 Apr 2024	☐
☐	CHMP members comments	15 Apr 2024	15 Apr 2024	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 Apr 2024	19 Apr 2024	☐
☐	Request for supplementary information	25 Apr 2024	25 Apr 2024	☐
	Submission of MAH's responses	16 Aug 2024	12 Aug 2024	
☐	Re-start of procedure	19 Aug 2024	19 Aug 2024	☐
☐	CHMP Rapporteur Assessment Report	17 Sep 2024	17 Sep 2024	☐
☐	PRAC Rapporteur Assessment Report	20 Sep 2024	18 Sep 2024	☐
☐	PRAC members comments	25 Sep 2024	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	26 Sep 2024	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	03 Oct 2024	03 Oct 2024	☐
☐	CHMP members comments	07 Oct 2024	07 Oct 2024	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 Oct 2024	09 Oct 2024	☐
☒	2nd Request for supplementary information	17 Oct 2024	17 Oct 2024	☐
	Submission of MAH's responses	20 Dec 2024		
☐	Re-start of procedure	01 Jan 2025		☐
☐	PRAC Rapporteur Assessment Report	06 Jan 2025		☐
☐	PRAC members comments	08 Jan 2025		☐
☐	Updated PRAC Rapporteur Assessment Report	09 Jan 2025		☐
☐	CHMP Rapporteur Assessment Report	15 Jan 2025		☐
☐	PRAC endorsed relevant sections of the	16 Jan 2025		☐

Status of this report and steps taken for the assessment				
	assessment report[3]			
☐	CHMP members comments	20 Jan 2025		☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 Jan 2025		☐
☐	Opinion	30 Jan 2025		☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Procedure resources	
Rapporteur:	Filip Josephson

Declarations

☒The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report, including in the Product Information, if any.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

Table of contents

List of abbreviations

ATC	Anatomical Therapeutic Chemical
ADaM	Analysis Data Model
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase; serum glutamic pyruvic transaminase (SGPT)
AML	acute myeloid leukemia
ANOVA	analysis of variance
AST	aspartate aminotransferase; serum glutamic oxaloacetic transaminase (SGOT)
AUC0-8	area under the curve from time zero to 8 hours post-dose
AUC0-24	area under the curve from time zero to 24 hours post-dose
AUC0-inf	area under the curve from time zero extrapolated to infinity
AUC0-last	area under the curve from time zero to the last quantifiable concentration
AUC0-t, or AUCtau	AUC0-24 area under the curve from time zero to 24 hr defined in this study as AUC0-24
BLQ	below the limit of quantification
BM	bone marrow
BSA	body surface area
Cavg	average concentration calculated as AUC0-24/24
Cavg(0-8)	average concentration calculated as AUC0-8/8
CBC	complete blood count
CDA	cytidine deaminase cedazuridine International Nonproprietary Name for E7727
CI	confidence interval
CL	clearance
CL/F	apparent oral clearance
CL ss	clearance at steady state
CL ss /F	apparent oral clearance at steady state
Cmax	maximum observed concentration
Cmin	minimum observed plasma concentration
CMML	chronic myelomonocytic leukemia
CR	complete response
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	last observed quantifiable concentration following dosing over multiple days
CV	coefficient of variation
CxDx	cycle number and day number, eg, C1D3
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EOI	end of infusion
EPR	epimer-to-parent ratio
EPR(AUC)	epimer-to-parent ratio of AUC0-24 (cedazuridine)
EPR(Cmax)	epimer-to-parent ratio of Cmax (cedazuridine)
ERT	eResearch Technology
FAB	French-American-British

FDA	Food and Drug Administration
FDC	fixed-dose combination
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
Geo.	geometric
geoCV% or %Geo CV	geometric coefficient of variation
GI	gastrointestinal
HDPE	high-density polyethylene
HI	hematologic improvement
HI-E	erythroid response
HI-N	neutrophil response
HI-P	platelet response
HMA	hypomethylating agent
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product (the specific Astex drug product under study)
IPSS	International Prognostic Scoring System
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRC	Independent Review Committee
IV	intravenous
IWG	International Working Group
LC-MS/MS	liquid chromatography with tandem-mass spectrometry
LFS	leukemia-free survival
LINE-1	Long Interspersed Nucleotide Elements-1
LLOQ	lower limit of quantification
ln-	natural logarithm-
LSM	least squares means
mCR	marrow complete response
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measure
MUGA	multiple gated acquisition scan
NCE	new chemical entity
NE	non-evaluable
OR	overall response
OS	overall survival
PAP	Pharmacometric Analysis Plan
PD	pharmacodynamic(s)
PICC	peripherally inserted central catheter
PK	pharmacokinetic(s)
PR	partial response
PT	Preferred Term
QTc; QTcB; QTcF	QT interval corrected; QTc using Bazett's correction formula; QTc using Fridericia's correction formula
R(AUC0-24)	accumulation ratio for AUC0-24
R(Cmax)	accumulation ratio for Cmax
R2adj	adjusted correlation coefficient
RBC	red blood cell

SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	standard operating procedure
SSC	Study Steering Committee
tau	dosing interval (24 hours in this study)
t½	apparent elimination half-life
TEAE	treatment-emergent adverse event
TI	transfusion independence
Tmax	time to maximum observed plasma concentration
TMF	trial master file
Tmin	time to minimum observed plasma concentration at steady state
ULN	upper limit of normal
USA	United States
Vss	volume of distribution at steady state
VZ	volume of distribution
VZ /F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
λ Z (lambda z)	elimination rate constant

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Otsuka Pharmaceutical Netherlands B.V. submitted to the European Medicines Agency on 15 December 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Grouped application consisting of:
C.I.6: Extension of indication to include treatment of adult patients with myelodysplastic syndromes (MDS) for INAQOVI.

C.I.6: Extension of indication to include treatment of adult patients with chronic myelomonocytic leukaemia (CMML) for INAQOVI.

Based on final results from studies ASTX727-01, ASTX727-02, ASTX727-04, E7727-01, and E7727-02. 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 1.1 of the RMP has also been submitted.
Furthermore, the PI is brought in line with the latest QRD template version 10.3. As part of the application the MAH is requesting a 1-year extension of the market protection.

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

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 did not seek Scientific advice at the CHMP.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Grouped application consisting of:
C.I.6: Extension of indication to include treatment of adult patients with myelodysplastic syndromes (MDS) for INAQOVI.

C.I.6: Extension of indication to include treatment of adult patients with chronic myelomonocytic leukaemia (CMML) for INAQOVI.

Based on final results from studies ASTX727-01, ASTX727-02, ASTX727-04, E7727-01, and E7727-02. 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 1.1 of the RMP has also been submitted.
Furthermore, the PI is brought in line with the latest QRD template version 10.3. As part of the application the MAH is requesting a 1-year extension of the market protection.

☐is recommended for approval.

☐is not recommended for approval.

☒is subject to a request for supplementary information (please refer to the RSI section <and the proposed Changes to the Product Information in a separate document>) before a recommendation can be made.

The responses timetable to the Request for Supplementary Information will be[1] [2]:

- ☐ 30 days (15 days to assess with clock-stop, 8 days to assess with immediate responses)
- ☒ 60 days (36 days to assess)

Amendments to the marketing authorisation

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

[1] Instructions to assessor: please select one of the two options. If no option is selected, a default 30-day assessment timetable will be applied.
[2] Note to MAH: this timetable refers to the assessment of the responses to the RSI and is determined by the Rapporteur/assessor; it does not refer to the clock-stop necessary for the preparation and submission of the responses which is determined by the MAH and communicated to the Procedure Assistant upon receipt of the assessment report.

3. Scientific discussion

3.1. Introduction

3.1.1. Problem statement

Disease or condition

Myelodysplastic syndromes (MDS) are clonal haematopoietic stem cell (HSC) disorders predominating in the elderly, characterised by ineffective haematopoiesis leading to blood cytopaenias and progression to acute myeloid leukaemia (AML) in one-fourth to one-third of cases. Median age at diagnosis of MDS is around 70 years and <10% are younger than 50 years. The incidence of MDS is about 4 cases/100 000 inhabitants/year (reaching 40-50/100 000 in patients aged ≥70 years.

Therapeutic indication

The originally proposed indication was:

Inaqovi is indicated for the treatment of adult patients with myelodysplastic syndromes (MDS) and adult patients with chronic myelomonocytic leukaemia (CMML).

With the response to the request for supplementary information, the MAH has updated the applied indication to:

Inaqovi is indicated as monotherapy for the treatment of adult patients with myelodysplastic syndromes (MDS) and a risk score of >3.5 according to the Revised International Prognostic Scoring System (IPSS-R)

Management

The treatment of MDS is based on the patient's risk category and cytogenetic profile. Treatment options include: lenalidomide (Revlimid), erythropoiesis stimulating agents (ESA; Eprex, Binocrit, Retacrit), luspatercept (Reblozyl), all indicated for treatment of anemia due to MDS, transfusions, stem cell transplantation, ChT or Hypomethylating agents (HMAs) (azacitidine [Vidaza] and decitabine [Dacogen]).

Higher-risk MDS carries a major risk of progression to AML and short survival, and treatment should aim to modify the disease course, with options including allo-SCT, HMAs and, less frequently, ChT (mainly intensive anthracycline-cytarabine combinations).

In the EU, azacitidine (Vidaza) is approved for the treatment of patients not eligible for HSCT with intermediate-2 and high-risk MDS according to the IPSS and CMML with 10% to 29% marrow blasts without myeloproliferative disorder (Vidaza® SmPC).

3.1.2. About the product

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

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 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.

Current indication:

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

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

No scientific advice from CHMP have been given regarding the currently applied indication.

A national scientific advice (22 September 2022), with the character of a pre-submission meeting, with the Swedish Medical Products Agency (MPA) regarding the clinical development plans have been conducted.

3.1.4. General comments on compliance with GCP

The applicant states that all studies were undertaken in accordance with the principles of the World Medical Association's Declaration of Helsinki, including amendments in force up to and including the time the study was conducted. The studies were conducted in accordance with applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and all applicable laws and regulations (including the Committee for Proprietary Medicinal Products Guideline CPMP/ICH/135/95, the European Union Clinical Trial Directive 2001/20/EC and the Code of Federal Regulations 21 CFR, Parts 50 and 56).

3.2. Non-clinical aspects

3.2.1. Toxicology

Repeat dose toxicity

Additional repeat-dose toxicology studies were conducted to support development of an additional indication (low-risk MDS). Due to the longer life expectancy of the low-risk MDS population receiving cedazuridine, the study had a longer study duration (chronic administration) of 6 months. Furthermore, a potential for use of dosing regimen for ASTX727 with duration of longer than 7 days was used. Therefore, a chronic 6-month study in mice was performed with administration of cedazuridine for 14-days followed by a 14-day non-dosing period (Study/Report No. 0862-18099). Adenomas of the pituitary pars intermedia were observed in only males at the mid- and high-dose

groups, as well in controls. This pathology change was reported with no dose response. Additionally, male and female control animals also presented with these tumors. Furthermore, neoplasia of the pituitary pars intermedia was a relatively common tumor in this strain of mouse. Due to this, the significance of these findings in a small number of cedazuridine administered animals is unknown and may not be cedazuridine-related. Once it became evident that a 14-day cycle is unlikely to be developed in the clinic, a follow up 6-month study in mice with a dosing regimen of 7-days on and 21-days off was conducted (Study/Report No. 0862-21490). No cedazuridine-related findings were observed and the NOEL was reported to be the highest dose. This dosing regimen has more relevance to the clinical study since the dosing regimen determined to be 5-days on and 23-days off.

Phototoxicity

The potential of decitabine to cause phototoxic effects was evaluated in an in vitro 3T3 neutral red uptake phototoxicity assay (Study/Report No. CRL 20426730). In this study, the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to decitabine and ultraviolet radiation (+UVR), as compared with the viability of fibroblasts exposed to decitabine in the absence of ultraviolet radiation (-UVR) was assessed. Decitabine did not show phototoxic potential in this assay.

3.2.2. Ecotoxicity/environmental risk assessment

Because the PECsw for both decitabine and cedazuridine for all uses in the treatment of AML, MDS and CMML are below the 0.01 ug/L cutoff and persistence, bioaccumulation and toxicity are not expected, no further review for environmental risk assessment for decitabine andcedazuridine is needed for these proposed uses.

3.2.3. Discussion on non-clinical aspects

For this application for the indication myelodysplastic syndrome, the MAH has provided data from two 6 month repeat dose toxicity studies in mice with cedazuridine. These studies are not considered to identify any further safety concern.

In addition, the MAH has provided data from an in vitro 3T3 phototoxicity assay with decitabine. An absence of a concern for phototoxic potential was concluded already in the original procedure based on an absence of light absorption. The in vitro study presented with this application confirms the lack of phototoxic potential.

3.2.4. Conclusion on the non-clinical aspects

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

3.3. Clinical aspects

3.3.1. 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

Study Number	Subject Population	Final DB Lock or Data Cutoff Date
Primary Efficacy and Safety Studies for MDS/CMML		
ASTX727-01-B (Phase 2) - final	MDS/CMML	16 Sep 2020
ASTX727-02 NA (Phase 3) - final	MDS/CMML	07 Jun 2021
ASTX727-02 EU (Phase 3) - final	AML	17 May 2023
Supportive Safety Studies		
ASTX727-01-A (Phase 1) - final	MDS (FIH, dose escalation)	16 Sep 2020
ASTX727-03	Low-risk MDS (low-dose tablet)	06 Jul 2023
ASTX727-04 - final	MDS/CMML (food effect study)	08 Jul 2019
ASTX727-06*	MDS/CMML/AML/Other Cancers (rollover study)	06 Jul 2023
ASTX727-07	AML (combination with venetoclax)	06 Jul 2023
ASTX727-10**	Intermediate to very high-risk MDS	14 Sep 2023
ASTX727-17	Cancer with/without renal impairment	06 Jul 2023
ASTX727-18	Cancer with moderate and severe hepatic impairment	06 Jul 2023
393-102-00002	Low-risk MDS (low-dose tablet in Japanese subjects)	06 Jul 2023
ASTX660-02	Relapsed/refractory AML (combination study)	13 Sep 2022
ASTX660-03	Relapsed/refractory peripheral T-cell lymphomas (single-agent and combination study)	06 Jul 2023
E7727-01 - final	Healthy volunteers (ADME)	19 Apr 2019
E7727-02 - final	Healthy volunteers (QTc)	21 Dec 2021

* Denotes that the extension study is ongoing while the food effect sub-study is complete and full CSR for the food-effect sub-study is included in the submission

** Denotes that the study terminated, and CSR synopsis is included in the submission

3.3.2. Pharmacokinetics

Apart from a supportive food-effect study (PK food-effect substudy within Study ASTX727-06), there are *no new clinical pharmacology in the current submission*. All data in MDS/CMML patients to assess the PK bridge between Inaqovi and i.v. decitabine was submitted in the initial submission (EMA/CHMP/402324/2023).

Inaqovi (ASTX727) is a fixed-dose combination tablet containing 35 mg decitabine and 100 mg cedazuridine that is intended to provide decitabine exposures equivalent to intravenous (IV) decitabine administered at a dose of 20 mg/m2 body surface area by intravenous infusion over 1 hour repeated daily for 5 consecutive days (i.e., a total of 5 doses per treatment cycle).

In the current application, the Applicant rely on a PK bridge, assuming that Inaqovi and IV decitabine have similar decitabine plasma exposure (total AUC over the 5-day cycle) for to a positive benefit/risk in MDS/CMML patients.

Decitabine is currently not approved in the EU for MDS/CMML. i.v. decitabine (as well as Inaqovi) is approved for the treatment of AML in the EU [Dacogen] for intravenous administration at a dose of 20 mg/m2 by intravenous infusion over 1 hour repeated daily for 5 consecutive days per treatment cycle). Cedazuridine is a cytidine deaminase (CDA) inhibitor currently not approved in the EU for MDS/CMML. The pharmacokinetic analyses should thus aim at describing the disposition of decitabine and cedazuridine in MDS/CMML patients, to emphasize potential differences between AML and MDS/CMML

patients. 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.

Assessor's comment:

Even though the MDS/CMML patients were considered supportive in the initial Inaqovi submission (EMA/CHMP/402324/2023), all available PK data in MDS/CMML patients were fully assessed and PK bioequivalence for $AUC_{0\text{-}5days}$ between Inaqovi and i.v. decitabine could be concluded.

Since the PK data in MDS/CMML patients were fully assessed in the initial Inaqovi submission (EMA/CHMP/402324/2023), the detailed PK results are not included in the current AR. The PK data and assessments are briefly presented in the current AR and with particular focus on the MDS/CMML subgroup for completeness of data. For all additional details concerning the PK assessment, the reader is referred to EMA/CHMP/402324/2023.

Absorption

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

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

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

Results

The primary analysis showed that the 5-Day AUC0-24 percentage ratio of geometric LSM for ASTX727 relative to IV decitabine was 98.93% (90% CI 92.66%, 105.6%). The 2 sided 90% CI was contained entirely within the prespecified range of 80% to 125% for the primary analysis. All sensitivity and secondary analyses that included additional subjects (N between 124 and 131 subjects for paired and unpaired comparisons) confirmed that the 2-sided 90% CI of the geometric LSM ratio was contained entirely within 80% to 125% (**Table *1***).

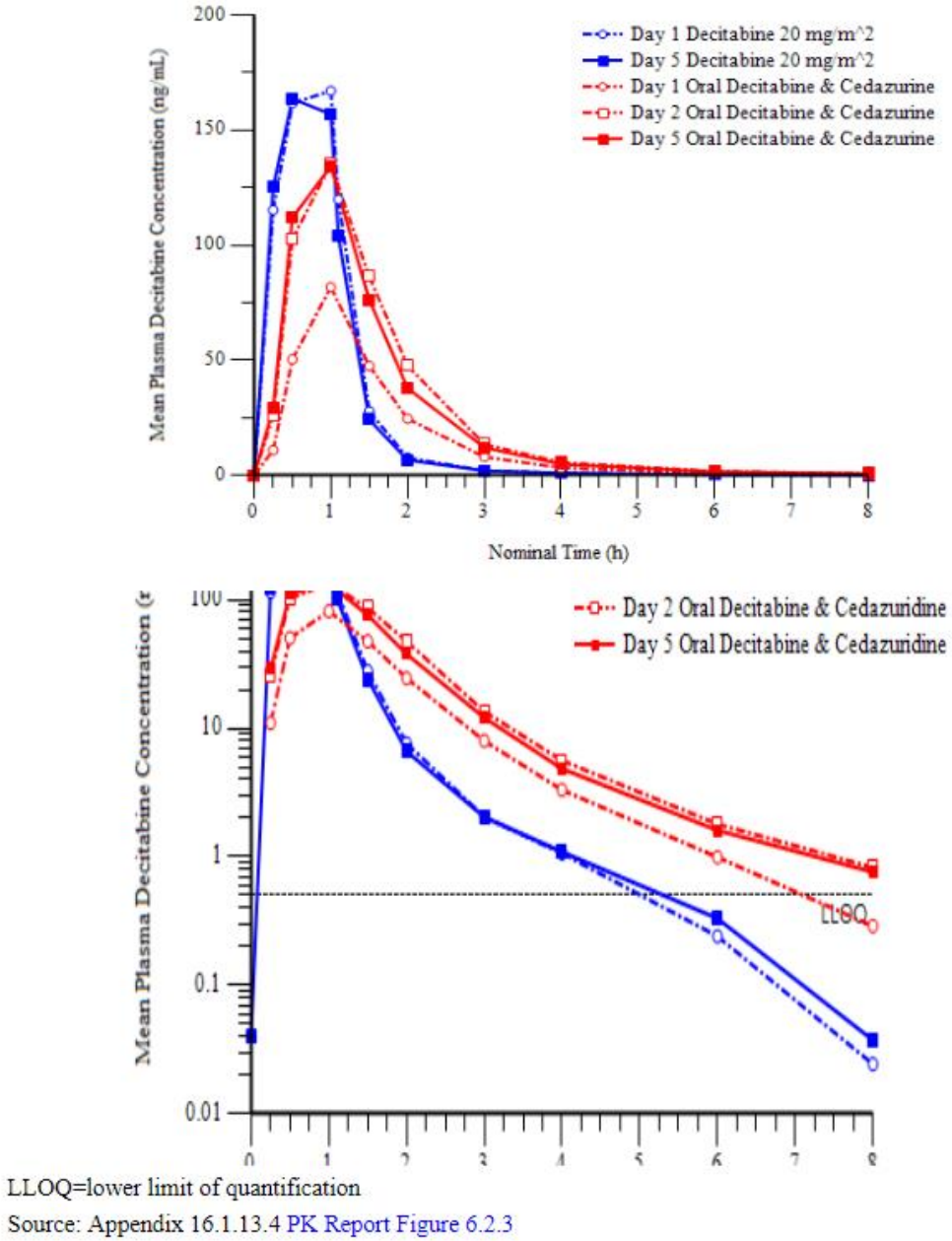
Table 1 Equivalence Analysis for Comparison of Decitabine AUC Exposures Between ASTX727 and Intravenous Decitabine – Primary Analysis of MDS/CMML Population (Study ASTX727 02 NA MDS/CMML)

Analysis		AUC Parameter (ng•h/mL)	IV Decitabine		Oral ASTX727		Percentage Ratio (%) of Geo. LSM (90% CI)		Intrasubject Variability (CV, %)
			N	Geo. LSM	N	Geo. LSM			
Primary	**Paired**	**5-Day $AUC_{0\text{-}24}$**	**123**	**864.94**	**123**	**855.69**	**98.93**	**(92.66, 105.6)**	**31.7**
Sensitivity	Unpaired	5-Day $AUC_{0\text{-}24}$	131	865.82	128	848.40	97.99	(91.84, 104.5)	32.2
	Paired	5-Day $AUC_{0\text{-}24}$	128	869.96	128	850.32	97.74	(91.58, 104.3)	32.2

ANOVA=analysis of variance; AUC=area under the concentration-time curve; AUC_{0-24}=area under the concentration-time curve from time zero to 24 hours postdose; CI=confidence interval; CMML=chronic myelomonocytic leukaemia; CSR=clinical study report; CV=coefficient of variation; Geo. LSM=geometric least squares mean; IV=intravenous(ly); MDS=myelodysplastic syndrome; N=number of subjects.

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

Overall, plasma decitabine concentrations were higher following multiple oral administration of ASTX727 tablets (Days 2 and 5) compared to single oral administration on Day 1. Peak decitabine plasma concentrations were reached after 1 hour following both IV and oral treatments (except on Day 5 after IV treatment, when peak decitabine was reached at 0.5 hour post-dose), but decitabine peak plasma concentrations were higher following IV administration than following oral administration (**Figure *1***).



LLOQ=lower limit of quantification

Source: Appendix 16.1.13.4 PK Report Figure 6.2.3

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

ASTX727-06 Food effect substudy

The objective of this PK substudy was to evaluate the PK of decitabine and cedazuridine when ASTX727 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 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).

On Days 1, 3, and 5, subjects will fast for at least 2 hours before and for 2 hours after dosing. Water is permitted as desired except from 1 hour before to 1 hour after dosing. On Day 2, subjects will fast overnight for at least 10 hours before and for 4 hours after dosing. Water will be restricted from 1 hour before dosing until 1 hour after dosing (except for the water given with study treatment). On Day 4 (the fed day), following an overnight fast of at least 10 hours, subjects will consume either a high-calorie, high-fat breakfast meal or a low-calorie, low-fat breakfast meal within 20 minutes, receive ASTX727 30 minutes after starting the meal, and fast for at least 4 hours after dosing.

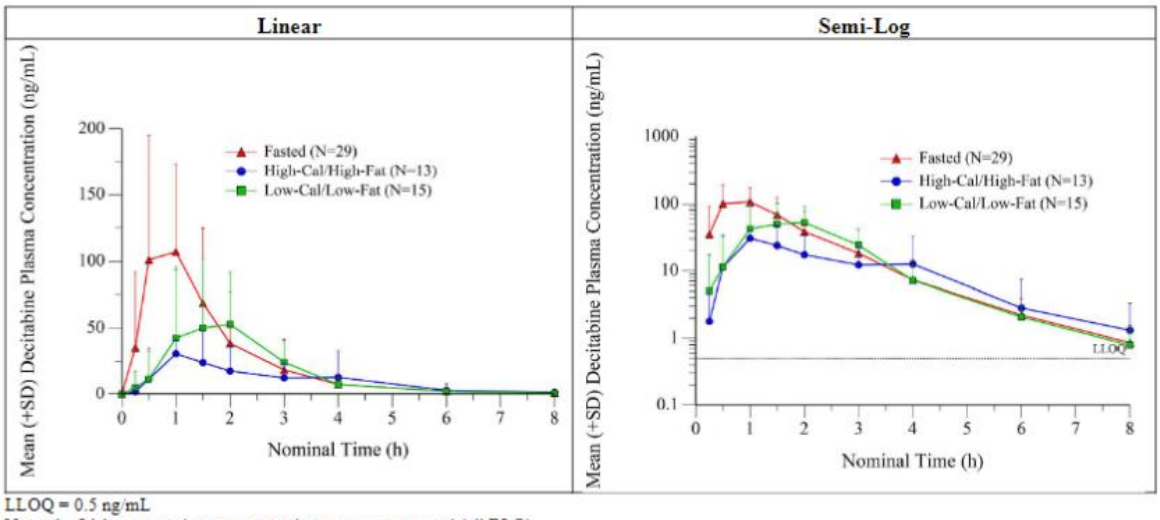
Table 2 PK sampling schedule

Timepoint	Day 1	Day 2	Day 3	Day 4	Day 5
Predose (Time 0)[a]		×	×[b]	×	×[b]
0.25 hours (±2 minutes) postdose		×		×	
0.5 hours (±2 minutes) postdose		×		×	
1 hour (±5 minutes) postdose		×		×	
1.5 hours (±5 minutes) postdose		×		×	
2 hours (±5 minutes) postdose		×		×	
3 hours (±10 minutes) postdose		×		×	
4 hours (±10 minutes) postdose		×		×	
6 hours (±10 minutes) postdose		×		×	
8 hours (±20 minutes) postdose		×		×	
24 hours (±60 minutes) postdose		×[b]		×[b]	

[a] Predose samples were to be collected within 30 minutes before administration of study treatment.
[b] The 24-hour post-dose samples on Days 2 and 4 were to be taken prior to dosing on Days 3 and 5, respectively.

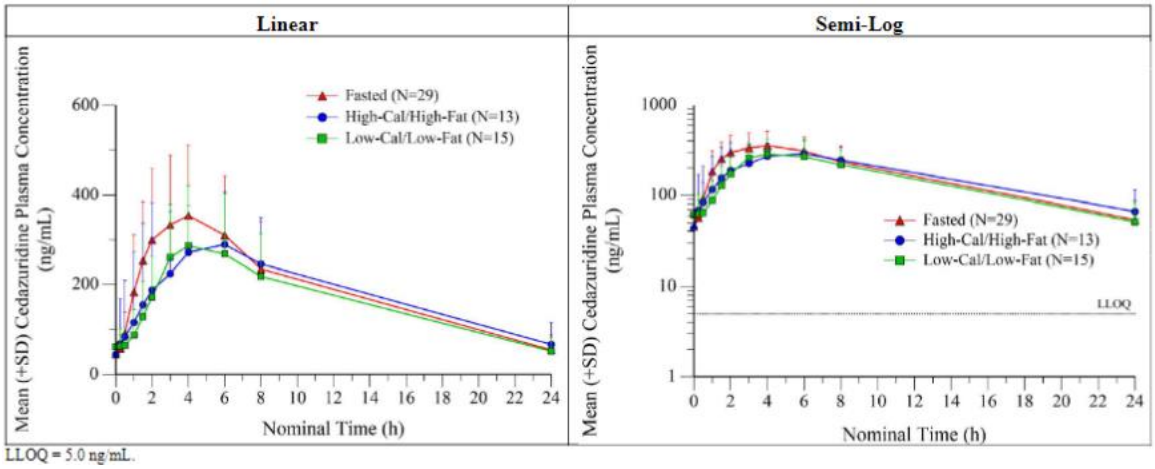
PK parameters of decitabine, cedazuridine, and cedazuridine-epimer in plasma were computed using Phoenix TM WinNonlin ® v.8.3 (or higher). Tables, listings, and figures were generated using Phoenix TM WinNonlin® v.8.3 (or higher), and Microsoft ® Office 365. Inferential statistics were obtained using an analysis of variance (ANOVA) with a mixed effect model using Phoenix TM WinNonlin ® v.8.3 (or higher). The PK results were presented as both pooled (fed vs. all fasted subjects) and pairwise analysis (fed vs. fasted subjects from their respective arms).

Figure 2 Mean (+SD) decitabine concentration vs. time profiles



LLOQ = 0.5 ng/mL
Note: the 24-hour post-dose concentration was not presented (all BLQ).

Figure 3 Mean (+SD) cedazuridine concentration vs. time profiles



Results of the statistical comparison of decitabine under fed (high-calorie/high-fat or low-calorie/low-fat) compared to fasted conditions (pooled fasted analysis) are presented in **Table *3* Decitabine PK Parameters equivalence assessmentTable *3***. 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 3 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 compared to fasted conditions are presented in **Table *4***. 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 4 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 was administered with food vs fasted.

Assessor's comment:

For ASTX727-06 food effect sub-study a validated previously assessed bioanalytical method was used. The bioanalytical report has been provided showing adequate method performance and acceptable ISR.

This food effect study was a post-marketing commitment with FDA, already ongoing at the time of the initial European MAA. In the initial MAA a phase 1b study, ASTX727-04, evaluating the food effect was included but deemed to variable for firm conclusions. In ASTX727-04 decitabine exposure parameters were approximately 40% (AUC) to 53.5% (Cmax) lower following a high-fat meal compared to those following fasted conditions and cedazuridine and cedazuridine-epimer exposure parameters were approximately 10% and 20% higher, respectively.

In ASTX27-06 decitabine exposure are decreased to a similar extent as in study ASTX27-04 while cedazuridine exposure were slightly decreased (more so for the low-calorie/low-fat group) in AST2X7-06 and slightly increased in the previous study. Cedazuridine-epimer exposure were similarly increased in both studies. Overall though the cedazuridine exposures are not considered changed to a clinically relevant extent in either study.

The variability in PK-parameters were high in the ASTX727-06 study especially for the high-calorie/high-fat group, above 100% CV for decitabine and 35-59% for cedazuridine. AUCs for both decitabine and cedazuridine following fasted conditions were about 20 % lower in the High-Cal/High-Fat group compared to the Low-Cal/Low-Fat group which may be an effect of the high variability and rather small groups (13-15 individuals).

It is currently recommended 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 are 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, however, section 5.2 should be updated including new information for example effect of a low calorie meal **(SmPC**).

3.3.3. Discussion on clinical pharmacology

The role of pharmacokinetics in the design of the studies supporting this application is establishment of PK equivalence between Inaqovi (ASTX727) and IV decitabine (total AUC over the 5-day cycle). Note that decitabine is currently not approved for MDS/CMML in the EU which means that a conventional PK bridge to an EU approved product is not applicable.

There were more MDS/CMML patients (n=138) than AML patients (n=89) from Phase III in the initial Inaqovi submission. The PK equivalence in $AUC_{0\text{-}5days}$ between Inaqovi and i.v. decitabine was based on a pooled dataset including both AML and MDS/CMML patients. Thus, the conclusion that Inaqovi and i.v. decitabine has equivalent $AUC_{0\text{-}5days}$ remains valid for MDS/CMML patients which is concerned in the current procedure.

Bioequivalence for 5-Day $AUC_{0\text{-}24}$ between oral and IV decitabine could be concluded for both the AML (EU) and the MDS/CMML (NA) population as well as for pooled data from the two studies in the initial application. The specific PK results in the current AR for MDS/CMML patients specifically, further confirms bioequivalence also in the target population relevant for this procedure.

As discussed in the initial Inaqovi submission (EMA/CHMP/402324/2023), there are differences in the decitabine plasma concentration curves between IV and oral administration. For example, differences in extent of exposure (AUC) between oral and IV administration is seen on day 1 which is likely due to less cedazuridine present systemically. This difference is not seen on subsequent days when steady state is expected for cedazuridine. C_{max} is also consistently lower for ASTX727 compared to IV decitabine; on Day 1 the difference was 54% (AML) and 55% (MDS/CMML) and on Day 5 28% (AML) and 22%(MDS/CMML).

In order to support that the lower C_{max} (and lower AUC on day 1) was not clinically relevant, the applicant has submitted supportive PD data which were assessed in the initial submission (EMA/CHMP/402324/2023). The PD endpoint, i.e., the maximum percent LINE-1 demethylation, was not significantly different between ASTX727 and IV decitabine in the Phase 3 Study ASTX727-02 in AML or in MDS/CMML patients. This supports that differences in PK profile between ASTX727 and IV decitabine are not expected to affect the primary pharmacodynamic effect.

As concluded in the initial Inaqovi submission, the PK characteristics of decitabine and cedazuridine are similar between AML and MDS/CMML patients.

In the food effect substudy of ASTX27-06 decitabine exposures were reduced (more than 50%) by both high calorie/high-fat and low-calorie/low-fat meals, which is in line with previous results. The recommendation to administer Inaqovi in the fasted state remains unchanged.

3.3.4. Conclusions on clinical pharmacology

This application includes demonstration of bioequivalence for 5-Day AUC0-24 between oral and IV decitabine as shown for both the AML (EU) and the MDS/CMML (NA) population as well as for pooled data from the two studies.

3.4. Clinical efficacy

3.4.1. Main studies

Primary efficacy studies for this application are Study ASTX727-02 NA (Phase 3 MDS/CMML) and Study ASTX727-01-B (Phase 2 MDS/CMML).

Table 5. Summary of Clinical Studies Supporting Efficacy of ASTX727 in MDS

Study ID	Efficacy Objectives	Design	Efficacy Endpoint(s)	Population	Median Treatment Exposure	Response[a] Rate, n (%)/ Time to Best Response	Median Duration of Response	Median Survival [b]	Median Follow-up
ASTX727-01-B	Response rate Duration of response	Phase 2 multicentre, randomised, open-label, crossover	Complete response (CR), partial response (PR), marrow complete response (mCR), haematologic improvement (HI)[c]	Males/females ≥18 yrs with MDS or CMML who are candidates for treatment with a hypo-methylating agent	7 cycles (range: 1, 44 cycles).	Best Response: CR: 14 (17.5%) (95% CI: 9.9, 27.6) Median Time to Best Response (CR, PR, or mCR): 72.5 days (2.4 months) (Range: 28, 303 days)	397 days (~13 months) (95% CI: 170, 420)[b]	OS: 589 days (19.4 months) (95% CI: 392.0, 864.0)	Reverse K-M 39.1 months (30.7, 41.8)
ASTX727-02 NA	Long-term response rate	Phase 3 multicentre, randomised, open-label, 2-period, 2-sequence crossover	Complete response (CR), partial response (PR), marrow complete response (mCR), haematologic improvement (HI)[c]	Males/females ≥18 yrs with MDS or CMML who were candidates to receive IV decitabine	9 cycles (range: 1, 28 cycles)	Best Response: CR: 29 (21.8%) (95% CI: 15.1, 29.8) Median Time to Best Response (CR, PR, mCR, HI): 100 days (3.3 months) (range: 28, 570 days)	354.0 days (~12 months) (95% CI: 289, 439)	OS: 966 days (31.7 months) (95% CI: 809, NE)	Reverse K-M 29.1 months (95% CI: 28.0, 30.2)

CI=confidence interval; CMML=chronic myelomonocytic leukaemia; CR=complete response; mCR=marrow complete response; MDS=myelodysplastic syndromes; NE=not estimable; OS=overall survival; PR=partial response

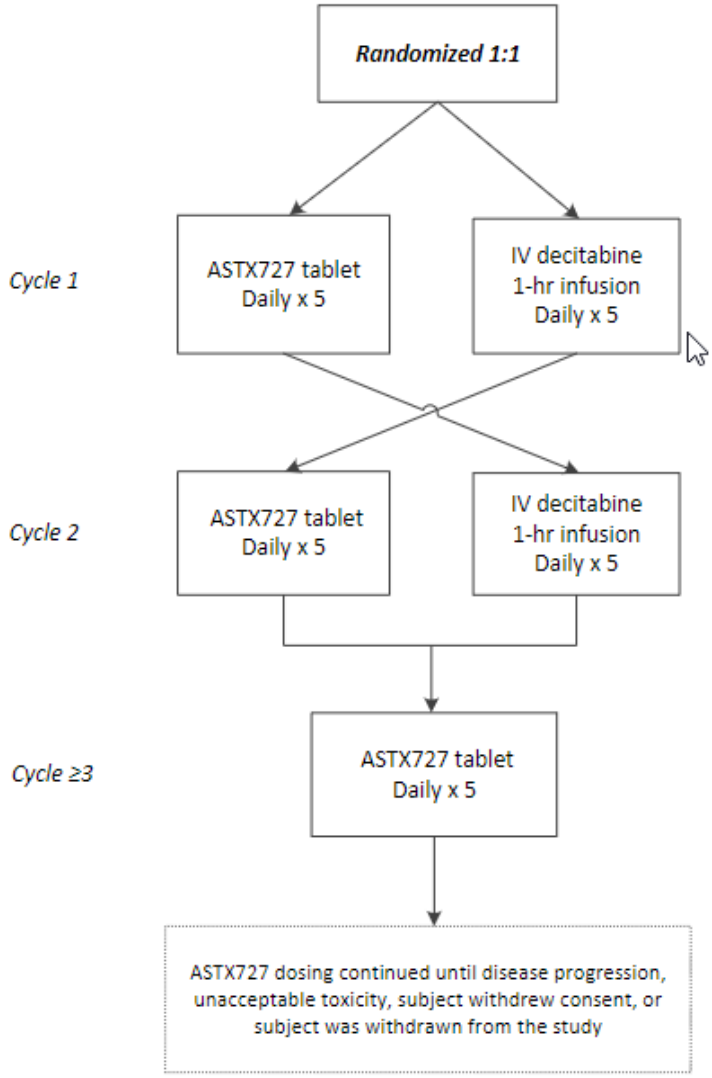
[a] All response criteria were based on 2006 IWG Response Criteria Cheson 2006

[b] Kaplan-Meier method

3.4.2. Study ASTX727-02 NA (Phase 3 MDS/CMML, NCT03306264)

A Phase 3, Randomized, Open-Label, Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) versus IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML).

Figure 4. Study ASTX727-02 design (MDS or CMML)



Assessor's comment

Patients were randomized 1:1 to receive oral decitabine/cedazuridine tablets 100/35 mg on days 1–5 of cycle 1 (28 days) and IV decitabine 20 mg/m2 on days 1–5 of cycle 2 (28 days) or the reverse sequence. From cycle 3 onwards, all patients received decitabine/cedazuridine 100/35 mg orally once daily on days 1–5 of each 28-day cycle until disease progression or unacceptable toxicity.

For the purpose of efficacy assessment, ASTX727-02 NA is treated as a SAT.

3.4.3. Methods

3.4.3.1. Study participants

Key inclusion criteria

1. Men or women ≥18 years who are candidates to receive IV decitabine, ie, subjects with MDS previously treated or untreated, with de novo or secondary MDS, including all French-American-British (FAB) subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and CMML), and subjects with MDS IPSS int-1, -2, or high-risk MDS.
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
3. Adequate organ function defined as follows:
    a. Hepatic: Total or direct bilirubin ≤2 × upper limit of normal (ULN); AST/SGOT and ALT/SGPT ≤2.5 × ULN.
    b. Renal: serum creatinine ≤1.5 × ULN or calculated creatinine clearance or glomerular filtration rate >50 mL/min/1.73 m2 for subjects with creatinine levels above institutional
    normal.
4. No major surgery within 30 days of first study treatment.
5. Life expectancy of at least 3 months.

Key exclusion criteria

1. Prior treatment with more than 1 cycle of azacitidine or decitabine.
2. Hospitalization for more than 2 days for documented febrile neutropenia, pneumonia, sepsis, or systemic infection in the 30 days before screening.
3. Treatment with any investigational drug or therapy within 2 weeks of study treatment, or 5 half-lives, whichever is longer, before the first dose of study treatment, or ongoing clinically significant adverse events (AEs) from previous treatment.
4. Cytotoxic chemotherapy or prior azacitidine or decitabine within 4 weeks of first dose of study treatment.
5. Concurrent MDS therapies, including lenalidomide, erythropoietin, cyclosporine/tacrolimus, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, etc. (Prior treatment with these agents is permitted, provided that completion is at least 1 week before the first dose of study treatment.)
6. Rapidly progressive or highly proliferative disease (total white blood cell count of >15 × 10 9 /L) or other criteria that render the subject at high risk of requiring intensive cytotoxic chemotherapy within the next 3 months.

Assessor's comment

The first inclusion criterion defines the studied population as patients who are candidates to receive IV decitabine. This definition matches the FDA approved label for IV decitabine and Inaqovi.

Indicated for treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French[1]American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

The currently proposed indication by the applicant is:

Inaqovi is indicated as monotherapy for the treatment of adult patients with myelodysplastic syndromes (MDS) and a risk score of >3.5 according to the Revised International Prognostic Scoring System (IPSS-R).

This is based on a post-hoc re-classification of patients from IPSS to IPSS-R and a definition of high-risk patients defined as IPSS-R >3.5. This cut off is supported by the consensus proposal for IWG2023 but it is also pointed out that the exact cut-off for high-risk do vary. The chosen definition of IPSS-R >3.5 falls within the IPSS-R intermediate risk category which ranges from >3.0-4.5.
Hence, the currently proposed indication may possibly still contain an intermediary risk patient population where preferred treatment is not firmly established. However, considering the consensus proposal for IWG2023 (Zeidan et.al.) the rapporteur propose to accept that the proposed definition of high-risk population defined as IPSS-R >3.5 is sufficient for the Inaqovi indication statement.

3.4.3.2. Treatments

- Test Product: ASTX727 tablet (100 mg cedazuridine and 35 mg decitabine).
    - Dose: one ASTX727 tablet administered orally Daily×5 in Cycle 1 or 2, then Daily ×5 in 28-day cycles.

  The ASTX727 tablet was to be taken at the same time on each dosing day. Subjects were instructed to fast from food and non-clear liquids for at least 2 hours before and 2 hours after dosing.

  Dose reductions were not allowed in Cycles 1 and 2. If a dose reduction was necessary in Cycles ≥3, the dose was reduced by decreasing the number of dosing days in a cycle to 4; if further reduction was necessary, the dose could have been reduced to 3 days. Dose delays up to 2 weeks were allowed for recovery of blood counts.

- Control (Reference) Product: Dacogen (decitabine) for Injection.
    - Dose: 20 mg/m 2 continuous 1-hour IV infusion Daily×5 in Cycle 1 or 2.

  On Days 1–5 of the IV decitabine cycle, subjects received a 1-hour infusion of IV decitabine 20 mg/m 2 (based on body surface area [BSA]).

  Decitabine was administered in either Cycle 1 or 2. No dose adjustments were allowed.

3.4.3.3. Objectives

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

Secondary Objectives
To assess the following:
• Long-term safety and efficacy (response rate) of ASTX727.
• Long interspersed nucleotide elements-1 (LINE-1) demethylation.
• Additional pharmacokinetics (PK) parameters.

3.4.3.4. Outcomes/endpoints

Primary Endpoint
Comparison between ASTX727 and IV decitabine:
Total 5-day AUC exposures of decitabine after treatment with ASTX727 versus IV decitabine.

Secondary Endpoints
Safety as assessed by AEs, concomitant medications, physical examination, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and electrocardiogram (ECG).

Maximum %LINE-1 demethylation.

Additional secondary PK parameters.

Clinical response (complete response [CR], marrow complete response [mCR], partial response (PR), and hematologic improvement [HI]) based on International Working Group (IWG) 2006 MDS response criteria (**Table *6***). DoR was calculated from the first documentation of response to the first documentation of disease progression or death due to any cause, whichever occurred first. In the absence of any event, the duration of response will be censored at the last observation at which an event was not observed. Anti-cancer therapy, except for HSCT, was considered an event. Patients missing two or more consecutive disease assessments were censored at the last disease assessment before missed assessments.

Red blood cell (RBC) or platelet transfusion independence (TI). Transfusion dependence (TD) and transfusion independence are defined as follows:

- Transfusion dependence at baseline: documentation of 2 units or more of transfusion within 56 days of the first dose of study treatment.
- Post-treatment transfusion independence: no transfusion for 56 consecutive days or more after the first dose of study treatment while maintaining hemoglobin ≥8 g/dL (RBC TI) or maintaining platelets ≥20×109 /L (Platelet TI).

Post-treatment transfusion independence rate will be calculated separately for RBC transfusion independence and platelet transfusion independence as the number of subjects who are transfusion independent post treatment (n) among those who were transfusion dependent at baseline (N). This will be calculated for 84-day and 112-day transfusion independence, defined as no transfusion for 84 consecutive and 112 consecutive days, respectively, while maintaining hemoglobin ≥8 g/dL (RBC TI) or maintaining platelets ≥20×109 /L (Platelet TI).

Leukemia- free survival, defined as the number of days from the date of randomization to the date when bone marrow or peripheral blood blasts reach ≥20%, or death from any cause.

Overall survival (OS), defined as the number of days from the date of randomization to the date of death from any cause.

Assessor's comment

Duration of response follows FDA preferred censoring rules with the exception of HSCT which is not considered an event.

Table 6. Modified Response Categories Based on IWG 2006 MDS Response Criteria

Complete Response (CR): the following for at least 4 weeks		
Peripheral: normal peripheral counts with persistent granulocyte count ≥1.0 x 10^9/L, platelet ≥100 x 10^9/L, and Hgb ≥11 g/dL. **Marrow:** normal bone marrow with persistent marrow blasts ≤5%; persistent dysplasia will be noted.		
Partial Response (PR): the following for at least 4 weeks		
Peripheral: normal peripheral counts with granulocyte count ≥1.0 x 10^9/L, platelet count ≥100 x 10^9/L, and Hgb ≥11g/dL. **Marrow:** normal bone marrow and marrow blasts >5% but were reduced by 50% or more.		
Marrow Complete Response (mCR): the following at least for 4 weeks		
Reduction of bone marrow blasts to ≤5% and decrease by 50% or more with or without normalization of peripheral counts.		
Hematological Improvement (HI): lasts at least 8 weeks		
Erythroid Response (HI-E):	Major Response:	Hemoglobin increase ≥1.5 g/dL in the absence of RBC transfusions.
Platelet Response (HI-P):	Major Response:	Absolute increase of platelet count from <20 to >20 X 10^9/L and by at least 100%, or if more than 20 x 10^9/L, by an absolute increase of at least 30 x 10^9/L in the absence of platelet transfusions.
Neutrophil Response (HI-N):	Major Response:	granulocyte increase ≥100%, and by an absolute increase ≥0.5 x 10^9/L.
[a] Abnormal baseline counts should be assessed within one week prior to therapy, not influenced by transfusions (no transfusion for at least 1 week).		

Persistent dysplasia was noted but did not preclude a CR conclusion. However, if dysplasia was not present at inclusion but detected after treatment this could disqualify from a CR classification.

3.4.3.5. Sample size

The sample size calculation was based on analysis of 5-day AUC in study ASTX727-01, which showed an estimate of intra-subject coefficient of variation (CV) of 0.5. A conservative CV value of 0.55 was chosen to calculate the sample size for the current study.

The total of 118 subjects planned for the primary analysis included in the 2 one-sided equivalence tests for the geometric mean ratio of ASTX727 5-day AUC relative to IV decitabine 5-day AUC was to provide 90% power at the statistical significance level of 0.05, when the true ratio of geometric means is 1.0, the CV under an unlogged scale is 0.55, and the 90% confidence interval (CI) equivalence limits for the ratio of geometric means are 0.8 and 1.25. Assuming 10% of subjects may not be evaluable in the study, approximately 132 subjects were planned to be randomized.

3.4.3.6. Randomisation

Eligible subjects were randomly assigned to Cycle 1 study treatment in a ratio of 1:1 to receive ASTX727 or IV decitabine. Subjects were to cross over to the other therapy in Cycle 2. Treatment

assignment was determined through a computer-generated randomization schedule and accessed through an interactive voice response system.

3.4.3.7. Blinding (masking)

Not applicable. The study was open label.

3.4.3.8. Statistical methods

Two formal analyses were planned for this study: The first analysis was performed after all evaluable subjects had completed Cycles 1 and 2 and included analyses of all PK endpoints, maximum %LINE-1 demethylation, and all available clinical response and safety data up to the data cutoff date. A second analysis was to be performed after all subjects have completed at least 6 months of follow up or have permanently discontinued treatment prior to 6 months of follow up from their first treatment dose.

No formal interim analyses were planned.

Statistical Analysis Plan was authored/signed on 28 February 2019. First subject randomized into study was on 13 February 2018.

Analysis data sets

Randomized Subject Analysis Set	all randomized subjects. Subjects were included in the treatment group according to their randomly assigned treatment.
Efficacy Analysis Set	all subjects who received any amount of study treatment. Subjects were included in the treatment sequence according to their randomly assigned treatment sequence.
Safety Analysis Set	all subjects who received any amount of study treatment. Subjects were included in the treatment sequence according to the treatment sequence received.
Primary Endpoint PK Analysis Set	included total cycle 5-day AUC based on AUC_{0-24} from subjects who received 5-day dosing of IV decitabine and ASTX727 in Cycles 1 and 2 and who met the criteria for both ASTX727 and IV decitabine dosing and PK assessments
Overall PK Analysis Set	included subjects who may not have been included in the Primary Endpoint PK Analysis Set and who received any amount of treatment, complied with the protocol sufficiently to ensure PK samples were collected as intended, and provided sufficient samples to measure plasma concentrations of decitabine, cedazuridine, and cedazuridine-epimer
Pharmacodynamics (PD) Analysis Set	included subjects who received any amount of treatment and who had LINE-1 methylation data at baseline (Day 1) of Cycle 1 or 2 and on either Day 8 or Day 15 of that cycle

Primary Pharmacokinetic Analyses

A mixed-effect model analysis was performed on the natural logarithm (ln-) transformed 5-day cumulative AUC_{0-24} parameter for plasma decitabine from FDC tablet formulation of ASTX727 vs IV

decitabine 20 mg/m^2 1-hour infusion. Only those subjects with evaluable 5-day AUC_{0-24} parameters for both treatments (ASTX727 and IV decitabine), i.e., "paired" subjects, were included in the analysis.

The model included treatment, period, and sequence as fixed effects, and subject nested in sequence as a random effect. Effects of the sequence and period were evaluated. Model output included least squares means (LSM), LSM differences between treatments and the standard error (SE) associated with these differences. For relative AUC equivalence assessment, the 90% CIs for the ratios of treatment LSM for ASTX727 relative to IV decitabine were calculated for the parameters of 5-day AUC_{0-24} (and secondary AUC parameters) using ln-transformed data. The ln-transformed results were back-transformed to the original scale by exponentiation to obtain geometric LSM for each treatment and geometric LSM ratios of 5-day AUC_{0-24} of oral versus IV treatment. ASTX727 and IV decitabine were to be considered equivalent if the two-sided 90% CI of the 5-day AUC_{0-24} ratio of LSM for oral/IV was contained entirely within the range of 0.80 – 1.25.

Of note, as steady state is achieved on the second consecutive day of dosing of ASTX727, PK exposures of decitabine and cedazuridine are somewhat lower on day 1 of dosing, and days 2 through 5 are equivalent. No carryover of IV decitabine was expected, and PK of IV decitabine on all dosing days was expected to be same.

Sensitivity analyses

As a sensitivity analysis, subjects with at least one valid 5-day AUC_{0-24} value in ASTX727 or IV decitabine were included using a Mixed-Effect Model Repeated Measure method (MMRM). As a secondary analysis, the same statistical comparisons were done for 5-day cumulative AUC_{0-inf} as for 5-day cumulative AUC_{0-24}. If there were subjects with complete data from only one cycle, i.e., unpaired subjects for both IV and oral dosing, a sensitivity analysis assessing the impact of inclusion of such subject(s) on the equivalence of the 5-day AUC_{0-24} between ASTX727 and IV decitabine were performed using the same methodology described above.

BLQ and missing concentration data

Below the limit of quantification (BLQ) values were set to zero for statistical summary of concentrations and calculation of PK parameters.

For the PK parameter calculations, imputation of missing data may have been done for missing plasma concentration at the end time of a predefined partial AUC, and for missing pre-dose values. Unless otherwise noted, data summaries were to be performed only on observed data.

In the case where subjects were dosed with any of the study drugs but discontinued treatment early, the concentration data were reported in the concentration tables and included in all summary statistics and PK analysis if sufficient concentration data were available to permit PK analysis for that treatment in that subject.

Secondary PK Parameters

Plasma PK parameters were listed and summarized by analyte, treatment, and cycle/days. The following (non-model-based) descriptive statistics were provided: n, mean, standard deviation (SD), CV%, median, min, max, geometric mean, and geometric CV%.

Efficacy

Response rates and rates of hematologic improvement (HI) were calculated as defined by the International Working Group (IWG) 2006 MDS Response Criteria. Efficacy variables were summarized using descriptive statistics, and no comparison analyses between treatments was performed. Evaluation of response rate was conducted by independent medical review of peripheral blood, bone marrow, and transfusion data. Data were listed and summarized using frequency counts and

proportion of subjects with each category of best response (i.e., subjects were counted once with best response) in the following hierarchy: Complete Response (CR), Partial Response (PR), Marrow Complete Response (mCR), Hematological Improvement (HI), stable disease, progressive disease, and non-evaluable (NE). Rates of best response were estimated using sample proportions and 95% Wald CI based on the number of subjects in the Efficacy Analysis Set.

Leukemia-free survival and Overall survival were analysed using Kaplan-Meier plot.

For transfusion independence rates, the 95% Clopper-Pearson CI will be provided.

LINE-1 Methylation Assay

For Cycles 1 and 2 independently, %LINE-1 methylation data were summarized descriptively by visit and treatment. The mean maximum %LINE-1 demethylation in Cycles 1 and 2 along with the corresponding 95% CIs are provided for ASTX727 and IV decitabine. The 95% CI for the difference in mean maximum %LINE-1 demethylation between ASTX727 and IV decitabine in Cycles 1 and 2 were generated based on an analysis of variance (ANOVA) model with treatment as factor.

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

Safety

The incidence and severity of adverse events (AEs) were summarized using descriptive statistics. Exposure to study treatment, deaths, and causes of deaths were tabulated.

Assessor's comments

The primary objective of the study was to assess equivalence of 5-day dosing between ASTX727 and IV decitabine which was assessed in a primary analysis of 5-day AUC_{0-24} parameters for both treatments. Equivalence was to be established using a standard approach based on two-sided 90% CI of the AUC_{0-24} ratio between treatments that was to be contained entirely within the range of 0.80 – 1.25. The analysis method is acceptable. The relevance of other pharmacokinetic parameters for establishment of equivalence as well as conclusions of the pharmacokinetic analyses are addressed in sections 5.3.2 – 5.3.6 of this report.

Efficacy variables were secondary and analysed using descriptive statistics. No comparison was planned between the treatment groups. Given that the primary objective of the study is equivalence of the 2 treatments, it is reasonable that secondary endpoints are not statistically tested for differences. However, with the exception of the cross-over design in the first 2 cycles, where equivalence is evaluated, the study design is based on a single arm. The analysis of efficacy endpoints was therefore limited to summaries for all patients in the study, or summaries by treatment sequence. In each case, efficacy results of the 2 treatments cannot be separated from each other. Thus, evaluation of efficacy of ASTX727 in study ASTX727-02 NA is limited due to the single arm design, with no statistical inference. Efficacy results are exploratory.

Further, it is unclear if any carry-over effects were envisaged between different treatments in cycle 1 and 2. It seems that the Applicant was not concerned about possible carry-over in the primary analysis, but only in the secondary analysis of maximum %LINE-1 methylation.

The statistical analysis plan was finalised during the ongoing open-label study, which cannot exclude that the analysis plan was not influenced by data on hand.

3.4.4. Results

3.4.4.1. Participant flow

Figure 5. Disposition of Subjects in Study ASTX727-02 (All Subjects and Randomized Subject Analysis Sets)

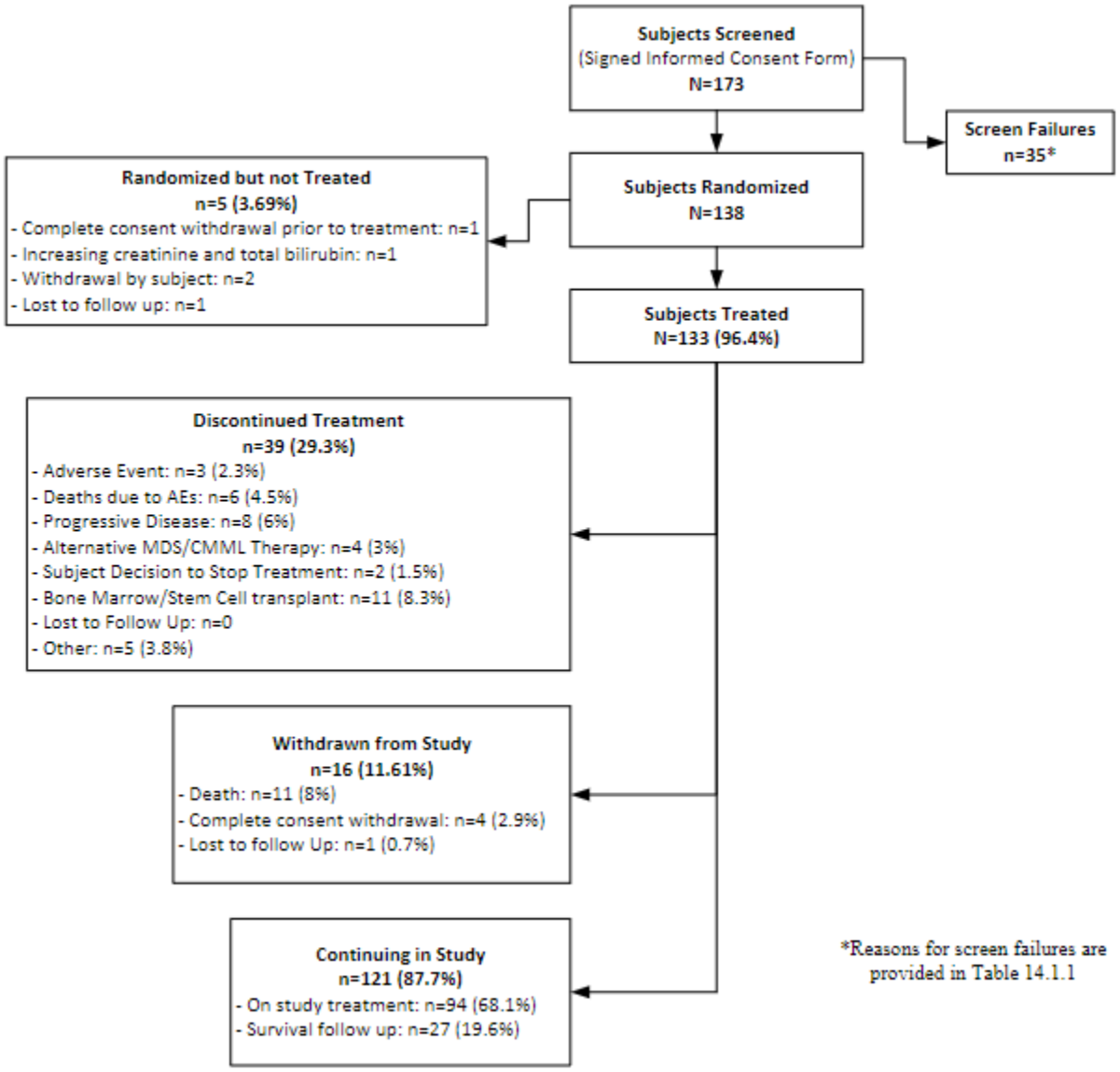


Table 7. Subject Disposition in ASTX727-02 (Randomized Subject Analysis Set)

Subject Disposition	Sequence A (N=69) n (%)	Sequence B (N=69) n (%)	Total (N=138) n (%)
Not treated	3 (4.3)	2 (2.9)	5 (3.6)
Received treatment	66 (95.7)	67 (97.1)	133 (96.4)
ASTX727 Only	1 (1.4)	0	1 (0.7)
IV Only	0	3 (4.3)	3 (2.2)
ASTX727 and IV	65 (94.2)	64 (92.8)	129 (93.5)
Discontinued treatment[a]	20 (30.3)	19 (28.4)	39 (29.3)
Adverse Event	1 (1.5)	2 (3.0)	3 (2.3)
Death	2 (3.0)	4 (6.0)	6 (4.5)
Progressive Disease	4 (6.1)	2 (3.0)	6 (4.5)
Alternative MDS/CMML Therapy[b]	1 (1.5)	1 (1.5)	2 (1.5)
Subject Decision to Permanently Stop Treatment	1 (1.5)	1 (1.5)	2 (1.5)
Bone Marrow/Stem Cell Transplant	9 (13.6)	7 (10.4)	16 (12.0)
Lost to follow up	0	0	0
Other[c]	2 (3.0)	2 (3.0)	4 (3.0)
Withdrawn from study	9 (13.0)	8 (11.6)	17 (12.3)
Death[d]	5 (7.2)	6 (8.7)	11 (8.0)
Consent Withdrawal	3 (4.3)	2 (2.9)	5 (3.6)
Lost to follow up	1 (1.4)	0	1 (0.7)
Continuing in study	60 (87.0)	61 (88.4)	121 (87.7)
On study treatment	46 (66.7)	48 (69.6)	94 (68.1)
Survival follow up (off study treatment)	14 (20.3)	13 (18.8)	27 (19.6)

[a] Percentages for discontinued treatment and reasons for treatment discontinuation are based on number of subjects treated.
[b] Including subsequent AML therapy.
[c] Other reasons include physician decision due to subject's inability to come to clinic for assessments, no clinical benefit/lack of response, and increased transfusion needs.
[d] Includes the 6 subjects who discontinued treatment due to death.
Sources: Table 14.1.4, Appendix 16.2.1.1

Table 8. Subject Disposition in ASTX727-02 (MDS IPSS-R score >3.5)

	ASTX727-02-NA (N=67) n (%)
Received treatment	67 (100.0)
At least 1 dose of ASTX727[a]	66 (98.5)
1 dose of IV decitabine	67 (100.0)
Discontinued treatment[b]	67 (100.0)
Adverse Event	4 (6.0)
Death	7 (10.4)
Progressive Disease	21 (31.3)
Alternative MDS/CMML Therapy	2 (3.0)
Patient Decision to Permanently Stop Treatment	5 (7.5)
Bone Marrow/Stem Cell Transplant	16 (23.9)
Lost to follow-up	0

	ASTX727-02-NA (N=67) n (%)
Alternative AML Therapy	0
Other	12 (17.9)
Withdrawn from study	67 (100.0)
Death	39 (58.2)
Adverse Event	0
Progressive Disease	0
Withdrawal by Subject	1 (1.5)
Lost to follow-up	0
Rollover	8 (11.9)
Study Terminated by Sponsor	19 (28.4)
Completed	0
Other[c]	0
Continuing in study	0
On study treatment	0
Survival follow-up	0

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

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

[C] One subject in Survival follow-up. This subject already discontinued the study. However, due to the site closure, withdrawn from study form was not completed. This was documented in NTF.

AML = acute myeloid leukaemia; CMML = chronic myelomonocytic leukaemia; IPSS-R = International Prognostic Scoring System-Revised; IWG = International Working Group; MDS = myelodysplastic syndrome; N = total number of subjects; n = a subset of subjects; NTF = note to file.

3.4.4.2. Recruitment

The first subject was randomized on 13 February 2018, and the last subject was randomized on 03 January 2019.

A total of 138 subjects were randomised 1:1 to sequence A (n=69) or sequence B (n=69). The study was conducted in North America, 30 centers (n=115) in US and 7 centers (n=23) in Canada.

Median follow up was 155 days (min, max: 57, 397 days).

Database lock presented is 07 June 2021 and represents the final analysis. This was performed after all subjects had completed at least 6 months of follow up or had permanently discontinued prior to 6 months of follow up from their first treatment dose.

Assessor's comment

The ASTX727-02 study was conducted at 37 centers in North America. No participants from the EU were included.

3.4.4.3. Conduct of the study

Protocol amendments

Original protocol: 06 September 2017

Amendment 1.1 Canada: 18 January 2018

Amendment 1.2 Canada: 22 May 2018

Protocol deviations

Table 9. Summary of Important Protocol Deviations

Deviation Category	Sequence A (N=69) n (%)	Sequence B (N=69) n (%)	Total (N=138) n (%)
Subjects with at least 1 important protocol deviation	9 (13.0)	6 (8.7)	15 (10.9)
Eligibility Criteria	2 (2.9)	0	2 (1.4)
Study Drug Administration	1 (1.4)	0	1 (0.7)
Study Procedures	5 (7.2)	4 (5.8)	9 (6.5)
Safety	1 (1.4)	2 (2.9)	3 (2.2)

Important protocol deviations were identified by the Astex medical monitor and PK subject matter expert.
Source: Table 14.1.5

Assessor's comment

The protocol was amended 2 times. The first change was introduced before the first patient was randomised. The changes introduced in amendment 1.2 were minor and is not considered to have had impacted the study outcome.

Protocol deviations raising no concerns for the evaluation.

3.4.4.4. Baseline data

Table 10. Demographics Characteristics (Safety Analysis Set)

Baseline Characteristics		Sequence A (N=66)	Sequence B (N=67)	Total (N=133)
Age (years)	Mean	68.7	70.7	69.7
	SD	10.22	8.40	9.37
	Median	70.0	72.0	71.0
	Min, Max	44, 85	49, 88	44, 88
Age (n, %)	18 – 64	21 (31.8)	15 (22.4)	36 (27.1)
	65 – 84	43 (65.2)	50 (74.6)	93 (69.9)
	≥85	2 (3.0)	2 (3.0)	4 (3.0)
Sex (n, %)	Male	42 (63.6)	45 (67.2)	87 (65.4)
	Female	24 (36.4)	22 (32.8)	46 (34.6)
Race (n, %)	American Indian or Alaska Native	0	0	0
	Asian	2 (3.0)	1 (1.5)	3 (2.3)
	Black or African American	1 (1.5)	3 (4.5)	4 (3.0)
	Native Hawaiian or Other Pacific Islander	0	0	0
	White	60 (90.9)	61 (91.0)	121 (91.0)
	Not Reported	3 (4.5)	2 (3.0)	5 (3.8)
Ethnicity (n, %)	Hispanic or Latino	3 (4.5)	3 (4.5)	6 (4.5)
	Not Hispanic or Latino	62 (93.9)	63 (94.0)	125 (94.0)
	Not Reported	1 (1.5)	1 (1.5)	2 (1.5)
Weight (kg)	n	66	67	133
	Mean	82.30	85.15	83.74
	SD	19.175	18.154	18.652
	Median	79.20	84.81	83.10
	Min, Max	45.0, 157.9	50.5, 127.4	45.0, 157.9
BSA (m^2)	n	64	67	131
	Mean	1.96	2.00	1.98
	SD	0.253	0.254	0.253
	Median	1.93	2.02	1.99
	Min, Max	1.4, 2.9	1.5, 2.6	1.4, 2.9

Sequence A: ASTX727 in Cycle 1; IV decitabine in Cycle 2.
Sequence B: IV decitabine in Cycle 1; ASTX727 in Cycle 2.
Source: Table 14.2.1.2.

Table 11. Baseline Disease Characteristics (Safety Analysis Set)

Baseline Characteristics		Sequence A (N=66)	Sequence B (N=67)	Total (N=133)
Study Disease, n (%)	MDS	61 (92.4)	56 (83.6)	117 (88.0)
	CMML	5 (7.6)	11 (16.4)	16 (12.0)
Time Since Diagnosis (Days)	Mean	444.8	651.5	548.9
	SD	1002.54	1109.85	1059.04
	Median	48.0	144.0	83.0
	Min, Max	5, 5606	11, 5550	5, 5606
IPSS[a] for MDS, n (%)	MDS High Risk	14 (21.2)	7 (10.4)	21 (15.8)
	MDS INT-1	29 (43.9)	30 (44.8)	59 (44.4)
	MDS INT-2	14 (21.2)	12 (17.9)	26 (19.5)
	MDS Low Risk[b]	4 (6.1)	7 (10.4)	11 (8.3)
	N/A[c]	5 (7.6)	11 (16.4)	16 (12.0)
Cytogenetic Risk Classification, n (%)	Poor-Risk	16 (24.2)	17 (25.4)	33 (24.8)
	Intermediate-Risk	17 (25.8)	21 (31.3)	38 (28.6)
	Better-Risk	26 (39.4)	24 (35.8)	50 (37.6)
	Not Evaluable	2 (3.0)	1 (1.5)	3 (2.3)
	Missing	5 (7.6)	4 (6.0)	9 (6.8)
Hemoglobin (g/L)	n	66	67	133
	Mean	94.34	93.04	93.68
	SD	14.815	17.096	15.957
	Median	91.75	88.00	89.50
	Min, Max	71.5, 139.0	64.0, 146.5	64.0, 146.5
	<80	11 (16.7)	15 (22.4)	26 (19.5)
	80 – <100	31 (47.0)	32 (47.8)	63 (47.4)
	100 – <110	14 (21.2)	7 (10.4)	21 (15.8)
	≥110	10 (15.2)	13 (19.4)	23 (17.3)
Neutrophils (10^9/L)	n	66	67	133
	Mean	1.565	1.978	1.774
	SD	1.5056	1.7094	1.6187
	Median	1.230	1.500	1.370
	Min, Max	0.05, 9.05	0.10, 6.77	0.05, 9.05
	<0.5	11 (16.7)	15 (22.4)	26 (19.5)
	0.5 – <1	17 (25.8)	6 (9.0)	23 (17.3)
	1 – 1.5	13 (19.7)	13 (19.4)	26 (19.5)
	>1.5	25 (37.9)	33 (49.3)	58 (43.6)
Platelets (10^9/L)	n	66	67	133
	Mean	108.7	128.3	118.5
	SD	96.09	136.32	118.05
	Median	71.8	76.0	72.5
	Min, Max	5, 530	10, 703	5, 703
	<25	8 (12.1)	7 (10.4)	15 (11.3)
	25 – <50	14 (21.2)	12 (17.9)	26 (19.5)
	50 – <75	13 (19.7)	14 (20.9)	27 (20.3)
	75 – <100	4 (6.1)	9 (13.4)	13 (9.8)
	≥100	27 (40.9)	25 (37.3)	52 (39.1)
RBC Transfusion Dependence, n (%)	Yes[d]	26 (39.4)	26 (38.8)	52 (39.1)
	No	40 (60.6)	41 (61.2)	81 (60.9)
Platelet Transfusion Dependence, n (%)	Yes[d]	6 (9.1)	4 (6.0)	10 (7.5)
	No	60 (90.9)	63 (94.0)	123 (92.5)
Bone Marrow Blasts (%)	n	61	65	126
	Mean	6.0	5.9	6.0
	SD	4.80	4.19	4.48
	Median	4.5	5.0	5.0
	Min, Max	0, 19	1, 18	0, 19
>5% Bone Marrow Blasts, n (%)		26 (42.6)	27 (41.5)	53 (42.1)
Peripheral Blood Blasts (%)	n	59	52	111
	Mean	0.8	0.5	0.6
	SD	2.22	1.67	1.98
	Median	0.0	0.0	0.0
	Min, Max	0, 14	0, 11	0, 14
Prior 1 Cycle HMA Therapy, n (%)				
Prior Azacitidine		3 (4.5)	3 (4.5)	6 (4.5)
Prior Decitabine		3 (4.5)	1 (1.5)	4 (3.0)
ECOG PS, n (%)	0	25 (37.9)	30 (44.8)	55 (41.4)
	1	41 (62.1)	37 (55.2)	78 (58.6)

Sequence A: ASTX727 in Cycle 1; IV decitabine in Cycle 2.
Sequence B: IV decitabine in Cycle 1; ASTX727 in Cycle 2.
[a] IPSS: International Prognostic Scoring System.
[b] Subjects with Low-Risk MDS were eligible according to the FAB classification criteria in the Dacogen label. (Dacogen USPI 2018).
[c] N/A= not applicable (CMML subjects).
[d] Two units or more of transfusion within 56 days of the first dose of study treatment.
Source: Table 14.2.1.2

Table 12. Demographics and baseline Characteristics (MDS IPSS-R >3.5)

		ASTX727-02-NA (N=67)	
Age (yr)			
n[a]		67	
Mean		70.5	
SD		8.37	
Median		70.0	
Min, Max		52, 88	
Age Group (yr), n (%)			
<18		0	
18 - 64		17 (25.4)	
65 - 84		47 (70.1)	
>=85		3 (4.5)	
Sex, n (%)			
Male		42 (62.7)	
Female		25 (37.3)	
Race, n (%)			
Asian		2 (3.0)	
Black or African American		2 (3.0)	
White		61 (91.0)	
Not Reported		2 (3.0)	
Ethnicity, n (%)			
Hispanic or Latino		3 (4.5)	
Not Hispanic or Latino		63 (94.0)	
Not Reported		1 (1.5)	
Weight (kg)			
n[a]		67	
Mean		82.15	
SD		19.736	
Median		77.00	
Min, Max		45.0, 157.9	
Weight, n (%)			
<100 kg		53 (79.1)	
>=100 kg		14 (20.9)	
Height (cm)			
n[a]		66	
Mean		169.905	
SD		10.8644	
Median		170.500	
Min, Max		143.60, 191.90	

		ASTX727-02-NA (N=67)	
BSA (m^2)			
n[a]		67	
Mean		1.951	
SD		0.2784	
Median		1.920	
Min, Max		1.40, 2.90	
ECOG, n (%)			
0		28 (41.8)	
1		39 (58.2)	
2		0	
Prior Anticancer Therapy, n (%)			
Yes		9 (13.4)	
No		58 (86.6)	
Prior HMA Therapy, n (%)			
Prior Azacitidine only		2 (3.0)	
Prior Decitabine only		2 (3.0)	
Study Disease, n (%)			
MDS		67 (100.0)	
Time Since Diagnosis (Days)			
n[a]		67	
Mean		394.8	
SD		1029.16	
Median		53.0	
Min, Max		5, 5550	
IPSS for MDS[b], n (%)			
INT-1/INT-2		49 (73.1)	
High Risk		18 (26.9)	
Cytogenetic Risk Classification for IPSS, n (%)			
Poor-Risk		29 (43.3)	
Intermediate-Risk		17 (25.4)	
Better-Risk		20 (29.9)	
Not Evaluable		1 (1.5)	
IPSS-R Risk Category for MDS[b], n (%)			
Intermediate		20 (29.9)	
High		24 (35.8)	
Very High		23 (34.3)	

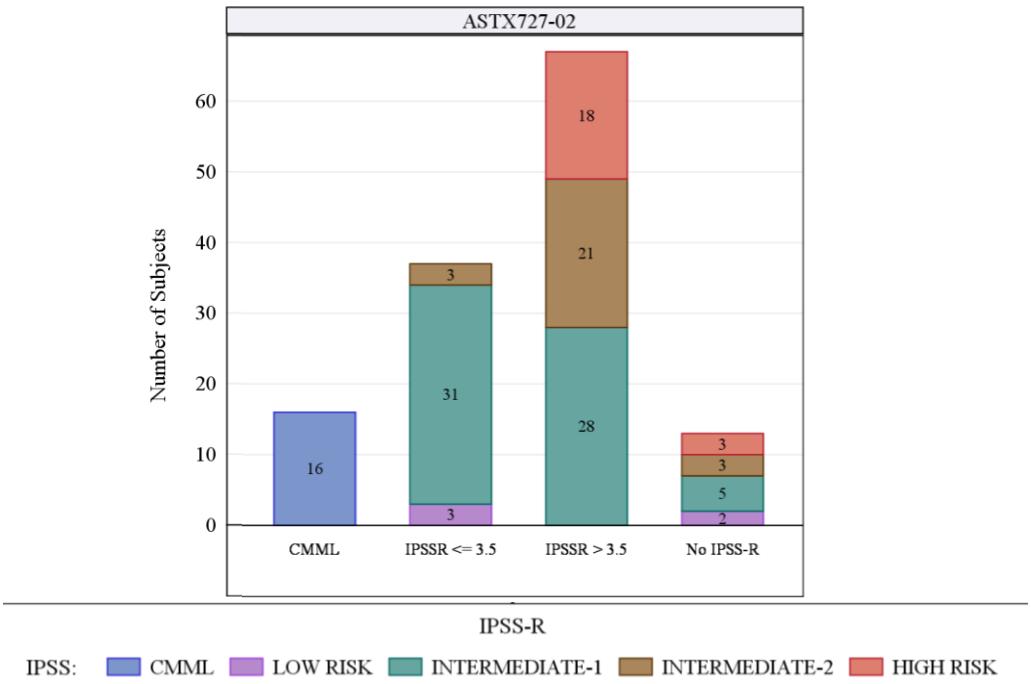
		ASTX727-02-NA (N=67)	
Overall IPSS-R Score			
>3.5		67 (100.0)	
Cytogenetic Risk Classification for IPSS-R, n (%)			
Very Poor Risk		27 (40.3)	
Poor Risk		6 (9.0)	
Intermediate Risk		10 (14.9)	
Good Risk		23 (34.3)	
Very Good Risk		1 (1.5)	
Baseline Haemoglobin (g/L)			
n[a]		67	
Mean		91.6530	
SD		15.13775	
Median		88.0000	
Min, Max		64.000, 146.500	
Baseline Haemoglobin (g/L)			
<80		14 (20.9)	
80 - <100		36 (53.7)	
100 - <110		11 (16.4)	
>=110		6 (9.0)	
Baseline Neutrophils (10^9/L)			
n[a]		67	
Mean		1.4435	
SD		1.56671	
Median		1.0450	
Min, Max		0.050, 9.046	
Baseline Neutrophils (10^9/L)			
<0.5		20 (29.9)	
0.5 - <1		13 (19.4)	
1 - 1.5		11 (16.4)	
>1.5		23 (34.3)	
Baseline Platelets (10^9/L)			
n[a]		67	
Mean		108.0112	
SD		124.31764	
Median		62.0000	
Min, Max		15.500, 703.000	
Baseline Platelets (10^9/L)			
<25		10 (14.9)	

		ASTX727-02-NA (N=67)	
25 - <50		19 (28.4)	
50 - <75		11 (16.4)	
75 - <100		6 (9.0)	
>=100		21 (31.3)	
RBC Transfusion Dependence[c], n (%)			
Yes		29 (43.3)	
No		38 (56.7)	
Platelet Transfusion Dependence[c], n (%)			
Yes		9 (13.4)	
No		58 (86.6)	
Baseline Bone Marrow Blasts (%)			
n[a]		67	
Mean		7.8164	
SD		4.61097	
Median		7.0000	
Min, Max		0.000, 19.000	
>5% Bone Marrow Blast, n (%)		41 (61.2)	
Baseline PB Blasts (%)			
n[a]		58	
Mean		0.8	
SD		2.43	
Median		0.0	
Min, Max		0, 14	
[a]n is the number of subjects who had valid data.			
[b]IPSS = International Prognostic Scoring System; IPSS-R = Revised International Prognostic Scoring System			
[c]Two units or more of transfusion within 56 days of the first dose of study treatment.			
Time since diagnosis is calculated as the (date of first dose minus date of diagnosis).			

Reclassification of risk categories by IPSS-R criteria for subjects with MDS

Post hoc, where it was possible, patients were reclassified using the IPSS-R score according to lower-risk (≤3.5) and higher-risk (>3.5) MDS.

Figure 6. Distribution of IPSS Risk Categories by Lower-Risk (≤3.5) and Higher-Risk Per IPSS-R (>3.5)



Assessor's comment

It is noted that, despite the inclusion criteria not included low-IPSS score 11 patients with low IPSS score were included, in total 8.3%.

43.3% of the patients with MDS IPSS-R >3.5 were RBC transfusion dependent and 13.4% were platelet transfusion dependent at study entry.

In relation to the CR criteria, it is noted that 61.2% had >5% BM blasts at inclusion of the patients with MDS IPSS-R >3.5. Furthermore, 9.0% have Hgb ≥110g/L, 31.3% have platelets ≥100x10^9/L and 50.7 % have neutrophils ≥1x10^9/L. Hence, a large proportion of patients fulfil at least parts of the CR criteria already at baseline.

Current prognostic systems include IPSS-R and IPSS-M. The IPSS-R system was presented 2012 as an improvement of IPSS. Reclassification of MDS patients using IPSS-R was done post hoc. 13 patients could not be re-classified. The IPSS-intermediate 1 group seem to distribute evenly between the IPSS-R low and high group while the majority of IPSS-intermediate 2 patients end up in the IPSS-R high group.

3.4.4.5. Numbers analysed

Table 13. Analysis Populations

Analysis Set	Total No. Subjects
All Subject (all screened subjects)	173
Randomized Subject	138
Primary Endpoint PK	123
Overall PK	131
Pharmacodynamic	130
Efficacy and Safety (all treated subjects)	133

Sources: Table 14.1.2, Table 14.1.1, PK Report Figure 6.1.1

For the new suggsted indication MDS IPSS >3.5 total no. Subjects =67.

Table 14. Follow Up (Efficacy Analysis Set)

	Sequence A (N=66)	Sequence B (N=67)	Total (N=133)
Follow Up (Days)			
n	66	67	133
Mean	987.4	993.8	990.6
SD	79.13	85.68	82.25
Median	966.0	973.0	966.0
Q1, Q3	917.0, 1050.0	917.0, 1057.0	917.0, 1050.0
IQR (Q3 – Q1)	133.0	140.0	133.0
Min, Max	875, 1183	868, 1208	868, 1208

Sequence A: ASTX727 in Cycle 1; IV decitabine in Cycle 2.
Sequence B: IV decitabine in Cycle 1; ASTX727 in Cycle 2.
Number of follow-up days is calculated as database cutoff date minus first treatment date regardless of survival status.
Source: Table 14.1.8.

Assessor's comment

For completeness, table of MDS IPSS-R >3.5 should be provided for follow-up time this should also specify BM>5%, ≤5% and total (**OC**).

3.4.4.6. Outcomes and estimation

Primary endpoint

Table 15. 5-Day Decitabine AUC0-24 Equivalence Assessment (Primary Endpoint PK Analysis Set)

		AUC Parameter (h*ng/mL)	IV Decitabine N	IV Decitabine Geo. LSM	Oral ASTX727 N	Oral ASTX727 Geo. LSM	Ratio (%) of Geo. LSM (90% CI)[a]		Intra-Subject (CV%)
Primary	**Paired**	**5-day AUC_{0-24}**	**123**	**864.94**	**123**	**855.69**	**98.93**	**(92.66, 105.6)**	**31.7**
Sensitivity	Unpaired	5-day AUC_{0-24}	131	865.82	128	848.40	97.99	(91.84, 104.5)	32.2
	Paired	5-day AUC_{0-24}	128	869.96	128	850.32	97.74	(91.58, 104.3)	32.2

CI=confidence interval; IV=intravenous; Geo. LSM=Geometric Least Squares Means.
Bold=primary analysis of the primary PK endpoint.
Test treatment=Oral ASTX727 FDC tablet (100 mg cedazuridine and 35 mg decitabine).
Reference treatment=20 mg/m^2 IV infusion (1 hr) of decitabine.
[a] Analysis is based on ANOVA model with treatment, cycle, and sequence as fixed effects, and subject nested in sequence as a random effect (ratio is Oral/IV).
Source: Appendix 16.1.13.4 PK Report Table 6.5.5

Assessor's comment

The primary endpoint shows that the two-sided 90% CIs of the 5-day AUC 0-24 ratios of geometric LSM for oral relative to IV are contained entirely within the prespecified range of 0.80 to 1.25 for the primary analysis. Similar exposure between oral and IV decitabine have been shown. For further discussion see 3.3.3.

However, considering that decitabine is not authorised in the EU for use in MDS bridging is not possible.

3.4.4.7. Ancillary analyses

Exploratory endpoints

Considering the currently proposed indication, results are focused on the patients included, MDS IPSS-R >3.5.

Response rate

CR was observed in 21.8% (95% CI 15.1, 29.8) of all 133 treated subjects.

Table 16. Analysis of Best Response – All Treated Subjects (Efficacy Analysis Set)

	All Subjects (N=133)		Excluding Subjects Non-Evaluable for Response (N=117)	
Type of Response[a]	n (%)	95%CI	n (%)	95%CI
Complete Response (CR)	29 (21.8)	(15.1, 29.8)	29 (24.8)	(17.3, 33.6)
Partial Response (PR)	0		0	
Marrow CR (mCR)	43 (32.3)	(24.5, 41.0)	43 (36.8)	(28.0, 46.2)
mCR with HI[a]	22 (16.5)	(10.7, 24.0)	22 (18.8)	(12.2, 27.1)
Hematologic Improvement (HI)	10 (7.5)	(3.7, 13.4)	10 (8.5)	(4.2, 15.2)
HI-E	2 (1.5)	(0.2, 5.3)	2 (1.7)	(0.2, 6.0)
HI-N	1 (0.8)	(0.0, 4.1)	1 (0.9)	(0.0, 4.7)
HI-P	7 (5.3)	(2.1, 10.5)	7 (6.0)	(2.4, 11.9)
Overall Response (CR+PR+mCR+HI)	82 (61.7)	(52.8, 69.9)	82 (70.1)	(60.9, 78.2)
Progressive Disease	6 (4.5)	(1.7, 9.6)	6 (5.1)	(1.9, 10.8)
No Response[b]	29 (21.8)	(15.1, 29.8)	29 (24.8)	(17.3, 33.6)
Non-Evaluable	16 (12.0)	(7.0, 18.8)	—	—

95% CI is the Clopper-Pearson confidence interval.

[a] mCR with HI is a subset of subjects with mCR who also achieved HI (with any overlap of the mCR period with the HI period).

[b] Stable Disease is included in No Response.

Sources: Table 14.3.1, Table 14.3.2

Response for MDS IPSS-R >3.5 for BM blasts at inclusion of >5% or ≤5%

CR was observed in 23.9% (95% CI 14.3, 35.9) of the 67 patients with IPSS-R >3.5. Of the 67 treated patients, 14 (20.9%) went on to receive stem cell transplant.

Among the 41 patients with IPSS-R >3.5 and BM blasts >5% at inclusion 7 (17.1%, 95% CI 7.2, 32.1) reached CR.

Table 17. Response with 95% Confidence Interval for MDS Subjects with IPSS-R Score >3.5 (Using IWG 2006)

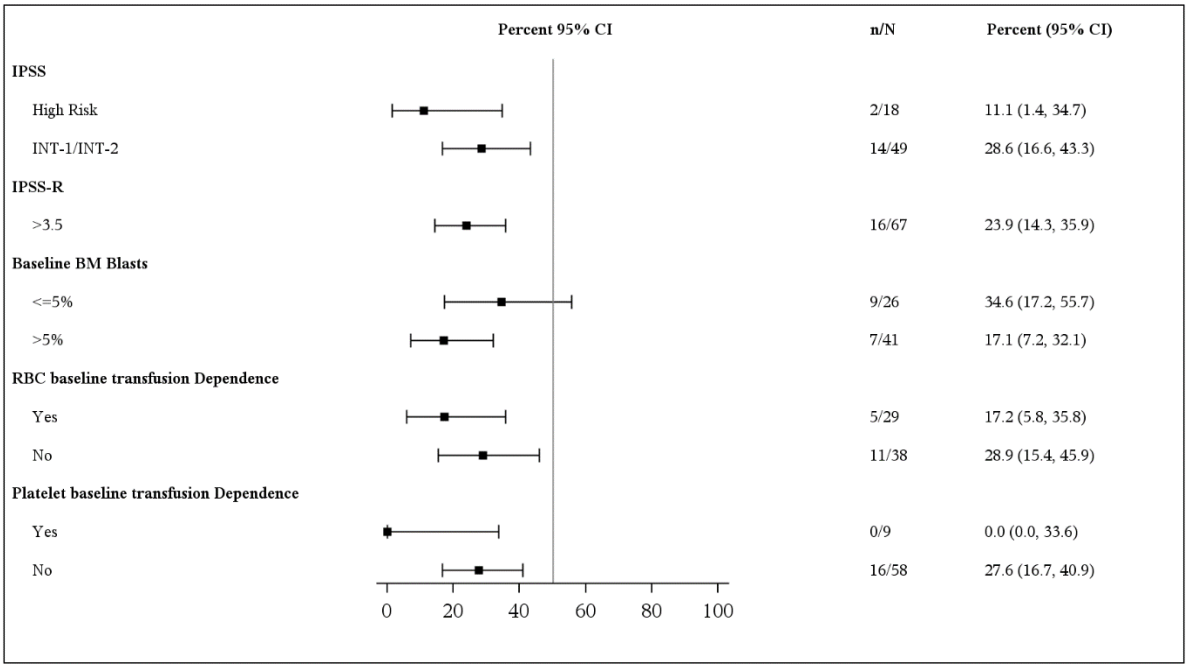
	ASTX727-02-NA (N=67)			Total (ASTX727-02-NA+ ASTX727-01-B) (N=103)		
Type of Response	BM>5% (N=41) n (%) (95% CI)	BM<=5% (N=26) n (%) (95% CI)	Total (N=67) n (%) (95% CI)	BM>5% (N=65) n (%) (95% CI)	BM<=5% (N=38) n (%) (95% CI)	Total (N=103) n (%) (95% CI)
Complete Response [CR]	7 (17.1)	9 (34.6)	16 (23.9)	11 (16.9)	11 (28.9)	22 (21.4)
	(7.2, 32.1)	(17.2, 55.7)	(14.3, 35.9)	(8.8, 28.3)	(15.4, 45.9)	(13.9, 30.5)
Partial Response [PR]	0	0	0	0	0	0

Type of Response	ASTX727-02-NA (N=67)			Total (ASTX727-02-NA+ ASTX727-01-B) (N=103)		
	BM>5% (N=41) n (%) (95% CI)	BM<=5% (N=26) n (%) (95% CI)	Total (N=67) n (%) (95% CI)	BM>5% (N=65) n (%) (95% CI)	BM<=5% (N=38) n (%) (95% CI)	Total (N=103) n (%) (95% CI)
	(0.0, 8.6)	(0.0, 13.2)	(0.0, 5.4)	(0.0, 5.5)	(0.0, 9.3)	(0.0, 3.5)
Marrow Complete Response [mCR]	20 (48.8)	5 (19.2)	25 (37.3)	29 (44.6)	5 (13.2)	34 (33.0)
	(32.9, 64.9)	(6.6, 39.4)	(25.8, 50.0)	(32.3, 57.5)	(4.4, 28.1)	(24.1, 43.0)
mCR with HI	12 (29.3)	1 (3.8)	13 (19.4)	14 (21.5)	1 (2.6)	15 (14.6)
	(16.1, 45.5)	(0.1, 19.6)	(10.8, 30.9)	(12.3, 33.5)	(0.1, 13.8)	(8.4, 22.9)
Haematological Improvement [HI]	1 (2.4)	2 (7.7)	3 (4.5)	2 (3.1)	7 (18.4)	9 (8.7)
	(0.1, 12.9)	(0.9, 25.1)	(0.9, 12.5)	(0.4, 10.7)	(7.7, 34.3)	(4.1, 15.9)
HI-E	0	0	0	0	4 (10.5)	4 (3.9)
	(0.0, 8.6)	(0.0, 13.2)	(0.0, 5.4)	(0.0, 5.5)	(2.9, 24.8)	(1.1, 9.6)
HI-N	0	0	0	0	1 (2.6)	1 (1.0)
	0	0	0	0	0	0
	(0.0, 8.6)	(0.0, 13.2)	(0.0, 5.4)	(0.0, 5.5)	(0.1, 13.8)	(0.0, 5.3)
HI-P	1 (2.4)	2 (7.7)	3 (4.5)	2 (3.1)	7 (18.4)	9 (8.7)
	(0.1, 12.9)	(0.9, 25.1)	(0.9, 12.5)	(0.4, 10.7)	(7.7, 34.3)	(4.1, 15.9)
Overall Response [CR+PR+mCR+HI]	28 (68.3)	16 (61.5)	44 (65.7)	42 (64.6)	23 (60.5)	65 (63.1)
	(51.9, 81.9)	(40.6, 79.8)	(53.1, 76.8)	(51.8, 76.1)	(43.4, 76.0)	(53.0, 72.4)
Progressive Disease [PD]	4 (9.8)	0	4 (6.0)	6 (9.2)	1 (2.6)	7 (6.8)
	(2.7, 23.1)	(0.0, 13.2)	(1.7, 14.6)	(3.5, 19.0)	(0.1, 13.8)	(2.8, 13.5)
No Response [NR]	6 (14.6)	4 (15.4)	10 (14.9)	14 (21.5)	8 (21.1)	22 (21.4)
	(5.6, 29.2)	(4.4, 34.9)	(7.4, 25.7)	(12.3, 33.5)	(9.6, 37.3)	(13.9, 30.5)
Non-Evaluable [NE]	3 (7.3)	6 (23.1)	9 (13.4)	3 (4.6)	6 (15.8)	9 (8.7)
	(1.5, 19.9)	(9.0, 43.6)	(6.3, 24.0)	(1.0, 12.9)	(6.0, 31.3)	(4.1, 15.9)

Response Assessment was performed by an Independent Reviewer committee using IWG 2006 MDS Response Criteria.
BM = bone marrow; CI = confidence interval; IPSS-R = International Prognostic Scoring System-Revised; IWG = International Working Group; MDS = myelodysplastic syndrome; N = total number of subjects; n = a subset of subjects.
The 95% CI is Clopper-Pearson confidence interval; mCR with HI: a subset of mCR subjects who also had HI (with any overlap of mCR period and HI period).
Stable Disease is included in No Response [NR].

Among the 9 patients not evaluable for assessment of response, 6 patients discontinued treatment earlier and 3 had no post-treatment BM.

Table 18. Subgroup results with CR in MDS Subjects with IPSS-R Score >3.5 in ASTX727-02-NA (Using IWG 2006)



BM = bone marrow; CI = confidence interval; CR = complete response; INT = interleukin; IPSS = International Prognostic Scoring System; IPSS-R = International Prognostic Scoring System-Revised; IWG = International Working Group; MDS = myelodysplastic syndrome; N = total number of subjects; n = a subset of subjects; RBC =red blood cells.

Assessor's comment

Several patients fulfilling the response criteria did fulfil these or part of these already at study inclusion. This was not prohibiting from being classified as response. This precludes the isolation of efficacy and the evaluation of the clinical benefit from treatment. In total from both ASTX727-02 NA and ASTX727-01-B only 36 patients did not fulfil any of the CR criteria of IWG2023 at baseline, i.e. displaying BM blasts >5% and tri-linage cytopenia.

14 patients proceeded to SCT following Inaqovi treatment in ASTX727-02 NA. Data on conditioning regiments and outcome of SCT was not routinely collected.

Time to Complete Response

Median time to CR was 5.2 months (min, max: 2, 19) for MDS patients with IPSS-R >3.5 in ASTX727-02 NA.

Table 19. Time to Complete Response for MDS Subjects with IPSS-R Score>3.5 (IWG 2006)

	ASTX727-02 NA (N=16)	Total (ASTX727-01 B and ASTX727-02 NA) (N=22)
Time to Response (CR) (Months)		
n	16	22
Mean	6.9	6.2
SD	4.89	4.39
Median	5.2	4.8
Min, Max	2, 19	2, 19

IPSS-R = International Prognostic Scoring System-Revised; IWG = International Working Group; MDS = myelodysplastic syndrome; MDS = myelodysplastic syndrome; N = total number of subjects; SD = standard deviation.

Assessor's comment

For completeness table of MDS IPSS-R >3.5 should be amended to include also time to response specified for BM>5%,≤5% and total **(OC)**.

Duration of Complete Response

Median duration of best response for subjects who achieved CR in the **efficacy population** was 413.0 days (range, 63 to 894 days). Median duration of best response for subjects who achieved mCR was 354.0 days (range, 71 to 1039 days). Median duration of best response was 365.0 days (range, 29 to 1039 days).

Table 20. Duration of Complete Response for MDS Subjects with IPSS-R Score>3.5 (IWG 2006)

Overall Survival	ASXT727-02 NA (N=16)	Total (ASXT727-02 NA, ASTX727-01 B) (N=22)
Number of Subjects, n (%)		
Censored	4 (25.0)	5 (22.7)
Event	12 (75.0)	17 (77.3)
KM Estimates, Months, (95% CI)		
25th percentile	8.3 (3.2, 12.9)	5.5 (1.1, 12.8)
Median	14.1 (8.3, 18.1)	12.9 (5.5, 16.4)
75th percentile	18.7 (14.1, NE)	18.1 (12.9, NE)
Survival Rate Estimate (95% CI)		
6-Month	0.88 (0.59, 0.97)	0.73 (0.49, 0.87)
1-Year	0.67 (0.38, 0.85)	0.57 (0.34, 0.75)
2-Year	0.13 (0.01, 0.39)	0.10 (0.01, 0.32)
3-Year	NE (NE, NE)	NE (NE, NE)

CI = confidence interval; IPSS-R = International Prognostic Scoring System-Revised; KM = Kaplan-Meier; MDS = myelodysplastic syndrome; N = total number of subjects; NE = non-evaluable.

Assessor's comment

For completeness table of MDS IPSS-R >3.5 should be amended to include also DoR specified for BM>5%,≤5% and total **(OC)**.

Provide reasons for censoring in the analysis of duration of response in a tabulated format for MDS IPSS-R >3.5 and also specified for BM>5%,≤5% and total **(OC)**.

Concomitant medications

All 133 subjects who received any amount of study treatment took at least 1 concomitant medication. The most commonly used concomitant medication classes were Antibacterials for Systemic Use (88.0%),
Analgesics (81.2%), and Antivirals for Systemic Use (72.2%).

Table 21. Concomitant Medication Classes Used by ≥20% of Subjects (Safety Analysis Set)

Therapeutic Group (ATC Level 2) Preferred Drug Term	No. (%) of Subjects Sequence A (N=66)	Sequence B (N=67)	Total (N=133)
ANY MEDICATION	66 (100)	67 (100)	133 (100)
Antibacterials for Systemic Use	57 (86.4)	60 (89.6)	117 (88.0)
Analgesics	55 (83.3)	53 (79.1)	108 (81.2)
Antivirals for Systemic Use	48 (72.2)	48 (71.6)	96 (72.2)
Antiemetics and Antinauseants	41 (62.1)	43 (64.2)	84 (63.2)
Antimycotics for Systemic Use	39 (59.1)	44 (65.7)	83 (62.4)
Vitamins	39 (59.1)	33 (49.3)	72 (54.1)
Psycholeptics	35 (53.0)	32 (47.8)	67 (50.4)
Drugs for Acid Related Disorders	27 (40.9)	38 (56.7)	65 (48.9)
Antihistamines for Systemic Use	34 (51.5)	29 (43.3)	63 (47.4)
Drugs for Constipation	30 (45.5)	32 (47.8)	62 (46.6)
Mineral Supplements	26 (39.4)	32 (47.8)	58 (43.6)
Corticosteroids for Systemic Use	24 (36.4)	33 (49.3)	57 (42.9)
Lipid Modifying Agents	29 (43.9)	25 (37.3)	54 (40.6)
Antithrombotic Agents	27 (40.9)	25 (37.3)	52 (39.1)
Anesthetics	27 (40.9)	23 (34.3)	50 (37.6)
Stomatological Preparations	24 (36.4)	22 (32.8)	46 (34.6)
Agents Acting on the Renin-Angiotensin System	26 (39.4)	18 (26.9)	44 (33.1)
Beta Blocking Agents	22 (33.3)	22 (32.8)	44 (33.1)
Diuretics	24 (36.4)	20 (29.9)	44 (33.1)
Blood Substitutes and Perfusion Solutions	19 (28.8)	24 (35.8)	43 (32.3)
Antianemic Preparations	22 (33.3)	20 (29.9)	42 (31.6)
Drugs for Obstructive Airway Diseases	18 (27.3)	20 (29.9)	38 (28.6)
Psychoanaleptics	26 (39.4)	12 (17.9)	38 (28.6)
Urologicals	18 (27.3)	16 (23.9)	34 (25.6)
Antiinflammatory and Antirheumatic Products	13 (19.7)	17 (25.4)	30 (22.6)

Sequence A: ASTX727 in Cycle 1; IV decitabine in Cycle 2.
Sequence B: IV decitabine in Cycle 1; ASTX727 in Cycle 2.
Coded using WHO Drug Dictionary B2 December 2017.
Source: Table 14.2.3

Table 22. Growth Factor Concomitant Medications (Safety Analysis Set)

Therapeutic Group (ATC Level 2) Preferred Drug Term	No. (%) of Subjects Sequence A (N=66)	Sequence B (N=67)	Total (N=133)
Subjects with Any Growth Factor Concomitant Medications	15 (22.7)	10 (14.9)	25 (18.8)
ANTIANEMIC PREPARATIONS	4 (6.1)	4 (6.0)	8 (6.0)
Epoetin Alfa	4 (6.1)	2 (3.0)	6 (4.5)
Darbepoetin Alfa	0	2 (3.0)	2 (1.5)
Epoetin Zeta	1 (1.5)	1 (1.5)	2 (1.5)
IMMUNOSTIMULANTS	13 (19.7)	8 (11.9)	21 (15.8)
Filgrastim	12 (18.2)	8 (11.9)	20 (15.0)
Pegfilgrastim	3 (4.5)	1 (1.5)	4 (3.0)
Sargramostim	1 (1.5)	2 (3.0)	3 (2.3)

Sequence A: ASTX727 in Cycle 1; IV decitabine in Cycle 2.
Sequence B: IV decitabine in Cycle 1; ASTX727 in Cycle 2.
Coded using WHO Drug Dictionary B2 December 2017.
Source: Table 14.2.5

Assessor's comment

Concomitant use of supportive treatment was allowed as per investigators discretion. Use of ESA was not prohibited. In total 8 (6.0%) patients received ESA during the study.

Concomitant supportive treatment should be provided for the MDS IPSS-R >3.5 population. This should also specify BM>5%, ≤5% and total. (**OC**)

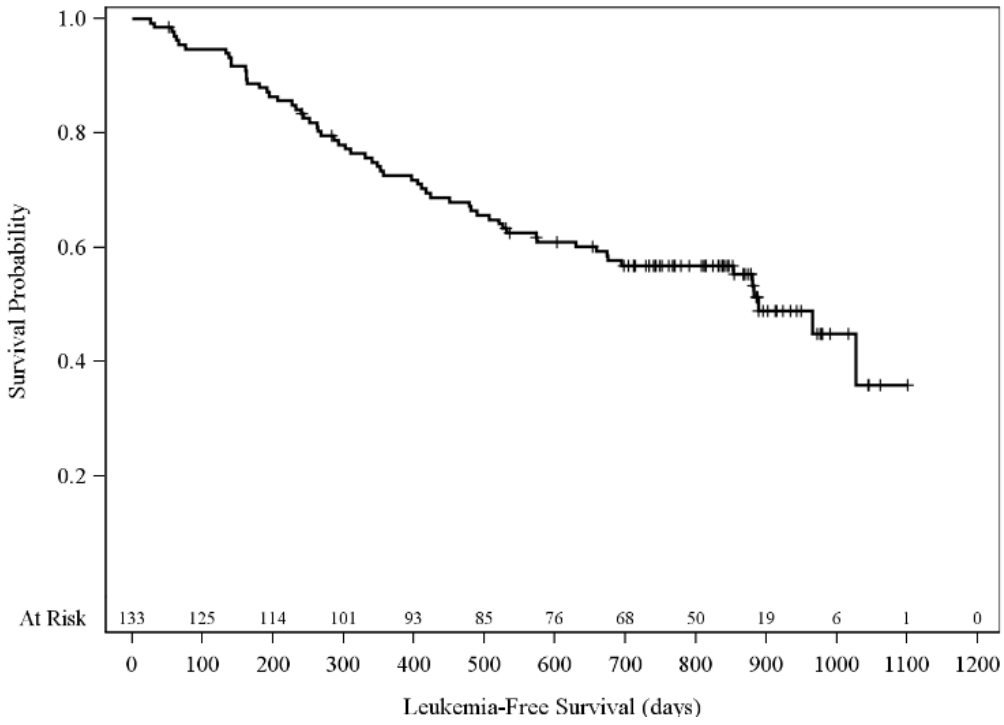
Leukemia-Free Survival

Table 23. Leukemia-Free Survival (Efficacy Analysis Set)

Characteristics	Sequence A (N=66)	Sequence B (N=67)	All Treated Subjects (N=133)
Number of Subjects, (n (%))			
Censored	30 (45.5%)	41 (61.2%)	71 (53.4%)
Event	36 (54.5%)	26 (38.8%)	62 (46.6%)
K-M Estimate (Days, (95% CI))			
25th percentile	264.0 (191.0, 450.0)	405 (268.0, 853.0)	340.0 (243.0, 479.0)
Median	659.0 (479.0, NE)	1027 (853.0, NE)	889.0 (674.0, NE)
75th percentile	NE (889.0, NE)	NE (1027.0, NE)	NE (1027.0, NE)

Sequence A: ASTX727 in Cycle 1; IV decitabine in Cycle 2.
Sequence B: IV decitabine in Cycle 1; ASTX727 in Cycle 2.
CI=confidence interval; K-M=Kaplan-Meier; NE=not estimable.
Source: Table 14.3.4.1

Figure 7. Kaplan-Meier Plot of Leukemia-Free Survival - Total (Efficacy Analysis Set)



Assessor's comment

This is in essence a SAT for efficacy assessment, hence time to event endpoints is not fit for efficacy inferences. No conclusions can be drawn regarding Leukemia free survival, apart from that this describes the prognosis of the studied population.

For completeness LFS should be provided for MDS IPSS-R >3.5 patients in both tabulated format and in KM curves. This should also specify BM>5%, ≤5% (**OC**).

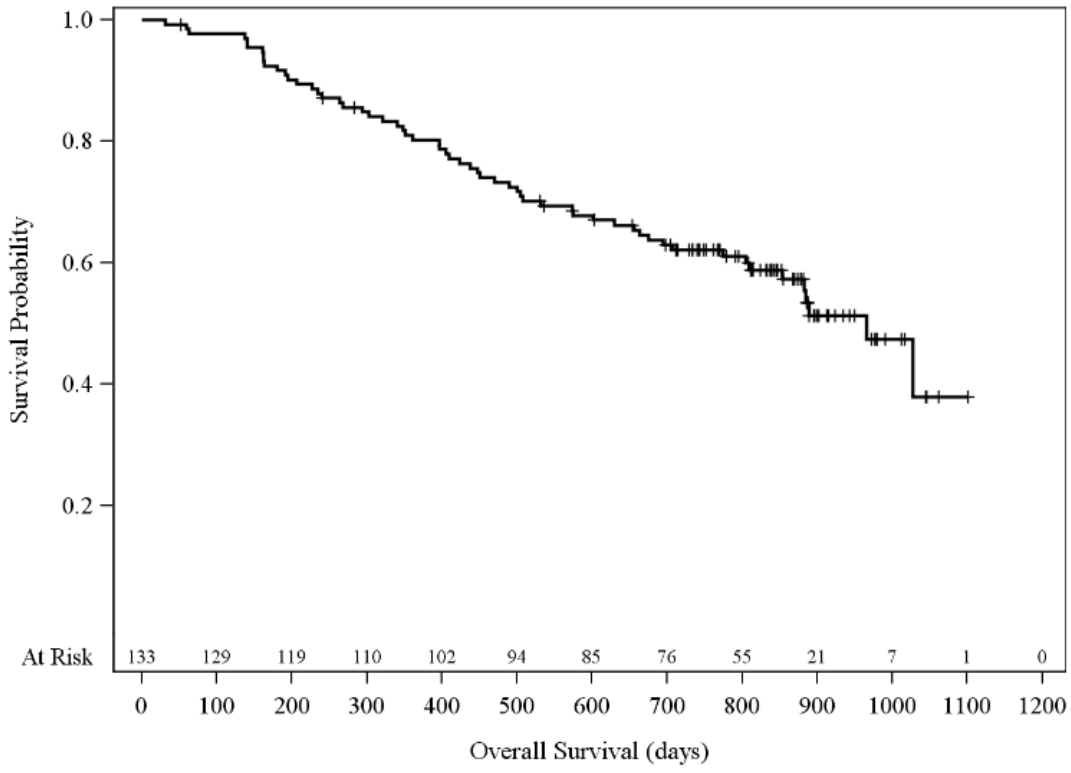
Overall Survival

Table 24. Overall Survival (Efficacy Analysis Set)

Characteristics	Sequence A (N=66)	Sequence B (N=67)	Total (N=133)
Number of Subjects, (n (%))			
Censored	33 (50.0%)	42 (62.7%)	75 (56.4%)
Event	33 (50.0%)	25 (37.3%)	58 (43.6%)
K-M Estimate (Days, (95% CI))			
25th percentile	450 (234.0, 602.0)	447 (321.0, 883.0)	447.0 (340.0, 602.0)
Median	809.0 (630.0, NE)	1027 (883.0, NE)	966.0 (809.0, NE)
75th percentile	NE (966.0, NE)	NE (1027.0, NE)	NE (1027.0, NE)

Sequence A: ASTX727 in Cycle 1; IV decitabine in Cycle 2.
Sequence B: IV decitabine in Cycle 1; ASTX727 in Cycle 2.
CI=confidence interval; K-M=Kaplan-Meier; NE=not estimable.
Source: Table 14.3.5.1

Figure 8. Kaplan-Meier Plot of Overall Survival - Total (Efficacy Analysis Set)



Assessor's comment

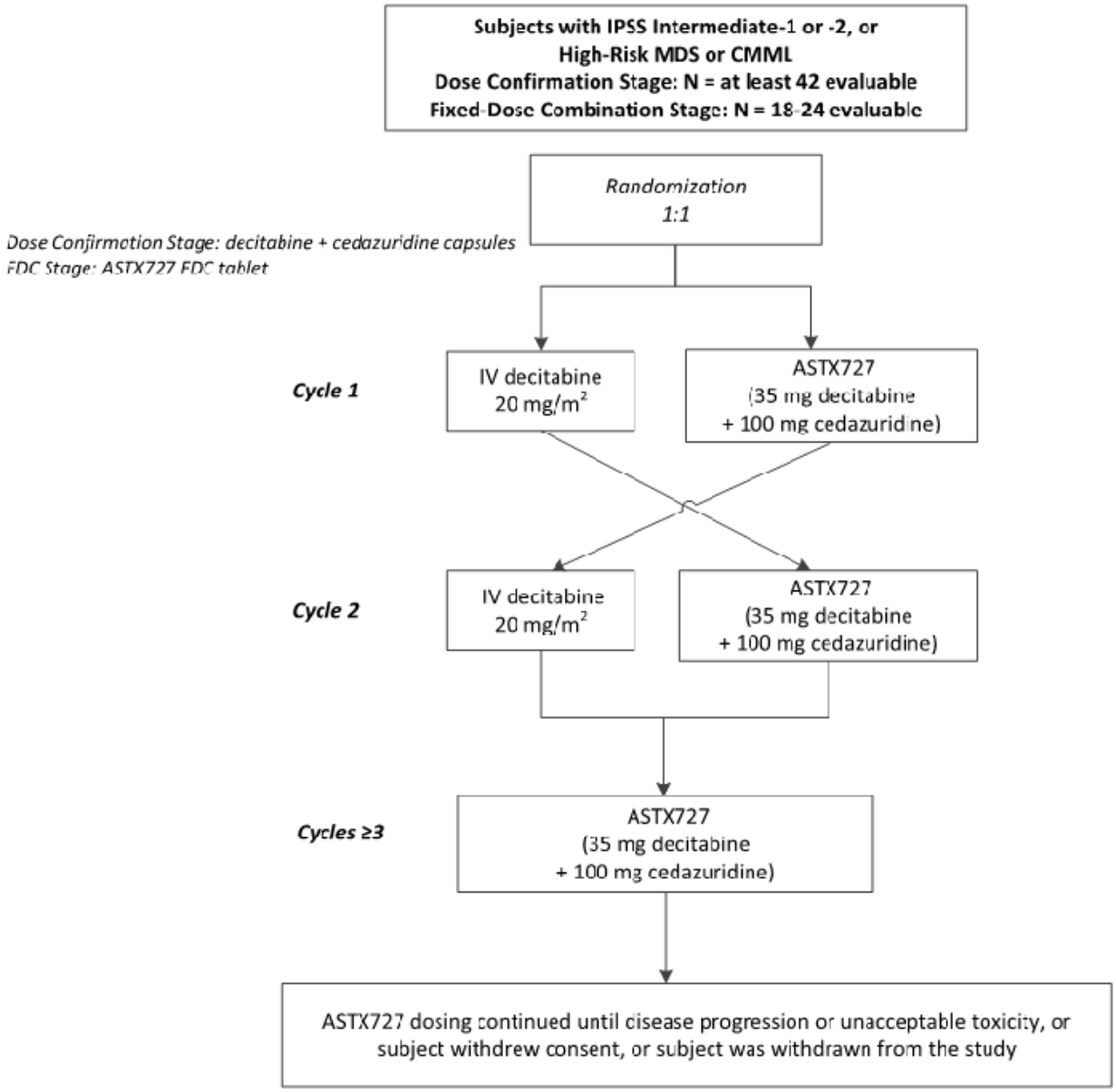
This is in essence a SAT for efficacy assessment, hence time to event endpoints is not fit for efficacy assessments. No inferences can be drawn regarding the impact of Inaqovi on OS.

For completeness OS should be provided for MDS IPSS-R >3.5 patients in both tabulated format and in KM curves. This should also specify BM>5%, ≤5% (**OC**).

3.4.5. Study ASTX727-01-B (Phase 2 MDS/CMML, NCT02103478)

A Phase 1-2 Pharmacokinetic Guided Dose-Escalation and Dose-Confirmation Study of ASTX727, a Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine in Subjects with Myelodysplastic Syndromes (MDS). This first-in-human trial, ASTX727-01, had 3 stages: Phase 1 Dose Escalation, Phase 2 Dose Confirmation, and Phase 2 FDC. Focus here are the Phase 2 parts ie, the Dose Confirmation Stage and FDC Stage of study ASTX727-01.

Figure 9. Study Schema – ASTX727-01-B Phase 2



3.4.6. Methods

3.4.6.1. Study participants

Key inclusion criteria

- Men or women ≥18 years with International Prognostic Scoring System (IPSS) intermediate-1, intermediate-2, or high risk MDS with peripheral blasts or bone marrow blasts <20% in all study stages, including subjects with CMML who are candidates for treatment with a hypomethylating agent.
- Subjects with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
- Subjects with adequate organ function defined as:
    - Hepatic: Total or direct bilirubin ≤2 × upper limit of normal (ULN); aspartate transaminase (AST)/ serum glutamic oxaloacetic transaminase (SGOT) and alanine transaminase (ALT)/serum glutamic pyruvic transaminase (SGPT) ≤2.5 × ULN.
    - Renal: serum creatinine ≤1.5 × ULN or creatinine clearance >50 mL/min/1.73 m2 for subjects with creatinine levels above institutional normal.
- For subjects with prior allogeneic stem cell transplant, no evidence of graft-versus-host disease and must be ≥2 weeks off systemic immunosuppressive therapy.
- Subjects with no major surgery within 2 weeks of first dose of study treatment.
- Subjects with no cytotoxic chemotherapy within 2 weeks of first dose of study treatment.

Key exclusion criteria

- Previous treatment with at least 2 cycles of decitabine (all stages) or azacitidine (Dose Confirmation Stage).
- Known or suspected hypersensitivity to decitabine or the components of cedazuridine.
- Treated with any investigational drug or therapy within 2 weeks of study treatment, or 5 half-lives, whichever is longer, before the protocol-defined first dose of study treatment, or ongoing clinically significant adverse events (AEs) from previous treatment with investigational drug or therapy.
- Poor medical risk because of other conditions such as uncontrolled systemic diseases or uncontrolled active infections.
- Diagnosis of AML with bone marrow or peripheral blast count ≥20% or other hematological malignancies.
- Life-threatening illness, medical condition or organ system dysfunction, or other reasons including laboratory abnormalities, which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of oral decitabine + cedazuridine, or compromise the integrity of the study outcomes.
- Known history of human immunodeficiency virus (HIV) or if known seropositive for hepatitis C virus (HCV) or hepatitis B virus (HBV).

3.4.6.2. Treatments

Dose Confirmation Stage
Test Product: oral decitabine capsules and oral cedazuridine capsules.
Test Product Dose: 35 mg decitabine (one 20-mg capsule + three 5-mg capsules) administered orally

concomitantly with 100 mg cedazuridine (five 20-mg capsules) Daily×5 in 28-day cycles.

Reference Product: IV decitabine (Dacogen®).
Reference Product Dose: 20 mg/m2 by continuous 1-hour IV infusion Daily×5 in 28-day cycles.

Initially in the ASTX727 cycle of the Dose Confirmation Stage, subjects received individual capsules of oral decitabine and cedazuridine. Ongoing subjects were later transitioned to the ASTX727 FDC tablet.

Fixed-Dose Combination Stage
Test Product: ASTX727 FDC tablet.
Test Product Dose: one ASTX727 FDC tablet (35 mg decitabine/100 mg cedazuridine) administered orally Daily×5 in 28-day cycles.

Reference Product: Dacogen (decitabine) for Injection.
Reference Product Dose: 20 mg/m2 continuous 1-hour IV infusion Daily×5 in 28-day cycles.

Table 25. Dosing Schedule by Stage and Cycle

Cycle (28 Days)	1	2	≥3
Study Day(s)	1-5	1-5	1-5
Dose Confirmation Stage			
If randomized to IV decitabine in Cycle 1, then:			
IV decitabine (20 mg/m^2)	×		
Oral decitabine + cedazuridine		×	×
If randomized to oral decitabine + cedazuridine in Cycle 1, then:			
Oral decitabine + cedazuridine	×		×
IV decitabine (20 mg/m^2)		×	
Fixed-Dose Combination Stage			
If randomized to IV decitabine in Cycle 1, then:			
IV decitabine (20 mg/m^2)	×		
FDC tablet		×	×
If randomized to the FDC tablet in Cycle 1, then:			
FDC tablet	×		×
IV decitabine (20 mg/m^2)		×	

FDC=fixed-dose combination; IMP=investigational medicinal product; IV=intravenous
On days when subjects were administered oral decitabine + cedazuridine (as capsules), subjects were to take the IMPs simultaneously (ie, cedazuridine followed immediately by oral decitabine). The IMPs were to be taken at the same time of day (±1 hour) on each dosing day, in at least the first 2 cycles of treatment.
Source: Protocol (Appendix 16.1.1)

3.4.6.3. Objectives

The goal of this Phase 2 study was (1) to confirm the selected doses of decitabine (35 mg) and cedazuridine (100 mg) based on decitabine AUC exposure, and (2) to confirm the comparability of decitabine AUC exposure (oral vs IV) using the ASTX727 FDC tablet.

3.4.6.4. Outcomes/endpoints

Primary endpoints

For the dose escalation stage:

Mean decitabine AUC oral/IV: Mean AUC of oral decitabine given with E7727 (Days 2 and/or 5) compared
with IV decitabine 20 mg/m2 (Day 1).

Incidence and severity grades of DLTs.

For the dose confirmation stage:

Mean decitabine AUC (estimated from 5 days of dosing) and mean maximum %LINE-1 demethylation after ASTX727 administration compared with IV decitabine 20 mg/m2.

Response rate in all subjects based on modified IWG 2006 MDS Response Criteria (Cheson et.al. 2006) **Table *6*. Modified Response Categories Based on IWG 2006 MDS Response CriteriaTable *6***.

Secondary endpoints

Adverse events with respective severity grades and clinically significant abnormal laboratory values.

Duration of response, haematological improvement, rate of transfusion independence, time to AML, and OS. Time to event endpoints are defined as time from first dose or response until the specified event.

Other PK parameters of ASTX727.

Duration of response will be using Kaplan-Meier method only for responders separately for CR, PR, mCR, and CR+PR+mCR from the first time a response category (CR, PR, and mCR) is initiated, as addressed in the Implementation Guide of Response Assessment in Appendix 1, to the earliest date of disease progression defined as below:

- Death date.
- AML conversion as described in Section 7.3.3.
- Disease progression date on the Subject Information CRF page.
- Last treatment date if the reason for treatment discontinuation is Progressive Disease.
- Study exit date on the Study Discontinuation CRF page if the reason for study discontinuation is Progressive Disease.
- Date of disease progression on the Survival Follow-up CRF page.

In the absence of progressive disease, subjects will be censored on the last date of disease assessment including Survival Follow-up on which clearly shows progressive disease have not occurred. Subjects who receive alternative anti-cancer therapy for MDS/CMML or subsequent AML (except for bone marrow transplant) will also be censored on the last date of disease assessment as described above before receiving the alternative therapy or progressive disease, whichever occurs earlier.

Transfusion dependence and independence is defined as follows:

- Transfusion dependence at baseline: documentation of 2 units or more of transfusion within 56 days of the first day of study treatment.
- Post-treatment transfusion independence: no transfusion for 56 consecutive days or more after the first dose of study treatment.

The same analyses will be performed for 84-day and 112-day transfusion independence, defined as no transfusion for 84 consecutive and 112 consecutive days respectively.

3.4.6.5. Sample size

Dose Confirmation Stage

At least 42 evaluable subjects were planned for enrollment into the Dose Confirmation Stage.

In an equivalence test of the mean decitabine AUCs of ASTX727 compared with IV decitabine using 2 one-sided tests on data from a 2×2 cross-over design, a sample size of 42 achieves 86% power at a 10% significance level when the true ratio of the means is 1.0, the coefficient of variation on the original, unlogged scale is 0.50 (which was estimated from a previous study described in the Dacogen Prescribing Information (2014)), and the equivalence limits of the mean ratio are 0.75 and 1.33.

This same sample size of 42 in the same 2×2 cross-over design achieves 80% power to detect the non-inferiority, with respect to the mean maximum %LINE-1 demethylation from baseline, of ASTX727 compared with IV decitabine using a one-sided t-test when the margin of non-inferiority is -0.05, the true mean difference is 0, the standard deviation (SD) is 0.15 and the significance level is 0.10. The SD of the paired differences of 0.15 was estimated from a previous Astex study.

Fixed-Dose Combination Stage

A total of 18-24 evaluable subjects included in the 2 one-sided equivalence tests for mean oral decitabine AUC compared with mean IV decitabine AUC would provide 75%-88% power at a 10% significance level when the true ratio of means is 1.0, the coefficient of variation under an unlogged scale is 0.55, and the equivalence limits for the ratio of means are 0.65 and 1.539.

This sample size of 18-24 subjects would provide 78%-86% power to detect non-inferiority, with respect to the mean maximum %LINE-1 demethylation from baseline, of the ASTX727 FDC tablet compared with IV decitabine using a one-sided t-test when the margin of non-inferiority is -0.075, the true mean difference is 0, the standard deviation (SD) is 0.15 and the significance level is 0.10.

Assessor's comment

The study sample size for the dose combination stage was justified based on information available from a previous study.

For the FDC stage, sample size was determined using equivalence limits of 65-153.9 for the ratio of AUC means. However, use of widened acceptance criteria should not be applicable for AUC, as stated in the CHMP guideline on the investigation of bioequivalence. The FDC stage is therefore probably underpowered. However, considerably more patients were actually included in both stages of the study than initially planned.

3.4.6.6. Randomisation

Individual subject treatment assignments were determined through a computer-generated randomization scheme. Subjects were randomized in a 1:1 ratio (and stratified by IPSS risk level) to either start with oral decitabine or IV. Subjects with CMML were randomly assigned into the IPSS Intermediate-2/high risk stratum.

3.4.6.7. Blinding (masking)

Not applicable. The study was open label.

3.4.6.8. Statistical methods

Primary analyses

Decitabine 5-day AUC_{0-t} was analysed in the log scale using a mixed effect model including fixed effects of sequence, period, and treatment, and a random effect of subject within sequence. The factors included in the model were based on the actual treatment sequence. A 90% CI for the geometric mean ratio of 5-day AUC_{0-t} was obtained by applying the exponential function on the 2-sided 90% CI for the difference of mean 5-day AUC_{0-t} between ASTX727 and IV decitabine in the log scale from the mixed effect model. Subjects without 5-day AUC_{0-t} data in both of ASTX727 and IV decitabine were not included.

Maximum %LINE-1 demethylation (defined as the largest percent decrease from baseline in methylation values within a subject between Day 8 and Day 22 of each treatment cycle) was analysed separately for cycle 1 and cycle 2 with baseline methylation defined as below:

- For cycle 1, baseline is defined as last value obtained before or on Day 1 pre-dose.
- For cycle 2, baseline is defined as the value obtained on Day 1.

Within each cycle, subjects to be included for analysis need to complete whole cycle of treatment. The 95% CIs for the difference of mean maximum %LINE-1 demethylation between ASTX727 and IV decitabine was generated using an analysis of variance (ANOVA) model separately for cycle 1 and cycle 2. A non-inferiority analysis of maximum %LINE-1 demethylation from baseline was initially planned based on the cross-over study design using an ANOVA model. This analysis was not performed due to concerns regarding the demethylation carry-over effect.

Response rates and rates of hematologic improvement (HI) were calculated as defined by the International Working Group (IWG) 2006 MDS Response Criteria. Rates of transfusion independence were
calculated based on the number of transfusion-dependent subjects who had no transfusion for at least 56 days during treatment. The 95% Clopper-Pearson CIs were provided for response rates and rates of transfusion independence. Overall survival was defined as the number of days from the date the subject received the first dose of study treatment to the date of death (regardless of cause).

Assessor's comment

Analysis data sets and methods of statistical analyses were principally similar as described for the main study ASTX727-02.

However, there were 3 primary endpoints specified study ASTX727-01-B: mean decitabine AUC (estimated from 5 days of dosing) and mean maximum %LINE-1 demethylation after ASTX727 administration compared with IV decitabine 20 mg/m2, as well as response rate in all subjects.

According to the statistical analysis plan (SAP), equivalence of AUC between treatments was to be determined using two-sided 90% CI of the AUC ratio. However, while the SAP did not stipulate any pre-defined equivalence (acceptance) range for the 90% CI, both the clinical study protocol and the clinical study report states that for the primary objective of the study to be achieved, the ratio of geometric least squares means and its 80% CI must have been fully contained within the prespecified limits of 75-133 (Dose Confirmation Stage) or 65-153.9 (FDC Stage). It is unclear why 80% CI was used instead of 90%. Further, the widened acceptance range for FDC was introduced into the clinical study protocol by amendment 3; however, the rationale for the change was not presented. It is also unclear why different widened acceptance ranges were specified in different parts of the study.

The CHMP guideline on the investigation of bioequivalence allows widened acceptance range to a maximum of 69.84 – 143 for C_{max} for highly variable drug products. Use of widened acceptance range

is not supported for AUC. Therefore, the acceptance ranges used for the primary analysis of AUC are questioned. However, full assessment and conclusions of the pharmacokinetic analyses as well as relevance of other pharmacokinetic parameters for establishment of equivalence are addressed elsewhere (please see sections 5.3.2 – 5.3.6 of this report).

In regards with the analysis of mean maximum %LINE-1 demethylation, the final clinical study protocol (version 5.0, April 2017) described a planned non-inferiority analysis which was in line with the non-inferiority onset in the sample size calculation. However, the plan for non-inferiority analysis was apparently abandoned during the study which was described in the SAP. The SAP was finalised on 8 August 2018, during the conduct of the FDC stage of the study and seems to have been influenced by at that time available study data.

Similarly to what is noted in the ASTX727-02 NA study, the purpose of the cross-over study design in the first 2 cycles was to evaluate equivalence based on the PK data, while rest of the study period has a single arm design. Presentation of efficacy results was therefore limited to summaries for all patients in the study, or summaries by treatment sequence.

With consideration to the seemingly data driven adaptions of the data analyses, and limitations in study design and analysis, the study results may only be considered for exploratory purpose.

3.4.7. Results

3.4.7.1. Participant flow

A total of 138 subjects were screened for participation in Phase 2. Of those, 52 failed screening.

Of the 86 subjects randomized in Phase 2, 80 were treated, as follows:
- Dose Confirmation Stage: N=52 randomized; N=50 treated
- FDC Stage: N=34 randomized; N=30 treated

Of all randomized subjects, 6 subjects did not receive any study treatment.

Table 26. Subject Disposition – Phase 2 Overall (All Subject Analysis Set)

Subject Disposition	Number (%) of Subjects Dose Confirmation Stage (N=52)	Fixed-Dose Combination Stage (N=34)	Phase 2 Overall (N=86)
Subjects Randomized	52 (100.0)	34 (100.0)	86 (100.0)
Subjects Treated[a]	50 (96.2)	30 (88.2)	80 (93.0)
ASTX727 and IV	47 (94.0)	26 (86.7)	73 (91.3)
ASTX727 only	2 (4.0)	3 (10.0)	5 (6.3)
IV only	1 (2.0)	1 (3.3)	2 (2.5)
Treatment Discontinuation (Primary Reason)[b]	50 (100.0)	30 (100.0)	80 (100.0)
Adverse Event	5 (10.0)	3 (10.0)	8 (10.0)
Death	4 (8.0)[c]	7 (23.3)	11 (13.8)
Progressive Disease	17 (34.0)	9 (30.0)	26 (32.5)
Bone Marrow/Stem Cell Transplant	7 (14.0)	5 (16.7)	12 (15.0)
Withdrawal by Subject	4 (8.0)	1 (3.3)	5 (6.3)
Lost to Follow-Up	0	0	0
Other[d]	13 (26.0)	5 (16.7)	18 (22.5)
Study Withdrawal[b]	50 (100.0)	30 (100.0)	80 (100.0)
Adverse Event	1 (2.0)	0	1 (1.3)
Death	29 (58.0)	21 (70.0)	50 (62.5)
Progressive Disease	3 (6.0)	1 (3.3)	4 (5.0)
Withdrawal by Subject	1 (2.0)	1 (3.3)	2 (2.5)
Lost to Follow-Up	0	1 (3.3)	1 (1.3)
Other[e]	16 (32.0)	6 (20.0)	22 (27.5)

CSR=clinical study report; IV=intravenous

[a] 'ASTX727 and IV' includes subjects who received both Cycles 1 and 2. 'ASTX727 only' or 'IV only' includes subjects who received only one cycle (ie, either ASTX727 or IV decitabine).

[b] Treatment Discontinuation and Study Withdrawal are based on the number of subjects who received any study medication.

[c] two subjects had their reason for treatment discontinuation changed from "death" to "adverse event" after the data cutoff date for the original CSR (05 June 2018)

[d] Included investigator decision (4 subjects).

[e] All subjects proceeded to stem cell transplant.

Table 27. Subject Disposition for MDS Subjects with IPSS-R Score >3.5

	ASTX727-01-B (N=36) n (%)
Received treatment	36 (100.0)
At least 1 dose of ASTX727[a]	35 (97.2)
1 dose of IV decitabine	33 (91.7)
Discontinued treatment[b]	36 (100.0)
Adverse Event	4 (11.1)
Death	6 (16.7)
Progressive Disease	8 (22.2)
Alternative MDS/CMML Therapy	0
Patient Decision to Permanently Stop Treatment	3 (8.3)
Bone Marrow/Stem Cell Transplant	9 (25.0)
Lost to follow-up	0
Alternative AML Therapy	0
Other	6 (16.7)
Withdrawn from study	36 (100.0)

	ASTX727-01-B (N=36) n (%)
Death	25 (69.4)
Adverse Event	0
Progressive Disease	1 (2.8)
Withdrawal by Subject	1 (2.8)
Lost to follow-up	0
Rollover	0
Study Terminated by Sponsor	0
Completed	2 (5.6)
Other[c]	7 (19.4)
Continuing in study	0
On study treatment	0
Survival follow-up	0

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

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

[C] One subject in Survival follow-up. This subject already discontinued the study. However, due to the site closure, withdrawn from study form was not completed. This was documented in NTF.

AML = acute myeloid leukaemia; CMML = chronic myelomonocytic leukaemia; IPSS-R = International Prognostic Scoring System-Revised; IWG = International Working Group; MDS = myelodysplastic syndrome; N = total number of subjects; n = a subset of subjects; NTF = note to file.

3.4.7.2. Recruitment

The enrollment period was 30 December 2015 (first subject date of written informed consent – Dose Confirmation Stage) to 05 June 2017 (last subject date of first study treatment – FDC Stage).

Complete data from all visits for all subjects were included in the database for this final CSR providing a median follow-up combined for all subjects in all stages (ie, n=80 overall in Phase 2) of 1563 days (min, max: 1199, 1710 days) from the last subject's first dose. Follow-up was defined as the number of days from date of first dose to the date of database lock. Database lock presented is 16 September 2020 and represents the final analysis.

The study was conducted in North America, 11 centers (n=69) in US and 4 centers (n=17) in Canada.

3.4.7.3. Conduct of the study

Protocol amendments

The original protocol was dated 10 January 2014. **Table *28*** summarizes the 4 protocol amendments. Nine patients were enrolled under the original protocol.

Table 28. Protocol Amendments and Subjects Enrolled (Randomized)

Protocol Amendment	Protocol Version	Main Changes in the Amendment Affecting Dose Escalation Stage	Date of Amendment	Number of Subjects Enrolled Under Amendment[a]
1	2.0	• Modified Phase 1 study design from 6+6 to 3+3 to allow earlier dose escalation (applicable only to Phase 1). • Eliminated requirement for hematology assessments on Days 2-5 in Cycles 1 and 2, to reduce burden of assessments.	24 November 2014	35
2	3.0	• Added PK assessments on Days 2, 3, and 4 during ASTX727 cycle in Dose Confirmation Stage to estimate PK over 5 dosing days. • Added content of administrative letters #2, #3, #4.	23 September 2015	53[b]
3	4.0	• Added FDC stage to confirm FDC tablet formulation yields PK and PD data similar to data for IV decitabine and to gather additional efficacy and safety data with the FDC. • Added content of administrative letter #5.	26 July 2016	33[b]
4	5.0	• Require transition of long-term ongoing subjects in Dose Confirmation Stage from oral decitabine and cedazuridine capsules to the FDC tablet. • Added content of administrative letter #6.	06 April 2017	0[c]

FDC=fixed-dose combination; IV=intravenous; PK=pharmacokinetic; PD=pharmacodynamic

[a] The number of subjects who signed an informed consent form under the protocol version.

[b] These subjects all enrolled in Phase 2.

[c] No new subjects were enrolled under Amendment 4 because the purpose of the amendment was to allow currently participating subjects to transition from decitabine + cedazuridine capsules to the ASTX727 FDC tablet.

Source: Appendix 16.1.1

Protocol deviations

Important protocol deviations were reported for 10 subjects. The majority of the deviations were related to study drug administration and study procedures deviations (ECG not completed at each visit).

Assessor's comment

The protocol amendments included changes to the PK assessments and the transition from providing oral decitabine and cedazuridine as separate capsules to the FDC tablet. Protocol deviation raises no concerns regarding the efficacy evaluation of phase 2 however, the SAP amendments have been done after the last protocol amendment. For a discussion please refere to 293.4.3.8.

Protocol deviations raising no concerns for the efficacy evaluation.

3.4.7.4. Baseline data

Table 29. Demographics and Baseline Characteristics (Efficacy and Safety Analysis Sets)

Characteristic	Phase 2 Overall		
	Sequence A (N=41)	Sequence B (N=39)	Total (N=80)
Age (years)			
n	41	39	80
Mean	69.5	69.9	69.7
SD	11.38	9.85	10.59
Median	71.0	71.0	71.0
Min, Max	32, 90	41, 86	32, 90
Sex, n (%)			
Male	32 (78.0)	29 (74.4)	61 (76.3)
Female	9 (22.0)	10 (25.6)	19 (23.8)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	0	1 (2.6)	1 (1.3)
Black or African American	1 (2.4)	1 (2.6)	2 (2.5)
Native Hawaiian or Pacific Islander	0	0	0
White	38 (92.7)	36 (92.3)	74 (92.5)
Other	2 (4.9)	1 (2.6)	3 (3.8)
Ethnicity, n (%)			
Hispanic or Latino	5 (12.2)	0	5 (6.3)
Not Hispanic or Latino	34 (82.9)	38 (97.4)	72 (90.0)
Not Reported	1 (2.4)	0	1 (1.3)
Unknown	1 (2.4)	1 (2.6)	2 (2.5)
Weight (kg)			
n	41	39	80
Mean	79.79	83.98	81.83
SD	18.172	14.705	16.603
Median	78.80	86.20	82.75
Min, Max	39.8, 122.0	41.8, 117.8	39.8, 122.0
Height (cm)			
n	40	38	78
Mean	172.19	171.66	171.94
SD	10.106	12.065	11.034
Median	172.70	172.85	172.70
Min, Max	149.9, 189.3	148.8, 192.5	148.8, 192.5
BSA (m^2)			
n	41	39	80
Mean	1.92	1.99	1.95
SD	0.260	0.230	0.247
Median	1.96	2.05	1.99
Min, Max	1.3, 2.4	1.3, 2.4	1.3, 2.4

BSA=body surface area; Max=maximum; Min=minimum; SD=standard deviation
Sequence A=ASTX727 in Cycle 1, IV decitabine in Cycle 2; Sequence B=IV decitabine in Cycle 1, ASTX727 in Cycle 2.
Efficacy Analysis Set and Safety Analysis Set are the same.
Source: Table 14.2.1.2

Table 30. Baseline Disease/Subject Characteristics (Efficacy and Safety Analysis Sets)

Characteristic	Phase 2 Overall		
	Sequence A (N=41)	Sequence B (N=39)	Total (N=80)
ECOG Performance Score, n (%)			
0	20 (48.8)	15 (38.5)	35 (43.8)
1	18 (43.9)	20 (51.3)	38 (47.5)
2	3 (7.3)	4 (10.3)	7 (8.8)
3	0	0	0
4	0	0	0
Missing	0	0	0
Prior HMA Therapy[a], n (%)	3	4	7
Prior Azacitidine	3 (100)	1 (25.0)	4 (57.1)
Prior Decitabine	0	3 (75.0)	3 (42.9)
Prior Azacitidine or Decitabine	3 (100)	4 (100)	7 (100)
Disease Category / IPSS, n (%)			
MDS INT-1	19 (46.3)	16 (41.0)	35 (43.8)
MDS INT-2	9 (22.0)	10 (25.6)	19 (23.8)
MDS High Risk	5 (12.2)	4 (10.3)	9 (11.3)
CMML	8 (19.5)	9 (23.1)	17 (21.3)
Hemoglobin (g/L)			
n	41	39	80
Mean	92.24	96.49	94.31
SD	18.074	15.262	16.793
Median	87.50	92.50	91.50
Min, Max	71.0, 149.0	68.0, 139.5	68.0, 149.0
Neutrophils (10^9/L)			
n	41	39	80
Mean	5.1005	5.4077	5.2503
SD	13.01443	13.59953	13.21914
Median	0.9401	0.7650	0.9089
Min, Max	0.034, 73.652	0.062, 63.408	0.034, 73.652
Platelets (10^9/L)			
n	41	39	80
Mean	98.06	76.97	87.78
SD	109.040	92.449	101.211
Median	58.50	60.00	59.25
Min, Max	2.0, 523.0	8.0, 569.5	2.0, 569.5
RBC Transfusion Dependence, n (%)			
Yes	20 (48.8)	18 (46.2)	38 (47.5)
No	21 (51.2)	21 (53.8)	42 (52.5)
Platelet Transfusion Dependence, n (%)			
Yes	8 (19.5)	4 (10.3)	12 (15.0)
No	33 (80.5)	35 (89.7)	68 (85.0)
Baseline Bone Marrow Blasts (%)			
n	38	39	77
Mean	7.1	6.8	7.0
SD	4.95	5.02	4.95
Median	7.0	5.0	6.0
Min, Max	0, 19	0, 17	0, 19
>5% Bone Marrow Blasts[b], n (%)	22 (57.9)	19 (48.7)	41 (53.2)

CMML=chronic myelomonocytic leukemia; ECOG=Eastern Cooperative Oncology Group; HMA=hypomethylating agent; INT=intermediate; IPSS=International Prognostic Scoring System; Max=maximum; MDS=myelodysplastic syndromes; Min=minimum; RBC=red blood cell; SD=standard deviation
Sequence A=ASTX727 in Cycle 1, IV decitabine in Cycle 2; Sequence B=IV decitabine in Cycle 1, ASTX727 in Cycle 2.
Efficacy Analysis Set and Safety Analysis Set are the same.
[a] One cycle only, per the Exclusion Criteria (Section 9.3.2).
[b] Denominator is number of subjects with baseline bone marrow blasts.

Table 31. Demographics and Baseline Characteristic for MDS Subjects with IPSS-R Score >3.5

	ASTX727-01-B (N=36)		
Age (yr)			
n[a]	36		
Mean	67.9		
SD	9.88		
Median	69.5		
Min, Max	40, 90		
Age Group (yr), n (%)			
<18	0		
18 - 64	9 (25.0)		
65 - 84	26 (72.2)		
>=85	1 (2.8)		
Sex, n (%)			
Male	24 (66.7)		
Female	12 (33.3)		
Race, n (%)			
Asian	1 (2.8)		
Black or African American	1 (2.8)		
White	34 (94.4)		
Not Reported	0		
Ethnicity, n (%)			
Hispanic or Latino	3 (8.3)		
Not Hispanic or Latino	33 (91.7)		
Not Reported	0		
Weight (kg)			
n[a]	36		
Mean	78.60		
SD	17.750		
Median	78.75		
Min, Max	39.8, 107.5		
Weight, n (%)			
<100 kg	32 (88.9)		
>=100 kg	4 (11.1)		
Height (cm)			
n[a]	35		
Mean	169.914		

	ASTX727-01-B (N=36)		
SD	11.5225		
Median	172.500		
Min, Max	148.80, 192.50		
BSA (m^2)			
n[a]	36		
Mean	1.893		
SD	0.2770		
Median	1.900		
Min, Max	1.27, 2.34		
ECOG, n (%)			
0	13 (36.1)		
1	20 (55.6)		
2	3 (8.3)		
Prior Anticancer Therapy, n (%)			
Yes	8 (22.2)		
No	28 (77.8)		
Prior HMA Therapy, n (%)			
Prior Azacitidine only	2 (5.6)		
Prior Decitabine only	3 (8.3)		
Study Disease, n (%)			
MDS	36 (100.0)		
Time Since Diagnosis (Days)			
n[a]	36		
Mean	346.8		
SD	682.32		
Median	42.0		
Min, Max	6, 3077		
IPSS for MDS[b], n (%)			
INT-1/INT-2	30 (83.3)		
High Risk	6 (16.7)		
Cytogenetic Risk Classification for IPSS, n (%)			
Poor-Risk	12 (33.3)		
Intermediate-Risk	12 (33.3)		
Better-Risk	12 (33.3)		
Not Evaluable	0		
IPSS-R Risk Category for MDS[b], n (%)			
Intermediate	8 (22.2)		

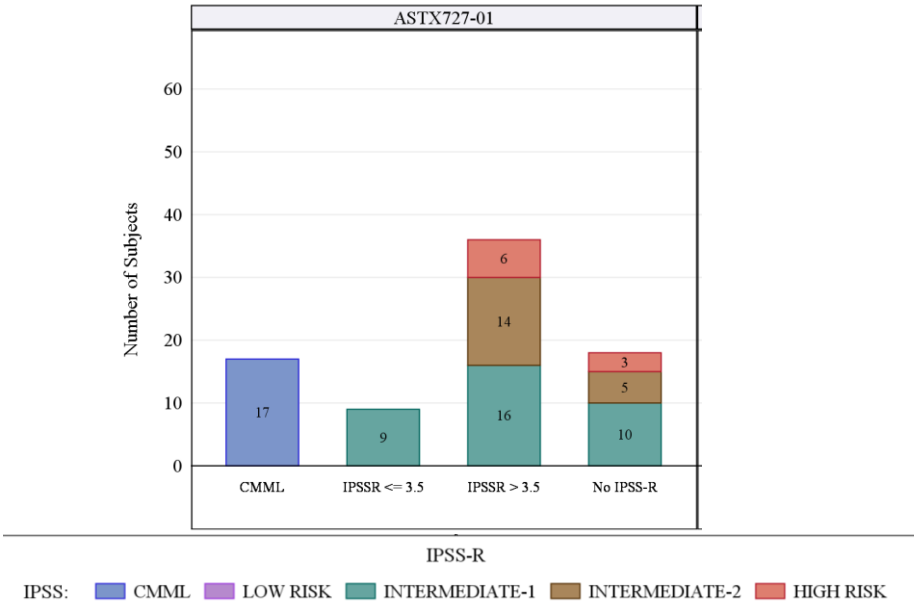
	ASTX727-01-B (N=36)		
High	15 (41.7)		
Very High	13 (36.1)		
Overall IPSS-R Score			
>3.5	36 (100.0)		
Cytogenetic Risk Classification for IPSS-R, n (%)			
Very Poor Risk	9 (25.0)		
Poor Risk	4 (11.1)		
Intermediate Risk	9 (25.0)		
Good Risk	13 (36.1)		
Very Good Risk	1 (2.8)		
Baseline Haemoglobin (g/L)			
n[a]	36		
Mean	92.7361		
SD	13.77860		
Median	91.5000		
Min, Max	71.000, 136.000		
Baseline Haemoglobin (g/L)			
<80	5 (13.9)		
80 - <100	23 (63.9)		
100 - <110	5 (13.9)		
>=110	3 (8.3)		
Baseline Neutrophils (10^9/L)			
n[a]	36		
Mean	1.4700		
SD	2.46128		
Median	0.7549		
Min, Max	0.136, 14.724		
Baseline Neutrophils (10^9/L)			
<0.5	10 (27.8)		
0.5 - <1	13 (36.1)		
1 - 1.5	3 (8.3)		
>1.5	10 (27.8)		
Baseline Platelets (10^9/L)			
n[a]	36		
Mean	94.2361		
SD	111.60821		
Median	60.5000		
Min, Max	8.000, 569.500		

	ASTX727-01-B (N=36)		
Baseline Platelets (10^9/L)			
<25	6 (16.7)		
25 - <50	7 (19.4)		
50 - <75	10 (27.8)		
75 - <100	3 (8.3)		
>=100	10 (27.8)		
RBC Transfusion Dependence[c], n (%)			
Yes	13 (36.1)		
No	23 (63.9)		
Platelet Transfusion Dependence[c], n (%)			
Yes	5 (13.9)		
No	31 (86.1)		
Baseline Bone Marrow Blasts (%)			
n[a]	36		
Mean	8.3167		
SD	4.56849		
Median	8.0000		
Min, Max	1.000, 18.000		
>5% Bone Marrow Blast, n (%)	24 (66.7)		
Baseline PB Blasts (%)			
n[a]	36		
Mean	1.4		
SD	3.74		
Median	0.0		
Min, Max	0, 17		
[a]n is the number of subjects who had valid data.			
[b]IPSS = International Prognostic Scoring System; IPSS-R = Revised International Prognostic Scoring System			
[c]Two units or more of transfusion within 56 days of the first dose of study treatment.			
Time since diagnosis is calculated as the (date of first dose minus date of diagnosis).			

Reclassification of risk categories by IPSS-R criteria for subjects with MDS

Post hoc, where it was possible, patients were reclassified using the IPSS-R score according to lower-risk (≤3.5) and higher-risk (>3.5) MDS.

Figure 10. Distribution of IPSS Risk Categories by Lower-Risk (≤3.5) and Higher-Risk Per IPSS-R (>3.5)



Assessor's comment

No patients with low-IPSS score were included which is in accordance with the stipulated inclusion criterion. The total number of CMML patients included were 21.3% (n=17).

47.5% (n=38) of the patients were RBC transfusion dependent and 15% (n=12) were platelet transfusion dependent at study entry.

In relation to the CR criteria, it is noted that 33.3% (n=12) had ≤5% BM blasts at inclusion - i.e. this criterion of CR is already fulfilled at baseline. The frequency of patients fulfilling criteria for CR in regard to Hgb was 8.3% (n=3), platelets 27.8% (n=10) and neutrophils 36.1% (n=13).

Current prognostic systems include IPSS-R and IPSS-M. The IPSS-R system was presented 2012 as an improvement of IPSS. Reclassification of MDS patients using IPSS-R was done post hoc. 18 patients could not be re-classified. Only 9 patients are classified as IPSS-R low.

3.4.7.5. Numbers analysed

Table 32. Analysis Data Sets for Efficacy, Safety, and Pharmacodynamics

Analysis Set	Dose Confirmation Stage	Fixed-Dose Combination Stage	Phase 2 Total
Efficacy Analysis Data Set (All Treated Subjects)	50	30	80
Safety Analysis Data Set (All Treated Subjects)	50	30	80
Pharmacodynamics (*LINE-1*) Analysis Data Set	48	30	78

Source: Table 14.1.1.2, Table 14.1.1.3

For the new suggsted indication MDS IPSS >3.5 total no. Subjects =36.

3.4.7.6. Outcomes and estimation

Primary endpoints

Table 33. Primary Analysis (Paired Population): Plasma Decitabine Results for AUC Equivalence Assessment – Dose Confirmation Stage

Parameter	N	IV Geo LSM	Oral Geo LSM	Ratio of Geo LSM[a] (%)	(80% CI)	(90% CI)	Intra-Subject (CV%)
5-day AUC_{0-t} (h*ng/mL)	**40**	**802.81**	**750.82**	**93.52**	**(82.10, 106.5)**	**(79.02, 110.7)**	**47.0**
5-day AUC_{0-24} (h*ng/mL)	36	789.03	760.51	96.39	(84.99, 109.3)	(81.90, 113.4)	42.5
5-day AUC_{0-inf} (h*ng/mL)	34	785.56	743.16	94.60	(82.78, 108.1)	(79.59, 112.4)	43.7

CI=confidence interval; CV=coefficient of variation; Geo LSM=geometric least squares means; IV=intravenous
See Table 7 for PK parameter definitions.
5-day AUC_{0-t} is the primary endpoint; results in bold.
5-day AUC_{0-24} and 5-day AUC_{0-inf} are secondary (sensitivity) analyses.
IV=20 mg/m^2 IV infusion (1h) of decitabine. Oral=35 mg decitabine and 100 mg cedazuridine capsules.
[a] Oral/IV.
Source: Appendix 16.1.13.4 PK Report Table 5.5.4

Table 34. Primary Analysis (Paired Population): Plasma Decitabine Results for AUC Equivalence Assessment – Fixed-Dose Combination Stage

Parameter	N	IV Geo LSM	Oral Geo LSM	Ratio of Geo LSM[a] (%)	(80% CI)	(90% CI)	Intra-Subject (CV%)
5-day AUC_{0-t} (h*ng/mL)	**24**	**745.26**	**727.29**	**97.59**	**(80.48, 118.3)**	**(75.96, 125.4)**	**53.8**
5-day AUC_{0-24} (h*ng/mL)	19	762.56	823.06	107.93	(85.48, 136.3)	(79.61, 146.3)	57.3
5-day AUC_{0-inf} (h*ng/mL)	19	763.25	822.08	107.71	(85.33, 136.0)	(79.48, 146.0)	57.2

CI=confidence interval; CV=coefficient of variation; Geo LSM=geometric least squares means; IV=intravenous
See Table 7 for PK parameter definitions.
5-day AUC_{0-t} is the primary endpoint; results in bold.
5-day AUC_{0-24} and 5-day AUC_{0-inf} are secondary (sensitivity) analyses.
IV=20 mg/m^2 IV infusion (1h) of decitabine. Oral=ASTX727 FDC tablet.
[a] Oral/IV.
Source: Appendix 16.1.13.4 PK Report Table 6.5.4

Assessor's comment

The primary analysis for the dose confirmation stage of the primary study endpoint (5-day AUC0-t) shows that the ratio (oral/IV) of geometric LSM (93.52) and its 80% CI (82.10, 106.5) are contained within the prespecified CI limits of 75-133.

The analysis (paired group) for the FDC stage of the primary study endpoint (5-day AUC0-t) shows that the ratio (oral/IV) of geometric LSM (97.59) and its 80% CI (80.48, 118.3) are fully contained within the prespecified CI limits of 65-153.9.

Similar exposure between oral and IV decitabine have been shown. For further discussion see 3.3.3.

However, considering that decitabine is not authorised in the EU for use in MDS bridging is not possible.

%LINE-1

The prespecified analysis for PD was the comparison of the mean maximum %LINE-1 demethylation (from Day 8 or 15) for each treatment by cycle.

Table 35. Maximum %LINE-1 Demethylation

					Maximum %*LINE-1* Demethylation		Difference[a]	
Study Stage	Cycle	N	Treatment	Mean Baseline	Least Squares Mean[b]	95% CI	Estimate	95% CI
Dose Confirmation	1	24	Oral Decitabine + Cedazuridine	80.050	11.159	(9.023, 13.294)	-0.144	(-3.165, 2.876)
		24	IV Decitabine	79.464	11.303	(9.167, 13.439)		
	2	22	Oral Decitabine + Cedazuridine	78.470	9.833	(7.446, 12.219)	-0.087	(-3.463, 3.288)
		22	IV Decitabine	77.571	9.920	(7.534, 12.307)		
Fixed-Dose Combination	1	16	ASTX727 FDC	78.296	10.077	(7.696, 12.459)	-2.588	(-6.074, 0.899)
		14	IV Decitabine	78.528	12.665	(10.12, 15.211)		
	2	9	ASTX727 FDC	75.563	8.134	(4.438, 11.830)	-0.096	(-5.080, 4.888)
		11	IV Decitabine	76.751	8.230	(4.887, 11.574)		
Phase 2 Overall	1	40	Oral Decitabine + Cedazuridine or ASTX727 FDC	79.349	10.726	(9.161, 12.291)	-1.079	(-3.320, 1.163)
		38	IV Decitabine	79.119	11.805	(10.20, 13.410)		
	2	31	Oral Decitabine + Cedazuridine or ASTX727 FDC	77.626	9.340	(7.387, 11.292)	-0.017	(-2.736, 2.701)
		33	IV Decitabine	77.298	9.357	(7.465, 11.249)		

ANOVA=analysis of variance; CI=confidence interval; FDC=fixed-dose combination; IV=intravenous; LSM=least squares means
For Cycle 1, baseline is the last available value on or before C1D1.
For Cycle 2, baseline is the value on C2D1.
[a] The 95% Cis for the difference (oral – IV) of mean maximum %*LINE-1* demethylation between ASTX727 and IV decitabine were generated using an ANOVA model separately for Cycle 1 and Cycle 2.
[b] LSM=least squares mean of maximum %*LINE-1* methylation change from baseline.
Source: Table 14.5.3

Response Rate

In the Efficacy Set (N=80), 17.5% achieved a complete response (CR) (95% CI: 9.9, 27.6).

Table 36. Analysis of Best Response (efficacy analysis set)

Type of Response[a]	Dose Confirmation Stage (N=50) n (%)	95%CI	Fixed-Dose Combination Stage (N=30) n (%)	95%CI	Phase 2 Overall (N=80) n (%)	95%CI
Complete Response [CR]	7 (14.0)	(5.8, 26.7)	7 (23.3)	(9.9, 42.3)	14 (17.5)	(9.9, 27.6)
Partial Response [PR]	0		0		0	
Marrow Complete Response [mCR]	14 (28.0)	(16.2, 42.5)	5 (16.7)	(5.6, 34.7)	19 (23.8)	(14.9, 34.6)
Hematologic Improvement [HI]	8 (16.0)	(7.2, 29.1)	7 (23.3)	(9.9, 42.3)	15 (18.8)	(10.9, 29.0)
HI-E	5 (10.0)	(3.3, 21.8)	5 (16.7)	(5.6, 34.7)	10 (12.5)	(6.2, 21.8)
HI-N	1 (2.0)	(0.1, 10.6)	1 (3.3)	(0.1, 17.2)	2 (2.5)	(0.3, 8.7)
HI-P	7 (14.0)	(5.8, 26.7)	6 (20.0)	(7.7, 38.6)	13 (16.3)	(8.9, 26.2)
Overall Response [CR+PR+mCR+HI]	29 (58.0)	(43.2, 71.8)	19 (63.3)	(43.9, 80.1)	48 (60.0)	(48.4, 70.8)
mCR with HI	5 (10.0)	(3.3, 21.8)	1 (3.3)	(0.1, 17.2)	6 (7.5)	(2.8, 15.6)
No Response	21 (42.0)	(28.2, 56.8)	11 (36.7)	(19.9, 56.1)	32 (40.0)	(29.2, 51.6)

CI=confidence interval; CR=complete response; HI=hematologic improvement; HI-E=hematologic improvement-erythroid response; HI-N=hematologic improvement – neutrophil response; HI-P=hematologic response – platelet response; mCR=marrow complete response; PR=partial response

[a] Subjects are counted only once by their best response, according to the following hierarchy: CR, PR, mCR, HI. Within HI, subjects may be counted in more than one lineage, according to the HI observed. The category 'mCR with HI' is a subset of subjects with mCR who also achieved HI.

Response for MDS IPSS-R >3.5 for BM blasts at inclusion of >5% or ≤5%

CR was observed in 16.7% (95% CI 6.4, 32.8) of the 36 patients with IPSS-R >3.5. Of the 36 treated patients, 8 (22.2%) went on to receive stem cell transplant.

Among the 24 patients with IPSS-R >3.5 and BM blasts >5% at inclusion 4 (16.7%, 95% CI 4.7, 37.4) reached CR.

Table 37. Response with 95% Confidence Interval for MDS Subjects with IPSS-R Score >3.5 (Using IWG 2006)

Type of Response	ASTX727-01-B (N=36) BM>5% (N=24) n (%) (95% CI)	BM<=5% (N=12) n (%) (95% CI)	Total (N=36) n (%) (95% CI)
Complete Response [CR]	4 (16.7)	2 (16.7)	6 (16.7)
	(4.7, 37.4)	(2.1, 48.4)	(6.4, 32.8)
Partial Response [PR]	0	0	0
	(0.0, 14.2)	(0.0, 26.5)	(0.0, 9.7)
Marrow Complete Response [mCR]	9 (37.5)	0	9 (25.0)
	(18.8, 59.4)	(0.0, 26.5)	(12.1, 42.2)
mCR with HI	2 (8.3)	0	2 (5.6)
	(1.0, 27.0)	(0.0, 26.5)	(0.7, 18.7)
Haematological Improvement [HI]	1 (4.2)	5 (41.7)	6 (16.7)

Type of Response	ASTX727-01-B (N=36)		
	BM>5% (N=24) n (%) (95% CI)	**BM<=5% (N=12)** n (%) (95% CI)	**Total (N=36)** n (%) (95% CI)
	(0.1, 21.1)	(15.2, 72.3)	(6.4, 32.8)
HI-E	0	4 (33.3)	4 (11.1)
	(0.0, 14.2)	(9.9, 65.1)	(3.1, 26.1)
HI-N	0	1 (8.3)	1 (2.8)
	0	0	0
	(0.0, 14.2)	(0.2, 38.5)	(0.1, 14.5)
HI-P	1 (4.2)	5 (41.7)	6 (16.7)
	(0.1, 21.1)	(15.2, 72.3)	(6.4, 32.8)
Overall Response [CR+PR+mCR+HI]	14 (58.3)	7 (58.3)	21 (58.3)
	(36.6, 77.9)	(27.7, 84.8)	(40.8, 74.5)
Progressive Disease [PD]	2 (8.3)	1 (8.3)	3 (8.3)
	(1.0, 27.0)	(0.2, 38.5)	(1.8, 22.5)
No Response [NR]	8 (33.3)	4 (33.3)	12 (33.3)
	(15.6, 55.3)	(9.9, 65.1)	(18.6, 51.0)
Non-Evaluable [NE]	0	0	0
	(0.0, 14.2)	(0.0, 26.5)	(0.0, 9.7)

Response Assessment was performed by an Independent Reviewer committee using IWG 2006 MDS Response Criteria.
BM = bone marrow; CI = confidence interval; IPSS-R = International Prognostic Scoring System-Revised; IWG = International Working Group; MDS = myelodysplastic syndrome; N = total number of subjects; n = a subset of subjects.
The 95% CI is Clopper-Pearson confidence interval; mCR with HI: a subset of mCR subjects who also had HI (with any overlap of mCR period and HI period).
Stable Disease is included in No Response [NR].

In the IWG 2006 criteria used in the primary analysis, for Study ASTX727-01-B, NE was included in No Response (NR), which refers to subjects for whom the post-treatment efficacy assessment was not valid or did not meet the specified response criteria such as CR, PR, or mCR. There were 12 higher risk MDS subjects with NR. Reasons for NR included early treatment discontinuation (n=6), no post-treatment BM blast information (n=2) and not meet the specified response criteria (n=4).

Assessor's comment

The response rate for CR appears numerically lower in the dose confirmation stage compared to the fixed-dose combination stage. However, sample sizes are small, and the ORR is similar. Overall, the rates presented for CR and ORR are similar to the results from the phase 3 study ASTX727-02.

Several patients fulfilling the response criteria did fulfil these or part of these already at study inclusion. This was not prohibiting from being classified as response. This precludes the isolation of efficacy and the evaluation of the clinical benefit from treatment. In total from both ASTX727-02 NA and ASTX727-01-B only 36 patients did not fulfil any of the CR criteria of IWG2023 at baseline, i.e. displaying BM blasts >5% and tri-linage cytopenia.

8 patients proceeded to SCT following Inaqovi treatment in ASTX727-02 NA. Data on conditioning regiments and outcome of SCT was not routinely collected.

3.4.7.7. Ancillary analyses

Exploratory endpoints

Duration of Complete Response and Time to Complete Response

Table 38. Duration of Complete Response for MDS Subjects with IPSS-R Score>3.5 (IWG 2006)

Overall Survival	**ASTX727-01 B (N=6)**
Number of Subjects, n (%)	
Censored	1 (16.7)
Event	5 (83.3)
KM Estimates, Months, (95% CI)	
25th percentile	3.7 (1.1, 5.5)
Median	4.7 (1.1, NE)
75th percentile	13.1 (3.7, NE)
Survival Rate Estimate (95% CI)	
6-Month	0.33 (0.05, 0.68)
1-Year	0.33 (0.05, 0.68)
2-Year	0.00 (NE, NE)
3-Year	0.00 (NE, NE)

CI = confidence interval; IPSS-R = International Prognostic Scoring System-Revised; KM = Kaplan-Meier; MDS = myelodysplastic syndrome; N = total number of subjects; NE = non-evaluable.
Source: Summary of Clinical Efficacy, Table 26a

Table 39. Time to Complete Response for MDS Subjects with IPSS-R Score>3.5 (IWG 2006)

	ASTX727-01 B (N=6)
Time to Response (CR) (Months)	
n	6
Mean	4.3
SD	1.75
Median	4.3
Min, Max	2, 6

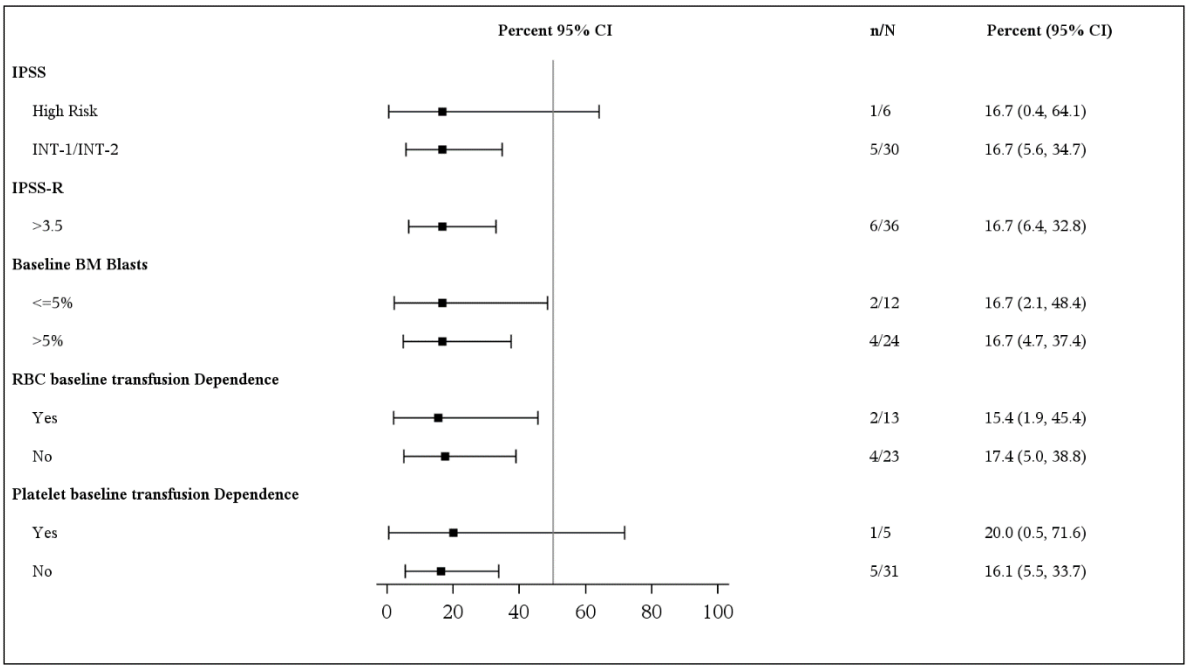
IPSS-R = International Prognostic Scoring System-Revised; IWG = International Working Group; MDS = myelodysplastic syndrome; MDS = myelodysplastic syndrome; N = total number of subjects; SD = standard deviation.

Assessor's comment

For completeness tables of MDS IPSS-R >3.5 should be amended to include also DoR and time to response specified for BM>5%,≤5% and total **(OC)**.

Provide reasons for censoring in the analysis of duration of response in a tabulated format for MDS IPSS-R >3.5 and also specified for BM>5%,≤5% and total **(OC)**.

Figure 11. Subgroup results with CR in MDS Subjects with IPSS-R Score >3.5 in ASTX727-01-B (Using IWG 2006)



BM = bone marrow; CI = confidence interval; CR = complete response; INT = interleukin; IPSS = International Prognostic Scoring System; IPSS-R = International Prognostic Scoring System-Revised; IWG = International Working Group; MDS = myelodysplastic syndrome; N = total number of subjects; n = a subset of subjects; RBC =red blood cells.

Concomitant medications

Classes of drugs most commonly used were antibacterials (75/80, 93.8%); analgesics (61/80, 76.3%); and antimycotics (54/80, 67.5%).

Table 40. Concomitant Medications (Level 2 Terms) in ≥20% of Subjects (by Phase 2 Overall)

	Number (%) of Subjects		
WHO Drug ATC Level 2 Term	Dose Confirmation Stage (N=50)	Fixed-Dose Combination Stage (N=30)	Phase 2 Overall (N=80)
Any Sponsor-Defined Concomitant Medication	50 (100.0)	30 (100.0)	80 (100.0)
Antibacterials for Systemic Use	46 (92.0)	29 (96.7)	75 (93.8)
Analgesics	38 (76.0)	25 (83.3)	63 (78.8)
Antimycotics for Systemic Use	37 (74.0)	18 (60.0)	55 (68.8)
Antivirals for Systemic Use	36 (72.0)	16 (53.3)	52 (65.0)
Vitamins	29 (58.0)	14 (46.7)	43 (53.8)
Drugs for Constipation	24 (48.0)	19 (63.3)	43 (53.8)
Drugs for Acid Related Disorders	22 (44.0)	19 (63.3)	41 (51.3)
Lipid Modifying Agents	27 (54.0)	14 (46.7)	41 (51.3)
Mineral Supplements	25 (50.0)	16 (53.3)	41 (51.3)
Antiemetics and Antinauseants	23 (46.0)	16 (53.3)	39 (48.8)
Antihistamines for Systemic Use	27 (54.0)	12 (40.0)	39 (48.8)
Psycholeptics	25 (50.0)	13 (43.3)	38 (47.5)
Agents Acting on the Renin-Angiotensin System	21 (42.0)	10 (33.3)	31 (38.8)
Beta Blocking Agents	20 (40.0)	9 (30.0)	29 (36.3)
Antithrombotic Agents	18 (36.0)	10 (33.3)	28 (35.0)
Diuretics	16 (32.0)	12 (40.0)	28 (35.0)
Anesthetics	18 (36.0)	9 (30.0)	27 (33.8)
Blood Substitutes and Perfusion Solutions	14 (28.0)	11 (36.7)	25 (31.3)
Corticosteroids for Systemic Use	15 (30.0)	9 (30.0)	24 (30.0)
Stomatological Preparations	15 (30.0)	7 (23.3)	22 (27.5)
Thyroid Therapy	15 (30.0)	7 (23.3)	22 (27.5)
Drugs for Obstructive Airway Diseases	14 (28.0)	8 (26.7)	22 (27.5)
Psychoanaleptics	10 (20.0)	10 (33.3)	20 (25.0)
Antiinflammatory and Antirheumatic Products	15 (30.0)	5 (16.7)	20 (25.0)
Antianemic Preparations	12 (24.0)	6 (20.0)	18 (22.5)
Antidiarrheals, Intestinal Antiinflammatory/Antiinfective agents	12 (24.0)	6 (20.0)	18 (22.5)
Urologicals	9 (18.0)	8 (26.7)	17 (21.3)

NOTE: Concomitant medications were defined according to Section 7.4.3 in the SAP (Appendix 16.1.9).
Source: Table 14.2.2

Hematopoietic growth factors were not to be routinely used. However, short-term use of granulocyte colony-stimulating factor for febrile neutropenia was permitted at the discretion of the treating physician and was to be guided by accepted practice or institutional guidelines.

Assessor's comment

Concomitant use of supportive treatment was allowed as per investigators discretion. Use of ESA was not prohibited.

Concomitant supportive treatment should be provided for the MDS IPSS-R >3.5 population. This should also specify BM>5%, ≤5% and total. (**OC**)

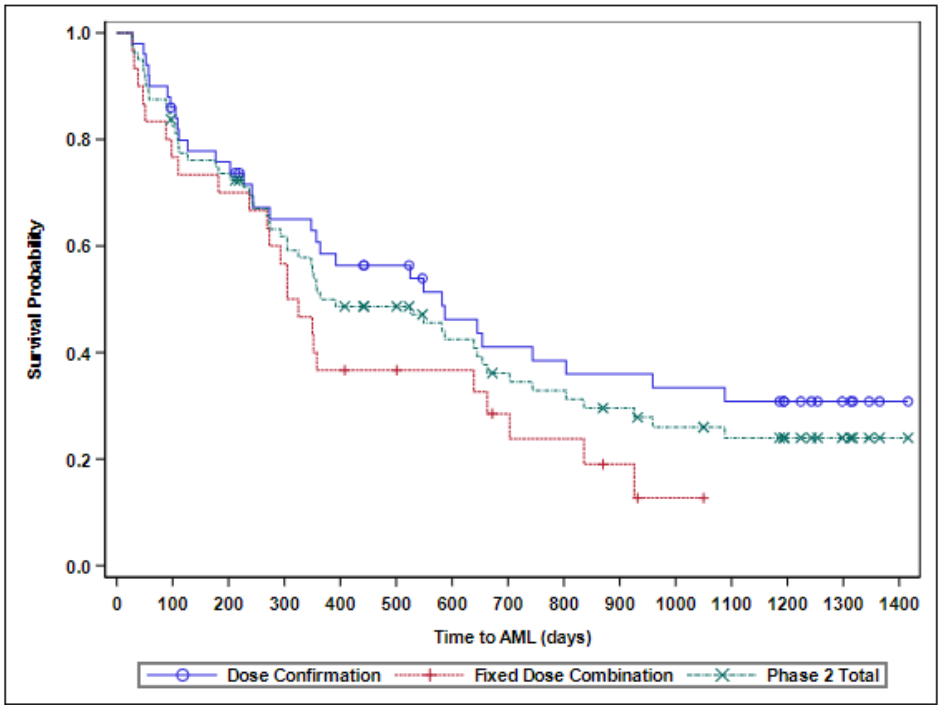
Time to AML or Death

Table 41. Time to AML or Death (efficacy analysis set)

Characteristics	Dose Confirmation Stage (N=50)	Fixed-Dose Combination Stage (N=30)	Phase 2 Overall (N=80)
Number of Subjects, (n (%))			
Censored	19 (38.0)	6 (20.0)	25 (31.3)
Event	31 (62.0)	24 (80.0)	55 (68.8)
K-M Estimate (Days, (95% CI))			
25th percentile	203.0 (96.0, 348.0)	110.0 (38.0, 273.0)	177.0 (96.0, 273.0)
Median	582.0 (274.0, 959.0)	315.0 (237.0, 639.0)	364.0 (305.0, 654.0)
75th percentile	NE (744.0, NE)	703.0 (352.0, NE)	1088.0 (703.0, NE)

AML=acute myeloid leukemia; CI=confidence interval; K-M=Kaplan-Meier; NE=not estimable
Source: Table 14.3.4.1

Figure 12. Kaplan-Meier Estimate for Time to AML or Death (efficacy analysis set)



Assessor's comment

This is in essence a SAT for efficacy assessment, hence time to event endpoints are not fit for efficacy assessments. No inferences can be drawn regarding Time to AML or Death.

For completeness LFS should be provided for MDS IPSS-R >3.5 patients in both tabulated format and in KM curves. This should also specify BM>5%, ≤5% (**OC**).

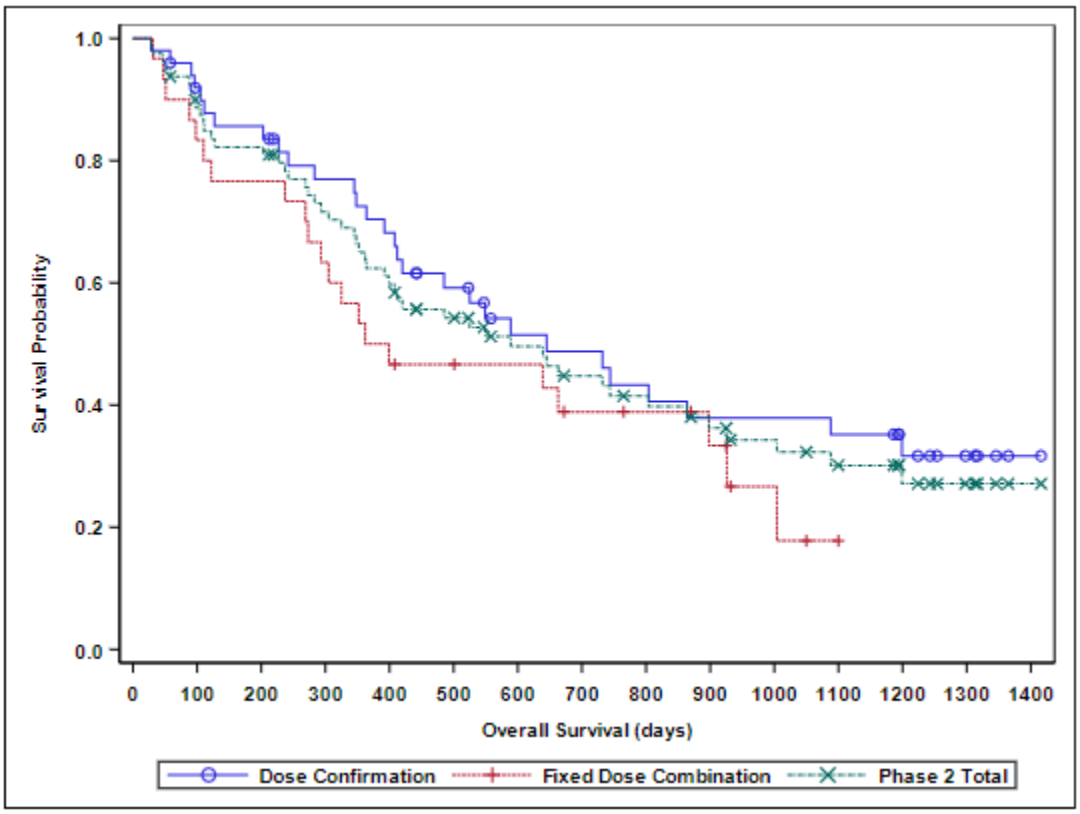
Overall Survival

Table 42. Overall Survival (efficacy analysis set)

Characteristics	Dose Confirmation Stage (N=50)	Fixed-Dose Combination Stage (N=30)	Phase 2 Overall (N=80)
Number of Subjects, (n (%))			
Censored	21 (42.0)	9 (30.0)	30 (37.5)
Event	29 (58.0)	21 (70.0)	50 (62.5)
K-M Estimate (Days, (95% CI))			
25th percentile	345.0 (111.0, 420.0)	237.0 (51.0, 305.0)	273.0 (111.0, 352.0)
Median	645.0 (412.0, 1088.0)	380.5 (273.0, 926.0)	589.0 (392.0, 864.0)
75th percentile	NE (864.0, NE)	1004.0 (639.0, NE)	NE (898.0, NE)

CI=confidence interval; K-M=Kaplan-Meier; NE=not estimable
Source: Table 14.3.5.1

Figure 13. Kaplan-Meier Estimate for Overall Survival (efficacy analysis set)



Assessor's comment

This is in essence a SAT for efficacy assessment, hence time to event endpoints are not fit for efficacy assessments. No inferences can be drawn regarding OS.

For completeness OS should be provided for MDS IPSS-R >3.5 patients in both tabulated format and in KM curves. This should also specify BM>5%, ≤5% (**OC**).

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 1. Summary of efficacy for trial ASTX727-02 NA

Title: A Phase 3, Randomized, Open-Label, Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) versus IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML)		
Study identifier	Protocol Number: ASTX727-02 Study Identifier ASTX727-02 NA CSR Number: ASTX727-02-B Trial Registry Number: NCT03306264 EudraCT Number: N/A for MDS/CMML part of the study	
Design	Phase 3, multicentre, randomised, open-label, 2-period (cycle), 2-sequence crossover study comparing decitabine AUC equivalence of ASTX727 and IV decitabine. Eligible subjects were randomly assigned in a 1:1 ratio to a treatment sequence for the first two cycles (Sequence A: ASTX727 in Cycle 1 and IV decitabine Cycle 2; or Sequence B: IV decitabine in Cycle 1 and ASTX727 in Cycle 2)	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	After completion of the first two 28-day treatment cycles, subjects continued to receive treatment with ASTX727 in 28-day cycles until disease progression, unacceptable toxicity, or the subject decides to discontinue treatment or withdraw from the study. Not applicable Not applicable
Hypothesis	The oral dose of ASTX727 will be considered equivalent to IV decitabine if the two-sided 90% CI ratio of the 5-day total decitabine AUC_{0-24} LS means of oral ASTX727 relative to IV decitabine lies entirely within the range of 0.80 – 1.25	
Treatments groups	IV decitabine	**Treatment:** 20 mg/m^2 decitabine by continuous 1-hour IV infusion Daily×5 in 28-day cycles. **Duration:** 1 28-day cycle (either Cycle 1 or Cycle 2) **Number randomized/treated:** 138/132
	ASTX727 Oral FDC	**Treatment:** one ASTX727 FDC tablet (35 mg decitabine/100 mg cedazuridine) administered orally Daily×5 in 28-day cycles **Duration:** until disease progression, unacceptable toxicity, treatment discontinuation or withdrawal from the study. **Number randomised/treated:** 138/130

Endpoints and definitions	Primary endpoint	5-day AUC_{0-24} (h*ng/mL)	**5-day decitabine AUC** AUC estimated from 5 days of dosing with: • Oral ASTX727 (FDC tablet) • IV decitabine
	Secondary endpoint	Maximum %*LINE-1* demethylation	**Maximum %*LINE-1* demethylation from baseline** Defined as the largest percent decrease from baseline methylation values within a subject between Day 8 and Day 22 of Cycle 1 and Cycle 2)
	Secondary endpoint	CR PR mCR HI OR [CR+PR+mCR+HI] mCR with HI	**Response rate** Response based on IWG 2006 MDS Response Criteria (Cheson et al 2006).
	Secondary endpoint	TI	**Post-treatment transfusion independence rate** Calculated separately for red blood cell (RBC) transfusion independence and platelet transfusion independence as the number of subjects who were transfusion independent post treatment divided by the number of subjects who were transfusion dependent at baseline.
	Secondary endpoint	LFS	**Leukemia-free survival** Defined as the number of days from the date of randomisation to the date when blasts in bone marrow or peripheral blood reach ≥20%, or death from any cause.
	Secondary endpoint	OS	**Overall survival** Defined as the number of days from the date of randomisation to the date of death from any cause.
Database lock	07 June 2021		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**Primary PK Analysis Set: 5-day decitabine AUC** All subjects who received 5-day dosing of ASTX727 and IV decitabine in Cycles 1 and 2 and who met the following criteria for both ASTX727 and IV decitabine dosing and PK assessments: • ASTX727: received full dose of ASTX727 (ie, Days 1 through 5) within 3 hours of the intended dosing time, and no vomiting occurred within 6 hours of dosing. • IV decitabine: received the full dose as a 1-hour infusion. • Subjects in this analysis set had at least 1 evaluable day of decitabine AUC_{0-24} measurement in the IV decitabine cycle, either Day 1 or Day 5. When both days were available, the average value was used to calculate total 5-day AUC_{0-24}. If data from 1 of the 2 available IV days were deemed to be extreme outlier and excluded, the data from the other IV day (Day 1 or Day 5) was used for analysis.		

Descriptive statistics and estimate variability	Treatment group	IV decitabine	ASTX727 Oral FDC
	Number of subjects	123	123

	5-day AUC_{0-t} (h*ng/mL) (Geometric LSM)	864.94		855.69	
Effect estimate per comparison	Primary endpoint	Comparison groups		ASTX727 Oral FDC IV decitabine	
		Ratio of Geometric LSM (Oral/IV)		98.93	
		80% CI		92.66, 105.6	
		Intra-subject variability (%CV) (based on ANOVA)		31.7	
Notes					
Analysis description	**Secondary Analysis**				
Analysis population and time point description	**PD Analysis Set: Maximum %*LINE-1* demethylation from baseline** Subjects who received any amount of study treatment and had *LINE-1* methylation data at baseline (Day 1) of Cycle 1 or 2 and on either Day 8 or Day 15 of the respective cycle to assess post-treatment demethylation.				
Descriptive statistics and estimate variability		**Cycle 1**		**Cycle 2**	
	Treatment group	IV decitabine	ASTX727 Oral FDC	IV decitabine	ASTX727 Oral FDC
	Number of subjects	62	62	63	63
	Maximum %*LINE-1* demethylation (LSM)	14.019	13.289	11.968	11.151
	95% CI	12.528, 15.510	11.798, 14.780	10.503, 13.434	9.685, 12.616
Effect estimate per comparison	Primary endpoint	Comparison groups	ASTX727 Oral FDC IV decitabine		
		Difference (Oral - IV)	**Cycle 1**	**Cycle 2**	
			-0.730	-0.818	
		95% CI (based on ANOVA)	-2.838, 1.378	-2.890, 1.255	
Notes					
Analysis description	**Secondary Analysis**				
Analysis population and time point description	**IPSS-R >3.5: Response rate** All subjects who received any amount of study treatment. No subjects were excluded because of protocol deviations.				
Descriptive statistics and estimate variability	Treatment group	IPSS-R >3.5			
	Number of subjects	67			
		n (%)	95% CI		
	CR	16 (23.9)	(14.3, 35.9)		
	PR	0			
	mCR	25 (37.3)	(25.8, 50.0)		
	HI	3 (4.5)	(0.9, 12.5)		

	OR [CR+PR+mCR+HI]	44 (65.7)	(53.1, 76.8)
	mCR with HI	13 (19.4)	(10.8, 30.9)
Effect estimate per comparison	Primary endpoint	Comparison groups	NA
Notes			
Analysis description	**Secondary Analysis**		
Analysis population and time point description	**Duration of CR in patients with IPSS-R >3.5**		
Descriptive statistics and estimate variability	Treatment group	Patients achieving CR	
	Number of subjects	16	
	Median, months	14.1	
	95% CI	(8.3, 18.1)	
Effect estimate per comparison	Primary endpoint	Comparison groups	NA

Table 2. Summary of efficacy for trial ASTX727-01-B

Title: A Phase 1-2 Pharmacokinetic Guided Dose-Escalation and Dose-Confirmation Study of ASTX727, a Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine in Subjects with Myelodysplastic Syndromes (MDS) Phase 2 Dose Confirmation and Fixed-Dose Combination		
Study identifier	Protocol Number: ASTX727-01 Study Identifier ASTX727-01 CSR Number: ASTX727-01-B Trial Registry Number: NCT02103478 EudraCT Number: N/A	
Design	Phase 2, multicentre, randomised, open-label, 2-period, 2-sequence crossover study comparing decitabine AUC equivalence of ASTX727 and IV decitabine	
	Duration of main phase:	After completion of the first two 28-day treatment cycles, subjects continued to receive treatment with ASTX727 in 28-day cycles until disease progression, unacceptable toxicity, or the subject decides to discontinue treatment or withdraw from the study.
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	**Dose Confirmation Stage:** The dose of oral decitabine + E7727 identified in the Dose Escalation Stage administered daily×5 that achieves mean decitabine AUC (estimated from 5 days of dosing) and LINE-1 DNA demethylation comparable to that of IV decitabine 20 mg/m2 daily×5. **FDC Stage:** The ASTX727 FDC tablet achieves mean decitabine AUC (estimated from 5 days of dosing) and LINE-1 DNA demethylation similar to that for IV decitabine 20 mg/m2 daily×5.	

Treatments groups	IV decitabine	**Treatment:** 20 mg/m^2 decitabine by continuous 1-hour IV infusion Daily×5 in 28-day cycles. **Duration:** 1 28-day cycle (either Cycle 1 or Cycle 2) **Number randomized/treated:** *Dose Confirmation Stage:* 52/48 *FDC Stage:* 34/27
	ASTX727 Oral decitabine + cedazuridine	**Treatment:** 35 mg decitabine (one 20-mg capsule + three 5-mg capsules) administered orally concomitantly with 100 mg cedazuridine (five 20-mg capsules) Daily×5 in 28-day cycles **Duration:** until disease progression, unacceptable toxicity, treatment discontinuation or withdrawal from the study. **Number randomized/treated:** *Dose Confirmation Stage:* 52/49
	ASTX727 Oral FDC	**Treatment:** one ASTX727 FDC tablet (35 mg decitabine/100 mg cedazuridine) administered orally Daily×5 in 28-day cycles

			Duration: until disease progression, unacceptable toxicity, treatment discontinuation or withdrawal from the study. **Number randomized/treated:** *FDC Stage:* 34/29
Endpoints and definitions	Primary endpoint	5-day AUC_{0-t} (h*ng/mL)	**5-day decitabine AUC** AUC estimated from 5 days of dosing with: • Oral ASTX727 (capsules) - *Dose Confirmation Stage* • Oral ASTX727 (FDC tablet) - *FDC Stage* • IV - *Dose Confirmation Stage and FDC Stage*
	Primary endpoint	Maximum %*LINE-1* demethylation	**Maximum %*LINE-1* demethylation from baseline** Defined as the largest percent decrease from baseline methylation values within a subject between Day 8 and Day 22 of Cycle 1 and Cycle 2)
	Primary endpoint	CR PR mCR HI OR [CR+PR+mCR+HI] mCR with HI	**Response rate** Response based on IWG 2006 MDS Response Criteria (Cheson et al 2006).
	Secondary endpoint	DoCR DomCR DoBR	**Duration of response** Defined for responders, separately for CR, PR, mCR, and CR+PR+mCR as the number of days from the first time a response category (CR, PR, and mCR) was initiated to the date of disease progression.
	Secondary endpoint	TI	**Post-treatment transfusion independence rate**

			Calculated separately for red blood cell (RBC) transfusion independence and platelet transfusion independence as the number of subjects who were transfusion independent post treatment divided by the number of subjects who were transfusion dependent at baseline.
	Secondary endpoint	TTAML	**Time to AML** Defined as the number of days from the date the subject received the first dose of study treatment to the date of MDS progression to AML as defined by ≥20% blasts in bone marrow or peripheral blood; or death from any cause.
	Secondary endpoint	OS	**Overall Survival** Defined as the number of days from the date the subject received the first dose of study treatment to the date of death (regardless of cause).
Database lock	16 September 2020		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**Primary PK Analysis Set - 5-day decitabine AUC** All randomised subjects who received 2 cycles of treatment and who had sufficient plasma concentration data to allow AUC_{0-t} determination for each cycle. *Dose Confirmation Stage*: data were reviewed after 6 to 12 subjects had complete PK and PD data from Cycles 1 and 2 to confirm the doses of the ASTX727 components. *FDC Stage:* data from subjects who had complete PK and PD data from Cycles 1 and 2 were reviewed to confirm that data with the ASTX727 FDC tablet were similar to data with IV decitabine.		
Dose Confirmation Stage			
Descriptive statistics and estimate variability	Treatment group	IV decitabine	ASTX727 Oral decitabine + cedazuridine
	Number of subjects	40	40
	5-day AUC_{0-t} (h*ng/mL) (Geometric LSM)	802.81	750.82
Effect estimate per comparison	Primary endpoint	Comparison groups	ASTX727 Oral decitabine + cedazuridine IV decitabine
		Ratio of Geometric LSM (Oral/IV)	93.52
		80% CI Intra-subject variability (%CV) (based on ANOVA)	82.10, 106.5 47.0
FDC Stage			
Descriptive statistics and estimate variability	Treatment group	IV decitabine	ASTX727 Oral FDC
	Number of subjects	24	24
	5-day AUC_{0-t} (h*ng/mL) (Geometric LSM)	745.26	727.29
Effect estimate per comparison	Primary endpoint	Comparison groups	ASTX727 Oral FDC IV decitabine
		Ratio of Geometric LSM (Oral/IV)	97.59
		80% CI Intra-subject variability (%CV) (based on ANOVA)	80.48, 118.3 53.8

Notes					
Analysis description	**Primary Analysis**				
Analysis population and time point description	**PD Analysis Set - Maximum %*LINE-1* demethylation from baseline** All randomised subjects who received at least one cycle (Days 1 through 5) of study treatment and had baseline and Day 8 or Day 15 *LINE-1* methylation data. *Dose Confirmation Stage*: data were reviewed after 6 to 12 subjects had complete PK and PD data from Cycles 1 and 2 to confirm the doses of the ASTX727 components. *FDC Stage:* data from subjects who had complete PK and PD data from Cycles 1 and 2 were reviewed to confirm that data with the ASTX727 FDC tablet were similar to data with IV decitabine.				
Dose Confirmation Stage					
Descriptive statistics and estimate variability		**Cycle 1**		**Cycle 2**	
	Treatment group	IV decitabine	ASTX727 Oral decitabine + cedazuridine	IV decitabine	ASTX727 Oral decitabine + cedazuridine
	Number of subjects	24	24	22	22
	Maximum %*LINE-1* demethylation (LSM)	11.303	11.159	9.920	9.833
	95% CI	9.167, 13.439	9.023, 13.294	7.534, 12.307	7.446, 12.219
Effect estimate per comparison	Primary endpoint	Comparison groups		ASTX727 Oral decitabine + cedazuridine IV decitabine	
				Cycle 1	**Cycle 2**
		Difference (Oral - IV)		-0.144	-0.087
		95% CI (based on ANOVA)		-3.165, 2.876	-3.463, 3.288
FDC Stage					
Descriptive statistics and estimate variability		**Cycle 1**		**Cycle 2**	
	Treatment group	IV decitabine	ASTX727 Oral FDC	IV decitabine	ASTX727 Oral FDC
	Number of subjects	14	16	11	9
	Maximum %*LINE-1* demethylation (LSM)	12.665	10.077	8.230	8.134
	95% CI	10.12, 15.211	7.696, 12.459	4.887, 11.574	4.438, 11.830
Effect estimate per comparison	Primary endpoint	Comparison groups		ASTX727 Oral FDC IV decitabine	

				Cycle 1	**Cycle 2**	
		Difference (Oral - IV)		-2.588	-0.096	
		95% CI (based on ANOVA)		-6.074, 0.899	-5.080, 4.888	
Notes						
Analysis description	**Primary Analysis**					
Analysis population and time point description	**IPSS-R >3.5 - Response rate** Included data from all randomised subjects who received any amount of study treatment.					
Descriptive statistics and estimate variability		**Dose Confirmation Stage**		**FDC Stage**		
	Treatment group	All Subjects		All Subjects		
	Number of subjects	50		30		
		n (%)	95% CI	n (%)	95% CI	
	CR	7 (14.0)	5.8, 26.7	7 (23.3)	9.9, 42.3	
	PR	0		0		
	mCR	14 (28.0)	16.2, 42.5	5 (16.7)	5.6, 34.7	
	HI	8 (16.0)	7.2, 29.1	7 (23.3)	9.9, 42.3	
	OR [CR+PR+mCR+HI]	29 (58.0)	43.2, 71.8	19 (63.3)	43.9, 80.1	
	mCR with HI	5 (10.0)	3.3, 21.8	1 (3.3)	0.1, 17.2	
Effect estimate per comparison	Primary endpoint	Comparison groups		NA		
Notes						
Analysis description	**Secondary Analysis**					
Analysis population and time point description	**Duration of CR in patients with IPSS-R >3.5**					
Descriptive statistics and estimate variability	Treatment group	Patients achieving CR				
	Number of subjects		6			
	Median, months		4.7			
	95% CI		(1.1, NE)			

Effect estimate per comparison	Primary endpoint	Comparison groups	NA

3.4.8. Supportive study(ies)

Phase 3 Randomised Studies with Decitabine in MDS/CMML

Two randomised studies (Kantarjian 2006, Lubbert 2011) explored best supportive care vs. IV decitabine using a regimen given at 15 mg/m^2 every 8 hours on Days 1-3 on 6-week dosing cycles. Both studies suggested positive clinical effects; however, these effects (clinical responses, hematologic improvement, improved event-free survival [EFS], and improved patient reported outcomes) did not translate into statistically significant improvement in overall survival.

The Kantarjian study resulted in approval of the 3-day (every 8-hour) decitabine regimen in the US.

Assessor's comment

Two RCTs have been conducted with IV decitabine 3-day regimen vs. best supportive care. The Kantarijan trial had ORR and time to AML transformation or death as co-primary endpoints. The ORR endpint was statistically significant. The Lübbert trial had OS as a primary endpoint and failed to meet this (HR: 0.88 95% CI 0.66, 1.17; two-sided p=0.38). An OS benefit for decitabine 3-day regimen over BSC have not been shown and IV decitabine does not have an approval for use in MDS in EU

Dose Optimisation of IV Decitabine – Initial 3 Day Regiment to a 5 Day Regiment

A different regiment for IV decitabine have been explored in several studies. A single-centre study, used an adaptive, randomised design, to evaluate multiple regimens: 20 mg/m^2 Days 1-5 every 28 days, 20 mg/m^2 subcutaneous (SC) twice a day (BID) on Days 1-5 every 28-day cycle, or 10 mg/m^2 IV daily on Days 1-10 every 28-day cycle (Kantarjian 2007). Furthermore, this 20 mg/m^2 Days 1-5 every 28 days regimen was studied in a multicentre Phase 2 trial focusing on the potential for an outpatient regimen (Steensma 2009). This study led to the approval of this posology in US.

Assessor's comment

The approved posology for Dacogen in EU for the AML indication is the 5-day regimen. This is also the approved posology by FDA for the MDS/CMML indication.

Key SAT Using the 5 Day Regiment of IV Decitabine

A meta-analysis comparing the 3- and 5-day regimens of IV decitabine based on 15 randomised controlled studies in 1278 patients with MDS/CMML have been presented (Yang 2017). The median OS for subjects given decitabine over a 3-day dosing schedule, a 5-day dosing schedule, or BSC ranged between 10.1 to 15 months, 11.9 to 22 months, and 8.5 to 14.9 months, respectively, with some variability among the studies. Compared to the 3-day regimen, subjects treated with the 5-day regimen had greater overall response (OR) (P=0.003; 25% and 51%, respectively) and CR rates (P=0.016; 13.7% and 24.2%, respectively).

Assessor's comment

The claimed supportive studies for the 5-day regimen are all SAT and hence time to event endpoint such as OS cannot be assessed based on these.

The metanalysis claims to aim at comparing efficacy and tolerability of different decitabine doses for treating intermediate and/or high-risk MDS. The highest CR rate is claimed to be found for the 100

mg/m2 course subgroup, i.e. the 5 day regimen. However, no head to head studies of the 3-day and the 5-day regimen have been presented.

Overall, the CR rates presented from the commented trials with IV decitabine appears to be in a similar range as the CR rates presented from the Inaqovi studies. However, this should be interpreted with caution considering that this is a cross study comparison of single arm trials.

IV Decitabine in the Context of HMAs and Real-World Data

No head-to-head studies have been conducted comparing decitabine vs. azacitidine to compare relative efficacy. Indirect comparisons have been made using methods such as network meta-analyses and registry follow-up, typically from regions where both agents are approved. A network meta-analysis compared 4 randomised studies (2 with azacitidine, 2 with decitabine) and concluded that both agents were broadly therapeutically equivalent (Almasri 2018). A population-based analysis studied some 973 high-risk MDS patients receiving HMA treatment in the US and noted no difference in mOS (13.4 months for azacitidine vs. 15.2 months for decitabine) (Zeidan 2022c).

Assessor's comment

No systematic literature review has been presented.

The applicant claims that published studies and indirect comparisons of the clinical experience over more than a decade of global use of the 2 approved HMAs (azacitidine and decitabine) suggests similar overall clinical activity. Any comparison to azacytidine is not supported by any evidence of similar exposure. Hence, no efficacy claims in relation to azacytidine can be accepted.

ASTX727-02 EU (phase 3 AML pivotal study) - Final efficacy data

At approval, Inaqovi, the CSR for the pivotal study was based on DCO 12 November 2021. With this variation the final database lock 25 May 2023 is included. Section 5.1 of the SmPC (DOR of CR and frequency of transfusion dependent patients) is suggested to be updated based on the final data.

Median follow-up time estimated using the reverse Kaplan-Meier method was 23.6 months (95% CI of 20.5, 24.5).

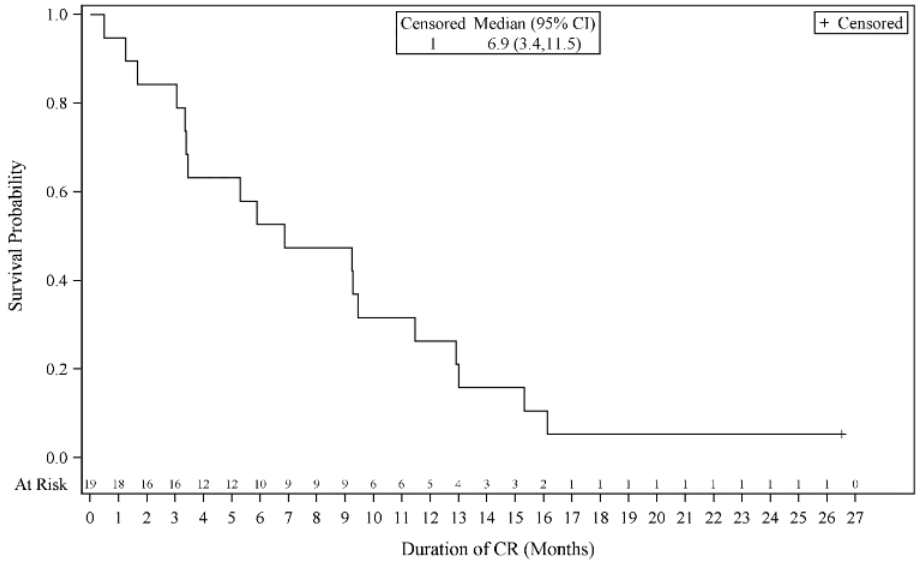
Median time to CR for subjects who achieved CR was 3.02 months (min, max: 1.9, 7.5 months).

Table 43. Duration of Response for Subjects who Achieved Complete Response (Efficacy Analysis Set)

Characteristics	Total (All Treated Subjects) (N=87)
Number of Subjects, n (%)	
Censored	1 (5.3)
Event	18 (94.7)
Death	3 (15.8)
Relapse	15 (78.9)
Start of new anticancer therapy (excluding HCT)	0
K-M Estimate, Months, (95% CI)	
25th percentile	3.4 (0.5, 5.9)
Median	6.9 (3.4, 11.5)
75th percentile	12.9 (6.9, 16.1)

CI=confidence interval; CR=complete response; HCT=hematopoietic stem cell transplant; K-M=Kaplan-Meier; N=total number of subjects; n=a subset of subjects
Subjects included in Duration of CR Analysis are subjects with a best response of CR (see Table 14.3.1).

Figure 14. Kaplan-Meier Plot for Duration of Response for Subjects who Achieved Complete Response (Efficacy Analysis Set)



CI=confidence interval; CR=complete response; NE=not estimable
Source: Figure 14.3.4.4

Overall, of the 87 subjects assessed for response, 41 subjects were dependent on any transfusion at baseline. Of these 41 subjects, 27 (65.9%) remained transfusion dependent postbaseline and 14 (34.1%) became transfusion independent postbaseline. Conversely, of the 46 subjects who were independent of any transfusion at baseline, 30 (65.2%) became transfusion dependent postbaseline and 16 (34.8%) subjects remained transfusion independent postbaseline. A subject was considered transfusion independent if the subject was both RBC and platelet transfusion free post-treatment for any ≥56 consecutive days.

Assessor's comment

Overall, the results are consistent with the previously presented. For the core data there were no changes to the response rates presented for the final analysis and the previous. The substantially increased follow-up time renders a slightly longer median DoR of patients with CR. For the patients that were independent of transfusions at baseline 4 more (12 vs. 16 out of 46) later had a period of transfusion independence for any ≥56 consecutive days post transfusion. The updates requested by the MAH for AML in the SmPC section 5.1 is considered acceptable.

Please refer to SmPC comments for the proposed updates.

3.4.9. Discussion on clinical efficacy

The applicant has applied to extend the marketing authorisation of Inaqovi. The latest proposal for new indication for Inaqovi is "*as monotherapy for the treatment of adult patients with myelodysplastic syndromes (MDS) and a risk score of >3.5 according to the revised international prognostic scoring system (IPSS-R).*"

Design and conduct of clinical studies

Two clinical studies have been performed to support the new indication, ASTX727-02 NA and ASTX727-01-B.

Study ASTX727-02 NA

A Phase 3, Randomized, Open-Label, Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) versus IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukaemia (CMML).

Patients were randomized 1:1 to receive oral decitabine/cedazuridine tablets 100/35 mg on days 1–5 of cycle 1 (28 days) and IV decitabine 20 mg/m2 on days 1–5 of cycle 2 (28 days) or the reverse sequence. From cycle 3 onwards, all patients received decitabine/cedazuridine 100/35 mg orally once daily on days 1–5 of each 28-day cycle until disease progression or unacceptable toxicity.

Primary objective of the ASTX727-02 NA study was to assess equivalence of 5-day dosing between ASTX727 and IV decitabine which was assessed in a primary analysis of 5-day AUC_{0-24} parameters for both treatments. Equivalence was to be established using a standard approach based on two-sided 90% CI of the AUC_{0-24} ratio between treatments that was to be contained entirely within the range of 0.80 – 1.25. The analysis method is acceptable. The PK/PD bridge is supported by similar LINE-demethylation.

Efficacy variables were secondary and analysed using descriptive statistics. No comparison was planned between the treatment groups, which is rational since PK equivalence was shown. Therefore, the study may effectively be viewed as a SAT with respect to the assessment of objective responses.

In summary, the evaluation of efficacy of ASTX727 in study ASTX727-02 NA is limited due to the single arm design, with no statistical inference. Efficacy results are exploratory.

The statistical analysis plan was finalised during the ongoing open-label study, which cannot exclude that the analysis plan was not influenced by data on hand.

Response rates was assessed based on modified IWG 2006 MDS criteria. At study entry, patients could potentially already fulfil one or more of the CR criteria. In the IPSS-R >3.5 subgroup consisting of 67 patients, 41 had BM blasts >5%. The clinical benefit of achieving CR in high-risk MDS need to be justified.

Study ASTX727-01-B

A Phase 1-2 Pharmacokinetic Guided Dose-Escalation and Dose-Confirmation Study of ASTX727, a Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine in Subjects with
Myelodysplastic Syndromes (MDS). This first-in-human trial, ASTX727-01, had 3 stages: Phase 1 Dose Escalation, Phase 2 Dose Confirmation, and Phase 2 fixed dose combination (FDC). Focus here are the Phase 2 parts ie, the Dose Confirmation Stage and FDC Stage of study ASTX727-01.

Patients were randomized 1:1 to receive oral decitabine/cedazuridine (doses 100/35 mg respectively) on days 1–5 of cycle 1 (28 days) and IV decitabine 20 mg/m2 on days 1–5 of cycle 2 (28 days) or the reverse sequence. From cycle 3 onwards, all patients received decitabine/cedazuridine 100/35 mg orally once daily on days 1–5 of each 28-day cycle.

Analysis data sets and methods of statistical analyses were principally similar as described for the main study ASTX727-02.

There were 3 primary endpoints specified study ASTX727-01-B: mean decitabine AUC (estimated from 5 days of dosing) and mean maximum %LINE-1 demethylation after ASTX727 administration compared with IV decitabine 20 mg/m2, as well as response rate in all subjects.

According to the statistical analysis plan (SAP), equivalence of AUC between treatments was to be determined using two-sided 90% CI of the AUC ratio. However, while the SAP did not stipulate any pre-defined equivalence (acceptance) range for the 90% CI, both the clinical study protocol and the clinical study report states that for the primary objective of the study to be achieved, the ratio of

geometric least squares means and its 80% CI must have been fully contained within the prespecified limits of 75-133 (Dose Confirmation Stage) or 65-153.9 (FDC Stage).

Similarly, to what is noted in the ASTX727-02 NA study, the purpose of the cross-over study design in the first 2 cycles was to evaluate equivalence based on the PK data, while rest of the study period has a single arm design. Presentation of efficacy results was therefore limited to summaries for all patients in the study, or summaries by treatment sequence. Efficacy results of the 2 treatments cannot be separated from each other.

The study conduct included adaptive elements and the application of wider than usual confidence intervals for equivalence. With consideration to the seemingly data driven adaptions of the data analyses, and limitations in study design and analysis, the study results may only be considered for exploratory purpose.

Response rates was assessed based on modified IWG 2006 MDS criteria. At study entry, patients could potentially already fulfil one or more of the CR criteria. In the IPSS-R >3.5 subgroup consisting of 36 patients, 24 had BM blasts >5%. The clinical benefit of achieving CR in high-risk MDS need to be justified.

Efficacy data and additional analyses

Study ASTX727-02 NA

The first subject was randomized on 13 February 2018, and the last subject was randomized on 03 January 2019. A total of 138 subjects were randomised to a treatment sequence in the ASTX727-02 NA study (N=69 each to Sequence A and Sequence B), and 133 received treatment. Median follow up was 155 days (min, max: 57, 397 days). Patients included within the currently proposed indication was 67.

The study was conducted in North America and in Canada.

Database lock presented is 07 June 2021 and represents the final analysis. This was performed after all subjects had completed at least 6 months of follow up or had permanently discontinued prior to 6 months of follow up from their first treatment dose.

Regarding the CR criteria, it is noted that in the IPSS-R >3.5 subgroup 61.2% had >5% BM blasts at inclusion. Furthermore, 9.0% have Hgb ≥110g/L, 31.3% have platelets ≥100x10^9/L and 50.7% have neutrophils ≥1x10^9/L. Hence, a large proportion of patients fulfil at least some key element of the CR criteria already at baseline.

Current prognostic systems include IPSS-R and IPSS-M. The IPSS-R system was presented 2012 as an improvement of IPSS. Reclassification of MDS patients using IPSS-R was done post hoc. 13 patients could not be re-classified. The IPSS-intermediate 1 group seem to distribute evenly between the IPSS-R lower-risk and higher-risk group defined by IPSS-R ≤ 3.5 and >3.5 respectively, while the majority of IPSS-intermediate 2 patients end up in the IPSS-R high group.

The primary endpoint shows that the two-sided 90% CIs of the 5-day AUC 0-24 ratios of geometric LSM for oral relative to IV are contained entirely within the prespecified range of 0.80 to 1.25 for the primary analysis. Similar exposure between oral and IV decitabine have been shown. For further discussion see 3.3.3. However, considering that decitabine is not authorised in the EU for use in MDS, a B/R conclusion based on simple PK bridging is not possible.

Since exposure was similar for the i.v. decitabine and Inaqovi, this allows for the treatment of this study with a PK cross-over design as a single arm trial isolating the effect of Inaqovi e.g. in terms of CR/mCR.

CR was observed in 21.8% (95% CI 15.1, 29.8) of all 133 treated subjects. The overall response rate (CR+PR+mCR+HI) was 61.7% (95% CI 52.8, 69.9).

In the IPSS-R >3.5 subgroup currently proposed to be encompassed by the indication CR was observed in 23.9% (95% CI 14.3, 35.9) of 67 patients. Among the 41 patients with IPSS-R >3.5 and BM blasts >5% at inclusion 7 (17.1%, 95% CI 7.2, 32.1) reached CR.

The IPSS-R >3.5 subgroup is small thereby hampering conclusions regarding subgroups. However, across reported subgroups of IPSS high vs. INT-1/INT-2, baseline BM blast ≤5% vs. >5%, RBC baseline transfusion dependence and baseline platelet transfusion dependence the CR rate appear fairly consistent.

Median time to CR was 5.2 months (min, max: 2, 19) in patients with IPSS-R >3.5. Median duration of CR in patients with IPSS-R >3.5 was 14.1 months (95% CI 8.3, 18.1). Reasons for censoring in this analysis should be provided in a tabulated format **(OC)**.

This is in essence a SAT for efficacy assessment, hence time to event endpoints is not fit for efficacy inferences. No conclusions can be drawn regarding the impact of Inaqovi on Leukemia free survival and OS.

Of the 67 treated patients with IPSS-R >3.5, 14 (20.9%) went on to receive stem cell transplantation. Patients proceeding to SCT were considered to have discontinued Inaqovi. Conditioning regiments for these patients were not collected and patients were only followed for survival and LFS. This is a small subgroup and data have not been collected to substantiate any claims in regard to using Inaqovi for cytoreductive therapy prior to allo-SCT.

Study ASTX727-01-B

Of the 86 subjects randomized in Phase 2, 80 were treated, as follows:
- Dose Confirmation Stage: N=52 randomized; N=50 treated
- FDC Stage: N=34 randomized; N=30 treated

Of all randomized subjects, 6 subjects did not receive any study treatment.

Data are presented from the final CSR providing a median follow-up combined for all subjects in all stages (ie, n=80 overall in Phase 2) of 1563 days (min, max: 1199, 1710 days) from the last subject's first dose.

The study was conducted in North America, and in Canada.

Regarding CR criteria, it is noted that 66.7% of the 36 IPSS-R >3.5 patients had >5% BM blasts at inclusion. Furthermore, 8.3% have Hgb ≥110g/L, 27.8% have platelets $\geq 100 \times 10^9$/L and 36.1% have neutrophils $\geq 1 \times 10^9$/L. Hence, a large proportion of patients fulfil at least some key element of the CR criteria already at baseline.

Current prognostic systems include IPSS-R and IPSS-M. The IPSS-R system was presented 2012 as an improvement of IPSS. Reclassification of MDS patients using IPSS-R was done post hoc. 18 patients could not be re-classified.

The primary analysis for the dose confirmation stage of the primary study endpoint (5-day AUC0-t) shows that the ratio (oral/IV) of geometric LSM (93.52) and its 80% CI (82.10, 106.5) are contained within the prespecified CI limits of 75-133.

The analysis (paired group) for the FDC stage of the primary study endpoint (5-day AUC0-t) shows that the ratio (oral/IV) of geometric LSM (97.59) and its 80% CI (80.48, 118.3) are fully contained within the prespecified CI limits of 65-153.9.

Similar exposure between oral and IV decitabine have been shown.

In the Efficacy Set (N=80), 17.5% achieved a complete response (CR) (95% CI: 9.9, 27.6).

In the IPSS-R >3.5 subgroup currently proposed to be encompassed by the indication CR was observed in 16.7% (95% CI 6.4, 32.8) of 36 patients. Among the 24 patients with IPSS-R >3.5 and BM blasts >5% at inclusion 4 (16.7%, 95% CI 4.7, 37.4) reached CR.

Median time to CR was 4.3 months (min, max: 2, 6) in patients with IPSS-R >3.5. Median duration of CR in patients with IPSS-R >3.5 was 4.7 months (95% CI 1.1, NE). Reasons for censoring in this analysis should be provided in a tabulated format **(OC)**.

This is in essence a SAT for efficacy assessment, hence time to event endpoints is not fit for efficacy inferences. No conclusions can be drawn regarding the impact of Inaqovi on Leukemia free survival and OS.

Of the 36 treated patients with IPSS-R >3.5, 8 (22.2%) went on to receive stem cell transplantation. Patients proceeding to SCT were considered to have discontinued Inaqovi. Conditioning regiments for these patients were not collected and patients were only followed for survival and LFS. This is a small subgroup and data have not been collected to substantiate any claims in regard to using Inaqovi for cytoreductive therapy prior to allo-SCT.

Supportive studies

Published literature is summarized to support the application. No systematic literature review is presented.

Two RCTs have been conducted with IV decitabine 3-day regimen vs. best supportive care. The Kantarijan trial had ORR and time to AML transformation or death as co-primary endpoints. The ORR endpoint was statistically significant. The Lübbert trial had OS as a primary endpoint and failed to meet this (HR: 0.88 95% CI 0.66, 1.17; two-sided p=0.38). No OS benefit for decitabine 3-day regimen over BSC has been shown.

The claimed supportive studies for the 5-day regimen are all SAT and hence time to event endpoint such as OS cannot be assessed based on these.

The metanalysis claims to aim at comparing efficacy and tolerability of different decitabine doses for treating intermediate and/or high-risk MDS. The highest CR rate is found for the 100 mg/m2 course subgroup, i.e. the 5-day regimen.

Overall, the CR rates presented from the commented trials with IV decitabine appears to be in a similar range as the CR rates presented from the Inaqovi studies. However, this should be interpreted with caution considering that this is a cross study comparison of single arms.

The applicant claims that published studies and indirect comparisons of the clinical experience over more than a decade of global use of the 2 approved HMAs (azacitidine and decitabine) suggests similar

overall clinical activity. However, the equivalence of azacytidine and decitabine has not been established. No bridging to azacytidine claims is possible.

Overall issues regarding the efficacy evaluation

The fact that AUC was similar for the i.v. decitabine and Inaqovi, allows for the treatment of this study, with a PK cross-over design, as a single arm trial isolating the effect of Inaqovi in terms of CR. However, since there is no indication for MDS or CMML for i.v. decitabine in the EU, a PK bridging approach is not possible.

The treatment paradigm for MDS stipulates cytopenia management regardless of risk assessment, as well as the use of cytoreductive, potentially disease modifying agents in higher risk patients.

CR reflects near-normalized haematological parameters in the bone marrow with <5% blasts. Such normalisation is not anticipated without treatment. However, a large proportion of patients fulfilled one or several criteria for CR already at baseline. In total from both ASTX727-02 NA and ASTX727-01-B only 36 patients with IPSS-R >3.5 did not fulfil any of the CR criteria of IWG2023 at baseline, i.e. displaying BM blasts >5% and tri-linage cytopenia. This is a very limited, post hoc defined population determine established efficacy based on CR. Furthermore, the clinical benefit of achieving CR in high-risk MDS need to be justified. **(MOs)**

From both ASTX727-01-B and ASTX727-02 A, a total of 22 patients later had an allo-SCT. This is a small subgroup and data have not been collected to substantiate any claims in regard to using Inaqovi for cytoreductive therapy prior to allo-SCT. Also considering that the only potentially curative treatment for MDS patients is allo-SCT, the proposed indication needs to exclude patients intended for HSCT **(MO)**.

Additional expert consultation

A request for a SAG-O meeting has been discussed by the CHMP on the proposal from the Rapporteur but not further pursued.

3.4.10. Conclusions on the clinical efficacy

The applicant need justify that the outcomes of the study program demonstrate a methodologically robust and clinically meaningful modicum of efficacy. Moreover, it should be justified that relevant efficacy have been established for patients with MDS with IPSS-R >3.5 **(MOs)**.

3.5. Clinical safety

3.5.1. Introduction

ASTX727 (Inaqovi) is approved in the EU as monotherapy for the 'treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy,' which is aligned with the indication as already approved for intravenous (IV) decitabine.

The original MAA for AML was primarily based on a PK bridge, demonstrating similar systemic exposure to decitabine following administration of ASTX727 and intravenous decitabine. In addition, data from the three main studies with ASTX727 (one study in AML and two in MDS/CMML) supported the conclusion that the oral administration and the addition of cedazuridine did not relevantly affect the safety profile of decitabine as compared with intravenous administration.

With the current application, the following new indication is presently proposed for Inaqovi:

- as monotherapy for the treatment of adult patients with myelodysplastic syndromes (MDS) and a risk score of >3.5 according to the revised international prognostic scoring system (IPSS-R).

This indication is not previously approved in the EU for intravenous decitabine, and the PK bridge to IV decitabine is therefore not relevant for the current application.

The proposed dose of Inaqovi for MDS/CMML is the same at the approved dose for AML, i.e. one tablet containing 35 mg of decitabine and 100 mg of cedazuridine taken orally without food once daily on Days 1 through 5 of each 28-day cycle for a minimum of 4 cycles.

Known safety profile of ASTX727

The pivotal studies in MDS/CMML, submitted with the current variation application, were already provided as supportive data with the initial marketing authorisation application (MAA) for ASTX727 for the AML indication. In line with the demonstration of a similar exposure to decitabine after administration of ASTX727 and IV decitabine, the overall safety profile observed in the Phase 3 studies with ASTX727 in AML or MDS/CMML patients (n=288) was similar to what has been previously reported for IV decitabine and what could be expected in these patient populations. Thus, haematologic suppression and gastrointestinal (GI) disorders were very commonly reported, as were different types of infections. Haematological toxicity and infections were the most commonly reported AEs of Grade 3 or higher. SAEs (assessed as unrelated or related) were also most commonly reported within SOCs Infections and infestations and Blood and lymphatic tissue disorders, followed by Gastrointestinal disorders. AEs leading to death were most commonly reported within SOC infection (n=21; 7.3% of the integrated population), but most of these cases were not considered treatment-related by the investigator, but rather to the underlying disease.

There were no marked differences in the safety profile in MDS/CMML compared with AML patients.

Importantly, in these clinical studies no new, important safety issues were identified that could be attributed to cedazuridine or to the oral administration of decitabine. There were also no signals from non-clinical studies with cedazuridine alone that warranted further clinical investigation.

As further described below, no new safety data from the pivotal MDS/CMML studies have been provided with the current variation application, as compared with the original MAA, while the AML study has been updated with longer-term follow-up data.

3.5.2. Patient exposure

The safety analysis supporting the proposed MDS/CMML indication is primarily based on the overall safety data from 208 subjects with MDS/CMML who received the final, recommended dose of 35 mg decitabine and 100 mg cedazuridine, either as the fixed-dose combination ASTX727 or, in 49 subjects, as separate capsules (hereafter, the administered treatment will be referred to ASTX727 for all subjects):

- Study ASTX727-02 North America (NA): Phase 3, open-label, randomised, crossover study in adult patients with MDS/CMML (N=133 of whom 130 received ASTX727). Database lock 07 June 2021
- Study ASTX727-01-B (dose confirmation study): Phase 2, open-label, randomised, crossover study, adult patients with in MDS/CMML (n=80 of whom 78 received ASTX727). Database lock 16 September 2020

The MAH also refers to the 'integrated population' (pooled population), which in addition to the 208 subjects in the MDS/CMML studies includes 80 subjects from the supportive AML study:

- Study ASTX727-02 EU: Phase 3 study in adult patients with AML (n=87, 80 of whom received ASTX727). Cutoff date 17 May 2023

In these three studies, oral decitabine + cedazuridine and IV decitabine were administered in Cycle 1 and 2 in a crossover fashion. Subjects were randomized in a 1:1 ratio to receive oral decitabine + cedazuridine Daily×5 in Cycle 1, followed by IV decitabine 20 mg/m2 Daily×5 in Cycle 2 (Sequence A), or the converse order (Sequence B). In subsequent cycles, all patients subjects received ASTX727.

The three main studies were discussed already in the original MAA for the AML indication. The two MDS/CMML studies were then completed, while for the AML study, the data from the cutoff date of the primary analysis was presented (10 September 2021). Since the original MAA, also the AML study has been completed. Thus, compared with the original MAA, in essence no new safety information from the pivotal MDS/CMML studies have been provided with the current application, while the AML study has been updated with some longer-term follow-up data.

The median duration of follow-up (using reverse Kaplan-Meier) was 30.2 months (95% CI: 29.0 to 30.7) for the 208 subjects with MDS/CMML and 24.0 months (95% CI: 20.5 to 24.5) for the 80 subjects with AML.

The study drug exposure is summarised in **Table *44***. In the combined MDS/CMML population (N=208), the median number of cycles received was 8.0 (range, 1 to 44), with 137 subjects (65.9%) receiving ≥6 cycles, and 72 subjects (34.6%) receiving ≥12 cycles. There were 155 subjects (74.5%) who had at least 1 delayed cycle.

Supportive data

In addition to the three pivotal studies, the MAH refers to safety data from four completed Phase 1 studies (including PK evaluation, dose escalation, food effect, mass-balance, and a thorough QTc study for cedazuridine) that were also included in the original MAA and will not be further discussed for the current variation application.

Further, the MAH's Summary of Clinical Safety (SCS) summarised data from ongoing studies, primarily in terms of rare and/or serious adverse events.

Table 44. Study Drug Exposure in the Integrated Population

Treatment Exposure	ASTX727-02 EU (AML)	ASTX727-01-B / ASTX727-02 NA (MDS/CMML)	All Subjects
Number of Subjects Treated	80	208	288
Duration of Treatment, months			
Mean	8.40	11.17	10.40
SD	7.625	9.594	9.162
Median	5.93	8.08	7.49
Min, Max	0.2, 27.8	0.1, 43.5	0.1, 43.5
Number of Cycles per subject[a]			
Mean	9.1	10.8	10.3
SD	7.67	8.65	8.41
Median	6.0	8.0	7.5
Min, Max	1, 31	1, 44	1, 44
Number of Cycles per subject[a], n (%)			
≥1	80 (100.0)	208 (100.0)	288 (100.0)
≥2	72 (90.0)	202 (97.1)	274 (95.1)
≥3	62 (77.5)	186 (89.4)	248 (86.1)
≥6	44 (55.0)	137 (65.9)	181 (62.8)
Delayed Cycles per subject, n (%)			
No delayed cycles	23 (28.8)	53 (25.5)	76 (26.4)
At least 1 delayed cycle	57 (71.3)	155 (74.5)	212 (73.6)
1	22 (27.5)	25 (12.0)	47 (16.3)
2	9 (11.3)	29 (13.9)	38 (13.2)
Number of Delayed Cycles per subject			
Mean	2.4	4.3	3.8
SD	2.97	5.13	4.71
Median	1.0	2.0	2.0
Min, Max	0, 12	0, 25	0, 25
Dose-reduced Cycles per subject, n (%)			
No dose-reduced cycles	65 (81.3)	99 (47.6)	164 (56.9)
At least 1 dose-reduced cycle	15 (18.8)	109 (52.4)	124 (43.1)
1	10 (12.5)	30 (14.4)	40 (13.9)
2	1 (1.3)	19 (9.1)	20 (6.9)

NOTE: Exposure data are included through the data cutoff dates for the respective CSRs and include all subjects who received 35 mg decitabine and 100 mg cedazuridine (separate capsules or as the ASTX727 FDC tablet).
[a] Completed or partially completed cycle.

Assessor's comment:

Most of the safety data presented in the currently submitted Summary of Clinical Safety (SCS) was discussed during the initial MAA, albeit with focus on the AML population and on the comparison with IV decitabine. As the current application for MDS/CMML is considered a stand-alone application and the comparison with IV decitabine is less relevant, the pivotal data for the assessment of the safety profile of ASTX727 in MDS/CMML will be presented again in this assessment report.

The study design of the three main studies was a crossover, in which subjects took IV decitabine followed by ASTX727 (or vice versa) in Cycles 1 and 2 and then ASTX727 thereafter. The comparison of the safety profile for ASTX727 and IV decitabine in Cycle 1 was thoroughly discussed in the AR for the original application, as this was largely based on a bridge to IV decitabine. In summary, the safety profiles with the two treatments were shown to be similar, and no new ADRs that could be attributed to cedazuridine or the oral administration of decitabine were identified. Thus, although subjects received IV decitabine in either Cycle 1 or Cycle 2, with a potential carryover effect to subsequent

cycles, this is not considered a problem for the current safety assessment of ASTX727 in MDS/CMML population. The studies can be assessed as single-arm trials.

3.5.3. Adverse events

3.5.3.1. Methods - Adverse event analysis

An updated Summary of Clinical Safety (SCS) was submitted with the current application. For the pooled analyses, all TEAEs from the Phase 3 ASTX727-02 study and the Phase 2 stages of the ASTX727-01 study (N=288) were recoded using MedDRA version 26.0. In the original application, MedDRA version 22.0 was used.

Assessor's comment:

Some differences in the numbers presented in the SCS (and in this AR), as compared with the corresponding tables in the SCS of the original submission have been identified, despite the two MDS/CMML studies being finalised already at the original submission. This is assumed to be due to the recoding of adverse events.

A treatment-emergent adverse event (TEAE) is defined as any new AE or any worsening of an existing condition with an onset date on or after the first study drug administration date (Cycle 1 Day 1 [C1D1]) and up to 30 days after the last dose of study treatment or the start of an alternative anticancer treatment (for MDS/CMML or AML), whichever occurred first. Events that occurred more than 30 days after the last dose of study treatment or the start of an alternative anticancer treatment (for MDS/CMML or AML) were also considered treatment-emergent if they were both serious and related to the study treatment.

Adverse event severity was graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3 for the Phase 3 ASTX727-02 study. For Study ASTX727-01, CTCAE version 4.0 was used to grade TEAE severity. The updated SCS used the same grading as in the original application.

3.5.3.2. Adverse event presentation in the Summary of Clinical Safety (SCS)

In the MAH's SCS, the overall cumulative TEAEs reported in all subjects in the integrated population (n=288) who received ASTX727 were presented separately for subjects with MDS/CMML and subjects with AML, as well as for all subjects combined.

The commonly used risk scoring system to assess prognosis of MDS are IPSS, IPSS-R, and IPSS-M. For the analyses of subjects in Studies ASTX727-01-B and ASTX727-02 NA, IPSS and IPSS-R are being utilised. As per the literature, using IPSS-R risk score ≤3.5 (lower-risk) or >3.5 (higher-risk), the overall survival rates among these 2 groups are distinctly different. Therefore, overall safety data for subjects with MDS only (N=175, not including subjects with CMML) were presented for subgroups based on IPSS-R score (≤3.5 versus >3.5).

In addition, data from supportive studies was presented as a combined analysis (n=414). This analysis is considered important primarily for evaluation of rare events that were not reported in the integrated population.

A brief summary of any new relevant safety findings and SAEs in the ongoing studies was included in the SCS from the ARGUS safety database between the data cutoff dates and 13 October 2023 (~60 days before the Type II variation submission).

3.5.3.3. Common Adverse events

A summary of TEAEs in the two completed studies in subjects with MDS/CMML or AML is presented in **Table *45***.

The incidences of SAEs and treatment-related SAEs were lower in subjects with MDS/CMML (73% and 17%, respectively) than in subjects with AML (81% and 26%, respectively). On the contrary, Grade ≥3 TEAEs and treatment-related Grade ≥3 TEAEs were higher in subjects with MDS/CMML (96% and 66%, respectively) than in subjects with AML (91% and 56%, respectively). Also the rate of any TEAEs and treatment-related TEAEs was slightly higher in MDS/CMML patients than in AML patients.

Table 45. Overall Summary of Adverse Events in the Integrated Population (Phase 2 and Phase 3 Subjects)

	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
All Adverse Events			
TEAE	80 (100.0)	208 (100)	288 (100.0)
TEAE Grade ≥3	73 (91.3)	199 (95.7)	272 (94.4)
TEAE Leading to Discontinuation of Study Treatment	15 (18.8)	13 (6.3)	28 (9.7)
Subjects with any SAE	65 (81.3)	151 (72.6)	216 (75.0)
Death	22 (27.5)	21 (10.1)	43 (14.9)
Other Subjects with SAEs[a]	43 (53.8)	130 (62.5)	173 (60.1)
TEAE Related to Any Study Medication			
TEAE	57 (71.3)	171 (82.2)	228 (79.2)
TEAE Grade ≥3	45 (56.3)	138 (66.3)	183 (63.5)
TEAE Leading to Discontinuation of Study Treatment	3 (3.8)	4 (1.9)	7 (2.4)
Subjects with any SAE	21 (26.3)	35 (16.8)	56 (19.4)
Death	1 (1.3)	5 (2.4)	6 (2.1)
Other Subjects with SAEs[a]	20 (25.0)	30 (14.4)	50 (17.4)

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

TEAEs occurring in ≥10% of subjects in any group of the integrated population are summarised in **Table *46***. The effects listed in the table have been grouped together using clinical judgment rather than MedDRA SOC.

In subjects with MDS/CMML (N=208), common TEAEs included myelosuppression, infectious complications of myelosuppression, and gastrointestinal effects.

Events of myelosuppression, infectious complications of myelosuppression, and GI effects were also observed among subjects with AML (N=80).

Also across all subjects in supportive, ongoing and completed studies (N=414), the most commonly reported TEAEs included myelosuppression (anaemia, neutropenia, and thrombocytopenia) and gastrointestinal effects (nausea, constipation, and diarrhoea).

Table 46. Treatment-Emergent Adverse Events Occurring in ≥10% of Subjects in Any Group in the Integrated Population

MedDRA System Organ Class MedDRA Preferred Term	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
Number (%) of subjects who reported at least one TEAE	80 (100.0)	208 (100.0)	288 (100.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	68 (85.0)	156 (75.0)	224 (77.8)
Anaemia	44 (55.0)	95 (45.7)	139 (48.3)
Febrile neutropenia	25 (31.3)	69 (33.2)	94 (32.6)
Thrombocytopenia	39 (48.8)	44 (21.2)	83 (28.8)
Neutropenia	28 (35.0)	48 (23.1)	76 (26.4)
GASTROINTESTINAL DISORDERS	44 (55.0)	181 (87.0)	225 (78.1)
Nausea	17 (21.3)	92 (44.2)	109 (37.8)
Constipation	15 (18.8)	93 (44.7)	108 (37.5)
Diarrhoea	18 (22.5)	81 (38.9)	99 (34.4)
Vomiting	10 (12.5)	37 (17.8)	47 (16.3)
Stomatitis	2 (2.5)	30 (14.4)	32 (11.1)
Abdominal pain	1 (1.3)	27 (13.0)	28 (9.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	53 (66.3)	152 (73.1)	205 (71.2)
Fatigue	9 (11.3)	103 (49.5)	112 (38.9)
Oedema peripheral	16 (20.0)	53 (25.5)	69 (24.0)
Pyrexia	19 (23.8)	46 (22.1)	65 (22.6)
Asthenia	22 (27.5)	13 (6.3)	35 (12.2)
INFECTIONS AND INFESTATIONS	59 (73.8)	143 (68.8)	202 (70.1)
Pneumonia	19 (23.8)	40 (19.2)	59 (20.5)
Urinary tract infection	11 (13.8)	24 (11.5)	35 (12.2)
Upper respiratory tract infection	3 (3.8)	27 (13.0)	30 (10.4)
Cellulitis	8 (10.0)	18 (8.7)	26 (9.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	16 (20.0)	90 (43.3)	106 (36.8)
Fall	9 (11.3)	29 (13.9)	38 (13.2)
Contusion	0	35 (16.8)	35 (12.2)
INVESTIGATIONS	36 (45.0)	150 (72.1)	186 (64.6)
Platelet count decreased	8 (10.0)	90 (43.3)	98 (34.0)
Neutrophil count decreased	2 (2.5)	76 (36.5)	78 (27.1)
White blood cell count decreased	5 (6.3)	49 (23.6)	54 (18.8)
Alanine aminotransferase increased	6 (7.5)	35 (16.8)	41 (14.2)
Blood creatinine increased	6 (7.5)	29 (13.9)	35 (12.2)
Aspartate aminotransferase increased	5 (6.3)	26 (12.5)	31 (10.8)
Weight decreased	4 (5.0)	22 (10.6)	26 (9.0)
METABOLISM AND NUTRITION DISORDERS	29 (36.3)	131 (63.0)	160 (55.6)
Decreased appetite	12 (15.0)	58 (27.9)	70 (24.3)
Hypokalaemia	15 (18.8)	37 (17.8)	52 (18.1)
Hypomagnesaemia	4 (5.0)	25 (12.0)	29 (10.1)
Hypocalcaemia	1 (1.3)	27 (13.0)	28 (9.7)
Hyperglycaemia	3 (3.8)	23 (11.1)	26 (9.0)
Hypoalbuminaemia	0	25 (12.0)	25 (8.7)
Hyponatraemia	2 (2.5)	23 (11.1)	25 (8.7)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	22 (27.5)	142 (68.3)	164 (56.9)
Arthralgia	9 (11.3)	63 (30.3)	72 (25.0)
Back Pain	9 (11.3)	41 (19.7)	50 (17.4)
Muscular weakness	0	40 (19.2)	40 (13.9)
Myalgia	1 (1.3)	31 (14.9)	32 (11.1)
Pain in extremity	2 (2.5)	27 (13.0)	29 (10.1)
NERVOUS SYSTEM DISORDERS	23 (28.8)	130 (62.5)	153 (53.1)
Dizziness	8 (10.0)	70 (33.7)	78 (27.1)
Headache	6 (7.5)	63 (30.3)	69 (24.0)
PSYCHIATRIC DISORDERS	18 (22.5)	55 (26.4)	73 (25.3)
Insomnia	9 (11.3)	29 (13.9)	38 (13.2)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	27 (33.8)	150 (72.1)	177 (61.5)
Dyspnoea	5 (6.3)	66 (31.7)	71 (24.7)
Cough	9 (11.3)	58 (27.9)	67 (23.3)
Oropharyngeal pain	1 (1.3)	36 (17.3)	37 (12.8)
Epistaxis	7 (8.8)	27 (13.0)	34 (11.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	17 (21.3)	108 (51.9)	125 (43.4)
Rash maculo-papular	3 (3.8)	23 (11.1)	26 (9.0)
VASCULAR DISORDERS	23 (28.8)	64 (30.8)	87 (30.2)
Hypertension	8 (10.0)	17 (8.2)	25 (8.7)
Hypotension	2 (2.5)	23 (11.1)	25 (8.7)
Haematoma	10 (12.5)	8 (3.8)	18 (6.3)

Assessor's comment:

As concluded during the original MAA for Inaqovi, the overall safety profile observed in the Phase 3 studies with ASTX727 in AML or MDS/CMML patients (n=288) was similar to what has been previously reported for IV decitabine and what could be expected in these patient populations. Thus, haematologic suppression and gastrointestinal (GI) disorders were very commonly reported, as were different types of infections. In addition, in MDS/CMML patients, AEs were also commonly reported (>60%) within the SOCs General disorders (e.g. fatigue and peripheral oedema), Investigations, Metabolism and nutrition disorders, Musculoskeletal disorders (e.g. arthralgia) and Respiratory disorders (e.g. dyspnoea).

With the exception of AEs within the SOCs Blood and lymphatic disorders and Infections, the rate of reported AEs within each SOC was higher in MDS/CMML patients than in AML patients, including haematological deviations based on laboratory data. A similar pattern was observed for adverse events that were considered treatment-related (see section 5.5.3.5). As noted in The incidences of SAEs and treatment-related SAEs were lower in subjects with MDS/CMML (73% and 17%, respectively) than in subjects with AML (81% and 26%, respectively). On the contrary, Grade ≥3 TEAEs and treatment-related Grade ≥3 TEAEs were higher in subjects with MDS/CMML (96% and 66%, respectively) than in subjects with AML (91% and 56%, respectively). Also the rate of any TEAEs and treatment-related TEAEs was slightly higher in MDS/CMML patients than in AML patients.

Table *45*, the rate of treatment-related TEAEs leading to discontinuation of treatment was, however, low in both groups and lowest in the MDS/CMML group (3.8% in AML patients and 1.9% in MDS/CMML patients), which indicates the treatment was not less well tolerated in the MDS/CMML group than in the AML group (see also section 5.5.3.9). The rate of dose modifications (interruptions or reductions) was largely similar between the MDS/CMML and the AML groups. Myelotoxicity and its complications were the most common reasons for dose modifications (see section 5.5.3.8).

3.5.3.4. Grade ≥3 Adverse Events

Grade ≥3 TEAEs occurring in ≥5% of subjects in any group of the integrated population are summarised in **Table *47***.

Among MDS/CMML subjects (N=208), 95.7% reported at least one Grade ≥3 TEAE. The Grade ≥3 TEAEs reported by ≥20% of subjects were related to myelosuppression.

In the subjects with AML (N=80), 91.3% reported at least one Grade ≥3 TEAE. The Grade ≥3 TEAEs reported by ≥20% of subjects were also related to myelosuppression and infectious complications.

Consistent with the integrated population, TEAEs Grade 3 or 4 reported across all subjects in supportive, ongoing and completed studies (N=414) were also related to myelosuppression and its infectious complications (not shown).

Table 47. Grade ≥3 Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects in Any Group in the Integrated Population

MedDRA System Organ Class MedDRA Preferred Term	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
Number of subjects who reported at least one TEAE	73 (91.3)	199 (95.7)	272 (94.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	59 (73.8)	145 (69.7)	204 (70.8)
Anaemia	33 (41.3)	84 (40.4)	117 (40.6)
Febrile neutropenia	23 (28.8)	69 (33.2)	92 (31.9)
Thrombocytopenia	33 (41.3)	41 (19.7)	74 (25.7)
Neutropenia	26 (32.5)	42 (20.2)	68 (23.6)
Leukopenia	4 (5.0)	12 (5.8)	16 (5.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	15 (18.8)	17 (8.2)	32 (11.1)
Asthenia	7 (8.8)	2 (1.0)	9 (3.1)
INFECTIONS AND INFESTATIONS	42 (52.5)	81 (38.9)	123 (42.7)
Pneumonia	18 (22.5)	32 (15.4)	50 (17.4)
Sepsis	3 (3.8)	18 (8.7)	21 (7.3)
Cellulitis	5 (6.3)	10 (4.8)	15 (5.2)
Infection	5 (6.3)	0	5 (1.7)
INVESTIGATIONS	17 (21.3)	112 (53.8)	129 (44.8)
Platelet count decreased	8 (10.0)	78 (37.5)	86 (29.9)
Neutrophil count decreased	2 (2.5)	76 (36.5)	78 (27.1)
White blood cell count decreased	5 (6.3)	43 (20.7)	48 (16.7)
METABOLISM AND NUTRITION DISORDERS	8 (10.0)	38 (18.3)	46 (16.0)
Hypokalaemia	5 (6.3)	8 (3.8)	13 (4.5)
RENAL AND URINARY DISORDERS	8 (10.0)	0	8 (2.8)
Acute kidney injury	4 (5.0)	0	4 (1.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	7 (8.8)	27 (13.0)	34 (11.8)
Dyspnoea	2 (2.5)	12 (5.8)	14 (4.9)

3.5.3.5. Treatment-related Adverse events

Treatment-related TEAEs occurring in ≥2% of subjects in any group in the integrated population are summarised in **Table *48***. Similar to trends observed among common TEAEs and TEAEs Grade ≥3, related TEAEs in the integrated population were myelosuppressive in nature.

Treatment-related Grade ≥3 TEAEs reported by ≥10% of subjects were primarily related to myelosuppression (**Table *49***).

Table 48. Related Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects in Any Group in ASTX727 Integrated Population

MedDRA System Organ Class MedDRA Preferred Term	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
Number (%) of subjects who reported at least one TEAE	57 (71.3)	171 (82.2)	228 (79.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	45 (56.3)	107 (51.4)	152 (52.8)
Anaemia	17 (21.3)	70 (33.7)	87 (30.2)
Neutropenia	20 (25.0)	31 (14.9)	51 (17.7)
Thrombocytopenia	18 (22.5)	28 (13.5)	46 (16.0)
Febrile neutropenia	9 (11.3)	25 (12.0)	34 (11.8)
Leukopenia	3 (3.8)	8 (3.8)	11 (3.8)
Myelosuppression	3 (3.8)	2 (1.0)	5 (1.7)
CARDIAC DISORDERS	3 (3.8)	2 (1.0)	5 (1.7)
Atrial fibrillation	2 (2.5)	0	2 (0.7)
EYE DISORDERS	3 (3.8)	5 (2.4)	8 (2.8)
Eye haemorrhage	2 (2.5)	0	2 (0.7)
GASTROINTESTINAL DISORDERS	20 (25.0)	92 (44.2)	112 (38.9)
Nausea	9 (11.3)	43 (20.7)	52 (18.1)
Diarrhoea	7 (8.8)	30 (14.4)	37 (12.8)
Constipation	5 (6.3)	28 (13.5)	33 (11.5)
Vomiting	3 (3.8)	10 (4.8)	13 (4.5)
Stomatitis	2 (2.5)	9 (4.3)	11 (3.8)
Dry mouth	2 (2.5)	2 (1.0)	4 (1.4)
Rectal haemorrhage	2 (2.5)	0	2 (0.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	17 (21.3)	71 (34.1)	88 (30.6)
Fatigue	3 (3.8)	51 (24.5)	54 (18.8)
Asthenia	8 (10.0)	4 (1.9)	12 (4.2)
Oedema peripheral	2 (2.5)	6 (2.9)	8 (2.8)
Pyrexia	2 (2.5)	6 (2.9)	8 (2.8)
Mucosal inflammation	1 (1.3)	6 (2.9)	7 (2.4)
INFECTIONS AND INFESTATIONS	13 (16.3)	28 (13.5)	41 (14.2)
Pneumonia	6 (7.5)	4 (1.9)	10 (3.5)
Urinary tract infection	1 (1.3)	6 (2.9)	7 (2.4)
Cellulitis	1 (1.3)	5 (2.4)	6 (2.1)
Sepsis	0	5 (2.4)	5 (1.7)
Anal abscess	2 (2.5)	0	2 (0.7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	12 (5.8)	12 (4.2)
Contusion	0	10 (4.8)	10 (3.5)
INVESTIGATIONS	12 (15.0)	106 (51.0)	118 (41.0)
Platelet count decreased	8 (10.0)	71 (34.1)	79 (27.4)
Neutrophil count decreased	2 (2.5)	67 (32.2)	69 (24.0)
White blood cell count decreased	1 (1.3)	44 (21.2)	45 (15.6)
Alanine aminotransferase increased	2 (2.5)	9 (4.3)	11 (3.8)
Lymphocyte count decreased	0	5 (2.4)	5 (1.7)
Weight decreased	0	5 (2.4)	5 (1.7)
METABOLISM AND NUTRITION DISORDERS	6 (7.5)	32 (15.4)	38 (13.2)
Decreased appetite	6 (7.5)	27 (13.0)	33 (11.5)
Hypokalaemia	2 (2.5)	0	2 (0.7)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	21 (10.1)	21 (7.3)
Myalgia	0	7 (3.4)	7 (2.4)
NERVOUS SYSTEM DISORDERS	3 (3.8)	32 (15.4)	35 (12.2)
Dizziness	0	15 (7.2)	15 (5.2)
Headache	0	13 (6.3)	13 (4.5)
Cerebral haemorrhage	2 (2.5)	0	2 (0.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (7.5)	22 (10.6)	28 (9.7)
Dyspnoea	0	10 (4.8)	10 (3.5)
Epistaxis	4 (5.0)	5 (2.4)	9 (3.1)

Table 49. Related Grade ≥3 Treatment-Emergent Adverse Events Occurring in ≥2% Subjects in Any Group in the Integrated Population

MedDRA System Organ Class MedDRA Preferred Term	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
Number of subjects who reported at least one TEAE	45 (56.3)	138 (66.3)	183 (63.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	39 (48.8)	97 (46.6)	136 (47.2)
Anaemia	14 (17.5)	58 (27.9)	72 (25.0)
Neutropenia	19 (23.8)	29 (13.9)	48 (16.7)
Thrombocytopenia	15 (18.8)	24 (11.5)	39 (13.5)
Febrile neutropenia	9 (11.3)	25 (12.0)	34 (11.8)
Leukopenia	2 (2.5)	8 (3.8)	10 (3.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7 (8.8)	7 (3.4)	14 (4.9)
Asthenia	4 (5.0)	1 (0.5)	5 (1.7)
Fatigue	0	5 (2.4)	5 (1.7)
INFECTIONS AND INFESTATIONS	9 (11.3)	15 (7.2)	24 (8.3)
Pneumonia	6 (7.5)	3 (1.4)	9 (3.1)
Sepsis	0	5 (2.4)	5 (1.7)
INVESTIGATIONS	8 (10.0)	98 (47.1)	106 (36.8)
Platelet count decreased	8 (10.0)	63 (30.3)	71 (24.7)
Neutrophil count decreased	2 (2.5)	66 (31.7)	68 (23.6)
White blood cell count decreased	1 (1.3)	40 (19.2)	41 (14.2)
NERVOUS SYSTEM DISORDERS	2 (2.5)	3 (1.4)	5 (1.7)
Cerebral haemorrhage	2 (2.5)	0	2 (0.7)

Assessor's comment:

The overall rate of treatment-related adverse events was higher in subjects with MDS/CMML (82%) than in subjects with AML (71%). The rates for MDS/CMML were higher than for AML primarily within the SOCs Gastrointestinal disorders, General disorders (with fatigue more commonly reported in MDS/CMML), Investigations (haematological laboratory parameters) and Metabolism and Nutrition disorders. The PT Contusion was only reported in MDS/CMML subjects, which may be considered in line with a high rate of decreased platelet counts in these diseases.

The overall rate of treatment-related Grade ≥3 TEAEs was also higher in subjects with MDS/CMML (66%) than in subjects with AML (56%). The difference for treatment-related Grade ≥3 events was primarily driven by events within SOC Investigations (haematological parameters), which were more commonly reported in MDS/CMML. This was also a more common reason for dose modifications in MDS/CMML than in AML.

3.5.3.6. Rare treatment-related serious adverse events in Phase 1 studies and ongoing studies, compared with the integrated population.

The MAH presented an analysis of rare events occurring in the overall population in completed Phase 1 studies and ongoing studies. This population consists of 414 subjects with different diagnoses, primarily MDS/CMML and AML.

Rare events were defined as those that occur with small probabilities but have a substantial impact and clinically significant complications.

For the purpose of this analysis, considering the available sample size of N=414 subjects (treated in completed Phase 1 and ongoing supportive studies), the MAH classified a rare event as a treatment-

related SAE occurring in one subject (1/414=0.25%) irrespective of severity grade and otherwise not observed in the integrated population.

Among 414 subjects, a total of 44 unique preferred terms (PTs) were reported as SAEs in 1 or more subject and classified as related to study drug irrespective of CTCAE severity grade. Of these 44 treatment-related PTs, 33 (75%) adverse events were reported in 1 subject only.

Among the 44 treatment-related PTs, 24 PTs were Grade 3 (55%), 3 were Grade 4 (7%) and 4 were Grade 5 (9%). A majority of the reported treatment-related PTs were Grade 3 and infectious in nature.

Of these 44 treatment-related PTs, 26 PTs were reported only the completed Phase 1 and ongoing studies (n=414) and were not reported in the integrated population (n=288). The reported CTCAE Grade 4 or 5 treatment-related PTs were in the setting of infection and its subsequent complications. Among the reported Grade 3 treatment-related PTs are tubulointerstitial nephritis and tumour lysis syndrome (TLS) (1 subject each). TLS was reported in Study ASTX727-07 (ASTX727 in combination with venetoclax administered to subjects with AML). Venetoclax in combination with an HMA is known to cause TLS. However, no case of TLS has been reported for subjects (AML or MDS/CMML) taking ASTX727 as monotherapy. Tubulointerstitial nephritis was reported in Study ASTX727-03 (low-dose program), 60 days after first dose of study drug. The investigator reported this event as related to ASTX727; however, the sponsor was not in agreement as the subject had baseline underlying renal disease and was on other confounding medications known to cause interstitial nephritis including allopurinol.

The MAH concludes that treatment related serious preferred terms observed in N=414 and not observed in N=288 were those that are anticipated with the use of ASTX727. Hence, the analysis of N=414 does not raise any new safety concerns.

3.5.3.7. Adverse events of interest

The MAH defined the following categories of Adverse Events of special Interest (AESIs): Myelosuppression events, bleeding (haemorrhagic events), infection events, gastrointestinal (including hepatobiliary) events, cardiac disorders, renal/urinary events, hypersensitivity events, and skin disorders.

AESIs are reported below for the MDS/CMML population in the pivotal studies (n=208).

Myelosuppression

In SOC Blood and Lymphatic System Disorders, all grades TEAEs were reported by 75.0% of subjects with MDS/CMML; TEAEs of CTCAE Grade ≥3 for the MDS/CMML population was 69.7%. The reported (and grouped) TEAEs for these myelosuppression events (all grades) were thrombocytopenia (63.0%), neutropenia (57.2%), leukopenia (28.8%), and pancytopenia (1.9%). Febrile neutropenia was reported by 33.2% subjects; all these events were CTCAE Grade 3 or 4. Anaemia was a grouped term in 47.1% subjects (Grade ≥3 in 40.4% of subjects).

Serious TEAEs in the Blood and Lymphatic System Disorders SOC were reported by 33.2% of the 208 subjects with MDS/CMML. The most commonly reported distinct SAE (≥5% subjects) was febrile neutropenia (29.8%). Related SAEs in this SOC were reported by 11.5% of subjects, most commonly febrile neutropenia (9.1%).

Among subjects with MDS/CMML, 71.6% to 87.0% of the subjects experienced a worsening from baseline of any grade for haemoglobin decreased, platelets decreased, neutrophils decreased, or leukocytes decreased. Worsening from baseline to CTCAE Grade 3 or 4 was observed in 57.2% to 81.3% of the subjects for these laboratory parameters.

Bleeding/Haemorrhagic Events

Among subjects with MDS/CMML (N=208), haemorrhagic TEAEs reported by ≥5% of subjects are epistaxis (13.0%), petechiae (12.0%), haematuria (6.7%), gastrointestinal haemorrhage and mouth haemorrhage (5.8% each), and eye haemorrhage (5.3%). The majority of these TEAEs are low CTCAE grade. CTCAE Grade 3 or higher events for any grouped haemorrhagic TEAE were gastrointestinal haemorrhage (6 subjects), subdural haematoma (2 subjects), epistaxis (2 subjects), mouth haemorrhage (1 subject), and haematoma (1 subject); these events are further described below. Distinct terms were pulmonary alveolar haemorrhage and haemoptysis with 1 subject each.

Haemorrhagic SAEs in subjects with MDS/CMML are gastrointestinal haemorrhage (5 subjects; 2.4%) and one subject each (0.5%) with gingival bleeding, rectal haemorrhage, upper gastrointestinal haemorrhage, post procedural haematoma, subdural haematoma, subdural haemorrhage, cerebral haemorrhage, epistaxis, haemoptysis, and haematoma. One related SAE was reported (gingival bleeding; 0.5%).

Infection events

Among subjects with MDS/CMML (N=208), grouped infection TEAEs (all grades) were reported by 73.1% of subjects, and CTCAE Grade 3 or 4 events were reported by 36.1% of subjects. Grouped TEAEs reported by 5% or more subjects are upper respiratory infection (27.4%), pneumonia (22.6%), cellulitis (19.2%), urinary tract infection (13.5%), viral infection (13.0%), sepsis (12.5%), and periodontitis and sinusitis (7.7% each). Grouped events of CTCAE Grade 3 or 4 events reported by 5% or more subjects were pneumonia (16.3%), sepsis (9.1%), and cellulitis (6.7).

Infection events with a fatal outcome occurred in 5.8% of subjects: sepsis (4 subjects, 1.9%); pneumonia and septic shock (3 subjects each, 1.4%), and fungal pneumonia and pulmonary sepsis (1 subject each, 0.5%). Serious TEAEs in the Infections and Infestations SOC were reported by 36.5% of subjects. Related infection SAEs were reported for 15 subjects (7.2%).

Gastrointestinal/hepatobiliary events

Among subjects with MDS/CMML (N=208), grouped gastrointestinal TEAEs (all grades) were reported by 87.0% of subjects and CTCAE Grade 3 or 4 events were reported by 13.0% of subjects. Grouped gastrointestinal TEAEs reported by ≥5% of subjects with MDS/CMML are constipation (44.7%), diarrhoea (38.9%), oral discomfort (24.5%), stomatitis (24.0%), and gastrointestinal disorder (11.5%). Most of these reported TEAEs were low grade (Grade <3) (ISS Table 31). Distinct TEAEs were nausea (44.2%) and vomiting (17.8%). Related TEAEs in the Gastrointestinal Disorders SOC, reported as 5% or more were: nausea (20.7%), diarrhoea (14.4%), and constipation (13.5%).

Distinct CTCAE Grade 3 TEAEs within the Gastrointestinal Disorders SOC were reported by 11.5% of subjects. These CTCAE Grade 3 events were diarrhoea and gastrointestinal haemorrhage (5 subjects each, 2.4%); colitis and proctitis (2 subjects each, 1.0%); and in 1 subject each (0.5%): abdominal pain, anal fissure, dysphagia, enteritis, enterovesical fistula, gastric haemorrhage, gingival bleeding, large intestinal obstruction, melaena, mouth ulceration, nausea, pancreatitis, proctalgia, rectal haemorrhage, small intestinal obstruction, and upper gastrointestinal haemorrhage. There were two CTCAE Grade 4 events of colitis and large intestine perforation (1 subject each, 0.5%), and no CTCAE Grade 5 events.

SAEs in the Gastrointestinal Disorders SOC were reported in 18 subjects (8.7%). Related SAEs were colitis, diarrhoea, and gingival bleeding in 1 subject (0.5%) each.

A grouped TEAE of hepatic enzyme increased was reported for 26.9% of subjects with MDS/CMML (all grades), and 8 subjects (3.8%) reported CTCAE Grade 3 or 4 events. An increase of any grade for the different hepatobiliary laboratory abnormalities was experienced by 19.4% to 43.8% of the subjects.

These abnormalities were primarily low grade (CTCAE Grade <3) with the exception of 2.9% of subjects with AST increase, ALT increase, or bilirubin increase, and 1% of subjects with alkaline phosphatase increase, where these subjects reported CTCAE Grade 3 or 4.

Cardiac events

Among subjects with MDS/CMML (N=208), grouped cardiac TEAEs (all grades) were reported by 18.8% and CTCAE Grade 3 or 4 events were reported by 2.4% of subjects. One grouped TEAE was reported by 5% or more subjects: arrhythmia (16.3%). The majority of distinct TEAEs were CTCAE Grade 1 (8.7%) and Grade 2 (7.2%). CTCAE Grade ≥3 events were Grade 3 myocardial infarction in 2 subjects, and in 1 subject each: atrial flutter, acute myocardial infarction, and sinus tachycardia; Grade 4 events were cardiogenic shock and acute coronary syndrome; Grade 5 events were cardiac arrest and myocarditis.

Distinct, serious TEAEs were reported by 7 (3.4%) subjects. Of these 8 serious TEAEs, 2 were reported as related: cardiogenic shock and myocarditis in 1 subject each.

In the Investigations SOC, 8 subjects (3.8%) had a TEAE of ECG QT prolonged, 2 subjects experienced cardiac murmur, 1 subject experienced ejection fraction decreased, and 1 subject experienced ECG PR prolongation. None of the cardiac related TEAEs in the Investigation SOC were considered related, and none were serious.

Renal and urinary events

Among subjects with MDS/CMML (N=208), grouped renal TEAEs (all grades) were reported by 32.7%. The most common grouped TEAE in greater than 5% of subjects (all grades) was acute kidney injury (18.3%). Distinct TEAEs in greater than 5% of subjects (all grades) were haematuria (6.7%), and pollakiuria (5.3%). No serious TEAEs were reported in the Renal and Urinary Disorders SOC. Renal TEAEs were reported as related to study drug in 4 (1.9%) subjects.

In terms of laboratory data, creatinine increased from baseline to Grade 3 or 4 was reported uncommonly whereas hyponatremia, hyperkalaemia and hypokalaemia were reported as commonly worsening to Grade 3 or 4.

Hypersensitivity events

In the MDS/CMML population (N=208), 5 subjects (2.4%) reported a TEAE within the grouped term of hypersensitivity. Distinct TEAEs were hypersensitivity and drug hypersensitivity in 2 subjects (1.0%) each and 1 (0.5%) subject with drug eruption.

All of these TEAEs were CTCAE Grade 1 or Grade 2 and unrelated to study drug with the exception of 1 instance of hypersensitivity reported as CTCAE Grade 4, serious and related. This hypersensitivity occurred in a subject with concurrent myocarditis, cardiogenic shock, endocarditis, and ultimately sepsis. A microscopic evaluation of the heart and pericardium revealed an inflammatory pattern compatible with a reaction to medication. Thus, the preliminary interpretation from the investigator was that of related to ASTX727. The company assessment, upon obtaining the histologic examination from autopsy, was that of being consistent with viral myocarditis. Accordingly, the hypersensitivity was assessed as not related to ASTX727.

Skin events

Among subjects with MDS/CMML (N=208), a total of 107 (51.4%) reported grouped TEAEs of skin and subcutaneous tissue disorders; CTCAE Grade 3 or 4 events were reported by 4 (1.9%) of subjects. Grouped skin and subcutaneous TEAEs reported by ≥5% of subjects with MDS/CMML are rash (52 subjects, 25.0%), petechiae (25 subjects, 12.0%), hyperhidrosis (23 subjects, 11.1%), and alopecia (14 subjects, 6.7%).

Four subjects reported distinct serious, not related TEAEs (1 each, 0.5%) of: acute febrile neutrophilic dermatosis, angioedema, cutaneous vasculitis, pyoderma gangrenosum, and rash. CTCAE Grade 2 acute febrile neutrophilic dermatosis was attributed to paraneoplastic syndrome which can occur in subjects with established cancer.

There were 2 serious, related TEAEs in one subject, cutaneous vasculitis CTCAE Grade 3 and pyoderma gangrenosum CTCAE Grade 3. The company attributed these events as not related to ASTX727 but rather to underlying disease. Bullous pyoderma gangrenosum is associated with hematologic malignancies, for which a biopsy can reveal leukocytoclastic vasculitis as well as dermal neutrophilic infiltration and necrosis of the vessels.

3.5.4. Serious adverse event and deaths

3.5.4.1. Deaths

A summary of all-cause deaths in the integrated population is presented in **Table *50***.

TEAEs with an outcome of death are summarised in Table 51. Such cases were reported in 10.1% of MDS/CMML subjects and 27.5% in AML subjects.

In subjects with MDS/CMML, five subjects had TEAEs with an outcome of death considered *treatment-related* by the investigator: myocarditis, pneumonia, pneumonia fungal, sepsis, and septic shock (1 subject each; 0.5%). However, the MAH assessed the myocarditis as not related to study treatment because of confounding medical history of coronary artery disease, hypertension, chronic obstructive pulmonary disease, and concomitant positive blood culture.

In subjects with AML, only one of the fatal TEAEs, cerebral haemorrhage, was suggested to be *treatment-related* by the investigator. The cerebral haemorrhage was, however, considered by the MAH to be unrelated to the study medication.

TEAEs with the outcome of death reported across all subjects in supportive, ongoing and completed studies (N=414) included primarily infections, some cardiac events and a few events of respiratory failure or multiple organ dysfunction syndrome (not shown).

Table 50. Summary of Deaths Occurring in the Integrated Population

Cause of Death	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
All Deaths	61 (76.3)	106 (51.0)	167 (58.0)
Progressive disease	28 (35.0)	23 (11.1)	51 (17.7)
Adverse event	27 (33.8)	28 (13.5)	55 (19.1)
Other[a]	6 (7.5)	9 (4.3)	15 (5.2)
Unknown[b]	0	46 (22.1)	46 (16.0)
Deaths During Treatment Period[c]	25 (31.3)	19 (9.1)	44 (15.3)
Progressive disease	7 (8.8)	2 (1.0)	9 (3.1)
Adverse event	18 (22.5)	16 (7.7)	34 (11.8)
Other	0	0	0
Unknown[b]	0	1 (0.5)	1 (0.3)
Deaths After Treatment Period[d]	36 (45.0)	87 (41.8)	123 (42.7)
Progressive disease	21 (26.3)	21 (10.1)	42 (14.6)
Adverse event	9 (11.3)	12 (5.8)	21 (7.3)
Other[a]	6 (7.5)	9 (4.3)	15 (5.2)
Unknown[b]	0	45 (21.6)	45 (15.6)

[a] "Other" deaths in ASTX727-02 EU included 1 cases of COVID-19 pneumonia, 2 cases of heart failure, 1 case of myocardial infarction with cardiovascular failure, 1 case of sepsis after stem cell transplant, and 1 case of worsening of clinical condition.
"Other" causes of death in ASTX727-02 NA included pneumonia, fulminant liver failure (see Section 5.5.5.1 for more explanation of this liver failure death), septic shock, lung cancer, sepsis, and coronary event.

[b] For subjects in Study ASTX727-01-B, if the cause of death was not attributed to a TEAE, it was reported as unknown.

[c] Date of death on or after the first dose date up to 30 days after the last dose date.

[d] Date of death more than 30 days after the last dose.

Table 51. Treatment-Emergent Adverse Events With an Outcome of Death in the Integrated Population

MedDRA System Organ Class MedDRA Preferred Term	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
Number (%) of subjects who reported at least one TEAE	22 (27.5)	21 (10.1)	43 (14.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (1.3)	0	1 (0.3)
Febrile neutropenia	1 (1.3)	0	1 (0.3)
CARDIAC DISORDERS	1 (1.3)	2 (1.0)	3 (1.0)
Cardiac arrest	0	1 (0.5)	1 (0.3)
Cardiac failure congestive	1 (1.3)	0	1 (0.3)
Myocarditis	0	1 (0.5)	1 (0.3)
GASTROINTESTINAL DISORDERS	2 (2.5)	0	2 (0.7)
Gastrointestinal perforation	1 (1.3)	0	1 (0.3)
Intestinal ischaemia	1 (1.3)	0	1 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (5.0)	1 (0.5)	5 (1.7)
Multiple organ dysfunction syndrome	2 (2.5)	0	2 (0.7)
Sudden death	1 (1.3)	1 (0.5)	2 (0.7)
General physical health deterioration	1 (1.3)	0	1 (0.3)
INFECTIONS AND INFESTATIONS	9 (11.3)	12 (5.8)	21 (7.3)
Pneumonia	6 (7.5)	3 (1.4)	9 (3.1)
Sepsis	2 (2.5)	4 (1.9)	6 (2.1)
Septic shock	1 (1.3)	3 (1.4)	4 (1.4)
Pneumonia fungal	0	1 (0.5)	1 (0.3)
Pulmonary sepsis	0	1 (0.5)	1 (0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (1.3)	0	1 (0.3)
Subdural haematoma	1 (1.3)	0	1 (0.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	2 (1.0)	2 (0.7)
Metastatic neoplasm	0	1 (0.5)	1 (0.3)
Small cell lung cancer	0	1 (0.5)	1 (0.3)
NERVOUS SYSTEM DISORDERS	2 (2.5)	1 (0.5)	3 (1.0)
Cerebral haemorrhage	1 (1.3)	1 (0.5)	2 (0.7)
Ischaemic stroke	1 (1.3)	0	1 (0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (2.5)	3 (1.4)	5 (1.7)
Respiratory failure	0	2 (1.0)	2 (0.7)
Dyspnoea	1 (1.3)	0	1 (0.3)
Pneumothorax	0	1 (0.5)	1 (0.3)
Respiratory distress	1 (1.3)	0	1 (0.3)

Deaths due to fatal SAEs in ongoing studies since the cutoff date of 06 July 2023 were presented separately. The MAH pointed out that the information is preliminary and based on emerging data. There were 5 subjects with fatal SAEs that occurred after the data cutoffs. (For more detailed information on the cases, refer to the SCS).

The case of TLS and its consequences renal and respiratory failure was considered related to treatment (venetoclax is known to cause TLS), while in the other four cases, the events were considered unrelated to treatment. These five cases do not change the overall safety profile of ASTX727.

Assessor's comment

Most cases of death due to AEs in the integrated population were not considered related to treatment with ASTX727 or IV decitabine. The pattern of fatal events is not unexpected in the study populations.

Fatal AE were most commonly reported within SOC infection, including the fatal AEs that were considered treatment-related by investigator and agreed by the MAH (n=4).

As discussed during assessment of the original application, the death due to gastric perforation in a subject with AML was confounded by co-morbidity, and it was agreed that a causal relationship with the oral administration of decitabine could not be considered at least a reasonable possibility.

It is agreed that the five fatal events reported in ongoing studies do not change previous conclusions on the safety profile of ASTX727.

3.5.4.2. Serious adverse events (SAEs)

Serious TEAEs that occurred in ≥2% subjects in the integrated population are summarised in **Table *52***.

In subjects with MDS/CMML (n=208), *treatment-related* SAEs occurred in 35 subjects (16.8%). Treatment-related SAEs in 2 or more subjects were febrile neutropenia (19 subjects; 9.1%), sepsis (5 subjects; 2.4%), pneumonia and cellulitis (3 subjects each; 1.4%), and urinary tract infection (2 subjects; 1.0%).

In subjects with AML (N=80), *treatment-related* SAEs occurred in 21 subjects (26.3%). Treatment-related SAEs in 2 or more subjects were febrile neutropenia (8 subjects; 10.0%), pneumonia (6 subjects; 7.5%), anaemia and cerebral haemorrhage (2 subjects each; 2.5%).

Across all subjects in supportive, ongoing and completed studies (N=414), SAEs occurring in ≥2% subjects included febrile neutropenia, pneumonia, sepsis, and anaemia.

Table 52. Serious Adverse Events Occurring in ≥2% of Subjects in Any Group in the Integrated Population

MedDRA System Organ Class MedDRA Preferred Term	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
Subjects with any Serious Treatment-Emergent Adverse Event[a]	65 (81.3)	151 (72.6)	216 (75.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	27 (33.8)	69 (33.2)	96 (33.3)
Febrile neutropenia	21 (26.3)	62 (29.8)	83 (28.8)
Anaemia	4 (5.0)	3 (1.4)	7 (2.4)
CARDIAC DISORDERS	3 (3.8)	7 (3.4)	10 (3.5)
Cardiac failure	2 (2.5)	0	2 (0.7)
GASTROINTESTINAL DISORDERS	10 (12.5)	18 (8.7)	28 (9.7)
Gastrointestinal haemorrhage	2 (2.5)	5 (2.4)	7 (2.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10 (12.5)	13 (6.3)	23 (8.0)
Pyrexia	1 (1.3)	7 (3.4)	8 (2.8)
Asthenia	3 (3.8)	1 (0.5)	4 (1.4)
Multiple organ dysfunction syndrome	2 (2.5)	1 (0.5)	3 (1.0)
INFECTIONS AND INFESTATIONS	41 (51.3)	76 (36.5)	117 (40.6)
Pneumonia	16 (20.0)	28 (13.5)	44 (15.3)
Sepsis	3 (3.8)	17 (8.2)	20 (6.9)
Cellulitis	4 (5.0)	10 (4.8)	14 (4.9)
Urinary tract infection	3 (3.8)	4 (1.9)	7 (2.4)
Bacteraemia	2 (2.5)	4 (1.9)	6 (2.1)
Infection	5 (6.3)	0	5 (1.7)
Influenza	0	5 (2.4)	5 (1.7)
Neutropenic sepsis	3 (3.8)	2 (1.0)	5 (1.7)
Pneumonia fungal	2 (2.5)	2 (1.0)	4 (1.4)
Bronchitis	3 (3.8)	0	3 (1.0)
Urosepsis	2 (2.5)	1 (0.5)	3 (1.0)
Escherichia bacteraemia	2 (2.5)	0	2 (0.7)
NERVOUS SYSTEM DISORDERS	5 (6.3)	11 (5.3)	16 (5.6)
Syncope	0	6 (2.9)	6 (2.1)
Cerebral haemorrhage	2 (2.5)	1 (0.5)	3 (1.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (6.3)	17 (8.2)	22 (7.6)
Dyspnoea	1 (1.3)	5 (2.4)	6 (2.1)
Pleural effusion	3 (3.8)	1 (0.5)	4 (1.4)

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

Assessor's comment

The pattern of SAEs is not unexpected for a myelosuppressive treatment and in these study populations.

3.5.5. Adverse events leading to dose interruption or dose reduction

Dose reduction was not allowed in Cycle 1 or 2 in the pivotal studies, i.e. during the cross-over evaluation.

Table *53* presents a summary of TEAEs resulting in drug interruption or dose reduction in ≥2% of subjects in the integrated population.

In subjects with MDS/CMML (N=208), TEAEs resulting in drug interruptions or dose reductions occurred in 104 subjects (50.0%). The most common TEAEs (≥3% of subjects) that resulted in drug interruption or dose reduction during treatment with ASTX727 were neutrophil count decreased (38

subjects; 18.3%), febrile neutropenia (17 subjects; 8.2%), neutropenia and anaemia (15 subjects each; 7.2%), platelet count decreased (14 subjects; 6.7%), white blood cell count decreased (10 subjects; 4.8%), and thrombocytopenia and pneumonia (7 subjects each; 3.4%). In general, the most common TEAEs resulting in drug interruptions or dose reductions were those related to myelosuppression.

In subjects with AML (N=80), TEAEs resulting in drug interruptions or dose reductions occurred in 43 (53.8%) of subjects. The most common TEAEs (≥3% of subjects) that resulted in drug interruption or dose reduction were neutropenia (14 subjects; 17.5%), pneumonia (6 subjects; 7.5%), febrile neutropenia (5 subjects; 6.3%), haematotoxicity and Covid-19 (4 subjects each; 5.0%) myelosuppression and thrombocytopenia (3 subjects each; 3.8%). In general, the most common TEAEs resulting in drug interruptions or dose reductions were those related to myelosuppression.

Table 53. TEAEs Leading to Drug Interruption or Dose Reduction Occurring in ≥2% of Subjects in Any Group in the Integrated Population

MedDRA System Organ Class MedDRA Preferred Term	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
Number (%) of subjects who reported at least one TEAE	43 (53.8)	104 (50.0)	147 (51.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	24 (30.0)	48 (23.1)	72 (25.0)
Neutropenia	14 (17.5)	15 (7.2)	29 (10.1)
Febrile neutropenia	5 (6.3)	17 (8.2)	22 (7.6)
Anaemia	1 (1.3)	15 (7.2)	16 (5.6)
Thrombocytopenia	3 (3.8)	7 (3.4)	10 (3.5)
Haematotoxicity	4 (5.0)	0	4 (1.4)
Myelosuppression	3 (3.8)	1 (0.5)	4 (1.4)
INFECTIONS AND INFESTATIONS	20 (25.0)	26 (12.5)	46 (16.0)
Pneumonia	6 (7.5)	7 (3.4)	13 (4.5)
Covid-19	4 (5.0)	0	4 (1.4)
Urinary tract infection	2 (2.5)	2 (1.0)	4 (1.4)
INVESTIGATIONS	5 (6.3)	50 (24.0)	55 (19.1)
Neutrophil count decreased	1 (1.3)	38 (18.3)	39 (13.5)
Platelet count decreased	0	14 (6.7)	14 (4.9)
White blood cell count decreased	0	10 (4.8)	10 (3.5)
C-reactive protein increased	2 (2.5)	0	2 (0.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (2.5)	5 (2.4)	7 (2.4)
Pleural effusion	2 (2.5)	0	2 (0.7)

Assessor's comment:

Dose modifications were made in about 50% of subjects with MDS/CMML and 53% with AML in the pivotal studies. As expected, most dose modifications were made due to myelotoxicity. The largest differences between MDS/CMML and AML patients is a higher rate of dose modifications based on laboratory data in MDS/CMML patients, while in AML patients the rate of dose modifications due to neutropenia and infections was higher.

In general, AEs appear to have been manageable by dose modifications, as the rate of TEAEs that were considered treatment-related and led to permanent discontinuation of treatment was low in both groups, 1.9% in MDS/CMML and 3.8% in AML. The TEAEs leading to permanent discontinuation are described in more detail in section 5.5.8 below.

3.5.6. Discontinuation due to adverse events

In subjects with MDS/CMML (N=208), 13 subjects (6.3%) had a TEAE leading to permanent treatment discontinuation (**Table *54***). The TEAEs leading to permanent treatment discontinuation which were reported for more than 1 subject were febrile neutropenia (2 subjects; 1.0%) and pneumonia (2 subjects; 1.0%). Four subjects (1.9%) had *related* TEAEs leading to permanent treatment discontinuation (febrile neutropenia in two subjects, pure red cell aplasia, cardiogenic shock/myocarditis and hypersensitivity in one subject each).

In subjects with AML (N=80), 15 subjects (18.8%) had a TEAE leading to permanent treatment discontinuation (**Table *54***). The TEAEs leading to permanent treatment discontinuation which were reported for more than 1 subject were pneumonia (4 subjects; 5.0%) and asthenia (2 subjects; 2.5%). Three subjects (3.8%) had *related* TEAEs leading to permanent treatment discontinuation (asthenia in two subjects and mucosal inflammation in one subject).

Table 54. Treatment-Emergent Adverse Events Leading to Permanent Treatment Discontinuation by SOC and PT

MedDRA System Organ Class MedDRA Preferred Term	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
Total Number of TEAEs	15	15	30
Number of subjects who reported at least one TEAE	15 (18.8)	13 (6.3)	28 (9.7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	3 (1.4)	3 (1.0)
Febrile Neutropenia	0	2 (1.0)	2 (0.7)
Aplasia Pure Red Cell	0	1 (0.5)	1 (0.3)
CARDIAC DISORDERS	1 (1.3)	1 (0.5)	2 (0.7)
Cardiac Failure Congestive	1 (1.3)	0	1 (0.3)
Cardiogenic Shock	0	1 (0.5)	1 (0.3)
Myocarditis	0	1 (0.5)	1 (0.3)
GASTROINTESTINAL DISORDERS	2 (2.5)	0	2 (0.7)
Gastrointestinal Perforation	1 (1.3)	0	1 (0.3)
Intestinal Ischaemia	1 (1.3)	0	1 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (6.3)	0	5 (1.7)
Asthenia	2 (2.5)	0	2 (0.7)
Mucosal Inflammation	1 (1.3)	0	1 (0.3)
Multiple Organ Dysfunction Syndrome	1 (1.3)	0	1 (0.3)
Sudden Death	1 (1.3)	0	1 (0.3)
IMMUNE SYSTEM DISORDERS	0	1 (0.5)	1 (0.3)
Hypersensitivity	0	1 (0.5)	1 (0.3)
INFECTIONS AND INFESTATIONS	5 (6.3)	3 (1.4)	8 (2.8)
Pneumonia	4 (5.0)	2 (1.0)	6 (2.1)
Liver Abscess	1 (1.3)	0	1 (0.3)
Sepsis	0	1 (0.5)	1 (0.3)
INVESTIGATIONS	1 (1.3)	0	1 (0.3)
Platelet Count Decreased	1 (1.3)	0	1 (0.3)
METABOLISM AND NUTRITION DISORDERS	0	1 (0.5)	1 (0.3)
Hypomagnesaemia	0	1 (0.5)	1 (0.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	2 (1.0)	2 (0.7)
Adenocarcinoma Gastric	0	1 (0.5)	1 (0.3)
Small Cell Lung Cancer	0	1 (0.5)	1 (0.3)
NERVOUS SYSTEM DISORDERS	1 (1.3)	1 (0.5)	2 (0.7)
Cerebrovascular Accident	0	1 (0.5)	1 (0.3)
Ischaemic Stroke	1 (1.3)	0	1 (0.3)

3.5.7. Laboratory findings

Relevant abnormal laboratory findings are listed in **Table *55***. This table describes the number of subjects with any worsening of laboratory CTCAE toxicity grade from baseline and those that had a worsening from baseline to CTCAE Grade 3 or 4. These laboratory parameters have also been discussed in Section 5.5.3.7, Adverse Events of Interest.

Table 55. Change from Baseline in Laboratory CTCAE Toxicity Grade

Lab Abnormality	Post-baseline NCI-CTCAE Grade	AML (N=80) n (%)	MDS/CMML (N=208) n (%)	All Subjects (N=288) n (%)
Alanine aminotransferase increased	n	73	206	279
	Any Grade Improving	0	3 (1.5)	3 (1.1)
	Any Grade Worsening	29 (39.7)	90 (43.7)	119 (42.7)
	Worsening to Grade 3, 4	3 (4.1)	6 (2.9)	9 (3.2)
	No Change in Grade	44 (60.3)	113 (54.9)	157 (56.3)
Alkaline phosphatase increased	n	71	203	274
	Any Grade Improving	0	1 (0.5)	1 (0.4)
	Any Grade Worsening	36 (50.7)	89 (43.8)	125 (45.6)
	Worsening to Grade 3, 4	0	2 (1.0)	2 (0.7)
	No Change in Grade	35 (49.3)	113 (55.7)	148 (54.0)
Aspartate aminotransferase increased	n	72	204	276
	Any Grade Improving	0	2 (1.0)	2 (0.7)
	Any Grade Worsening	28 (38.9)	68 (33.3)	96 (34.8)
	Worsening to Grade 3, 4	2 (2.8)	6 (2.9)	8 (2.9)
	No Change in Grade	44 (61.1)	134 (65.7)	178 (64.5)
Bilirubin increased	n	73	206	279
	Any Grade Improving	2 (2.7)	6 (2.9)	8 (2.9)
	Any Grade Worsening	19 (26.0)	40 (19.4)	59 (21.1)
	Worsening to Grade 3, 4	2 (2.7)	6 (2.9)	8 (2.9)
	No Change in Grade	52 (71.2)	160 (77.7)	212 (76.0)
Creatinine increased	n	73	205	278
	Any Grade Improving	1 (1.4)	5 (2.4)	6 (2.2)
	Any Grade Worsening	27 (37.0)	65 (31.7)	92 (33.1)
	Worsening to Grade 3, 4	3 (4.1)	1 (0.5)	4 (1.4)
	No Change in Grade	45 (61.6)	135 (65.9)	180 (64.7)
Glucose hyperglycaemia	n	72	205	277
	Any Grade Improving	3 (4.2)	3 (1.5)	6 (2.2)
	Any Grade Worsening	47 (65.3)	121 (59.0)	168 (60.6)
	Worsening to Grade 3, 4	4 (5.6)	17 (8.3)	21 (7.6)
	No Change in Grade	22 (30.6)	81 (39.5)	103 (37.2)
Haemoglobin decreased	n	80	208	288
	Any Grade Improving	2 (2.5)	0	2 (0.7)
	Any Grade Worsening	56 (70.0)	149 (71.6)	205 (71.2)
	Worsening to Grade 3, 4	50 (62.5)	119 (57.2)	169 (58.7)
	No Change in Grade	22 (27.5)	59 (28.4)	81 (28.1)

(continued)

Leukocytes decreased	n	80	208	288
	Any Grade Improving	1 (1.3)	1 (0.5)	2 (0.7)
	Any Grade Worsening	65 (81.3)	181 (87.0)	246 (85.4)
	Worsening to Grade 3, 4	56 (70.0)	169 (81.3)	225 (78.1)
	No Change in Grade	14 (17.5)	26 (12.5)	40 (13.9)
Magnesium hypermagnesaemia	n	69	201	270
	Any Grade Improving	3 (4.3)	9 (4.5)	12 (4.4)
	Any Grade Worsening	13 (18.8)	45 (22.4)	58 (21.5)
	Worsening to Grade 3, 4	0	2 (1.0)	2 (0.7)
	No Change in Grade	53 (76.8)	147 (73.1)	200 (74.1)
Magnesium hypomagnesaemia	n	69	201	270
	Any Grade Improving	1 (1.4)	3 (1.5)	4 (1.5)
	Any Grade Worsening	12 (17.4)	22 (10.9)	34 (12.6)
	Worsening to Grade 3, 4	6 (8.7)	1 (0.5)	7 (2.6)
	No Change in Grade	56 (81.2)	176 (87.6)	232 (85.9)
Neutrophils decreased	n	79	208	287
	Any Grade Improving	0	1 (0.5)	1 (0.3)
	Any Grade Worsening	33 (41.8)	151 (72.6)	184 (64.1)
	Worsening to Grade 3, 4	33 (41.8)	146 (70.2)	179 (62.4)
	No Change in Grade	46 (58.2)	56 (26.9)	102 (35.5)
Platelets decreased	n	80	208	288
	Any Grade Improving	0	0	0
	Any Grade Worsening	59 (73.8)	171 (82.2)	230 (79.9)
	Worsening to Grade 3, 4	55 (68.8)	157 (75.5)	212 (73.6)
	No Change in Grade	21 (26.3)	37 (17.8)	58 (20.1)
Potassium hyperkalaemia	n	73	205	278
	Any Grade Improving	0	2 (1.0)	2 (0.7)
	Any Grade Worsening	12 (16.4)	42 (20.5)	54 (19.4)
	Worsening to Grade 3, 4	1 (1.4)	6 (2.9)	7 (2.5)
	No Change in Grade	61 (83.6)	161 (78.5)	222 (79.9)
Potassium hypokalaemia	n	73	205	278
	Any Grade Improving	2 (2.7)	4 (2.0)	6 (2.2)
	Any Grade Worsening	27 (37.0)	40 (19.5)	67 (24.1)
	Worsening to Grade 3, 4	6 (8.2)	10 (4.9)	16 (5.8)
	No Change in Grade	44 (60.3)	161 (78.5)	205 (73.7)
Sodium hyponatraemia	n	73	205	278
	Any Grade Improving	0	5 (2.4)	5 (1.8)
	Any Grade Worsening	30 (41.1)	66 (32.2)	96 (34.5)
	Worsening to Grade 3, 4	6 (8.2)	12 (5.9)	18 (6.5)
	No Change in Grade	43 (58.9)	134 (65.4)	177 (63.7)

3.5.7.1. Potential Hy's law cases

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

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

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

Assessor's comment

The six potential Hy's law cases were discussed already during assessment of the original application. The cases are confounded by sepsis (four cases) and sepsis and death due to disease progression (1 case). In the sixth case, the patient died from fulminant liver failure 110 days after her last dose of ASTX727. The MAH suggests that these cases may be considered not likely related to ASTX727, which is agreed.

3.5.8. Electrocardiogram

A thorough QT study was performed with cedazuridine. This study was discussed during the original MAA and will not be presented here. It was concluded that cedazuridine at the studied doses had no clinically relevant effects on studied ECG parameters.

The ECG findings in the pivotal MDS/CMML studies are described below:

Phase 3 Study ASTX727-02 NA (Subjects with MDS/CMML)

An analysis of ECG data was performed on the 130 subjects who received ASTX727 and the 129 subjects who received IV decitabine during Cycle 1. An outlier analysis used categorical cut points to determine whether a subject showed a signal of a potential effect on cardiac repolarisation not manifested in the central tendency data.

Results showed no clear effect on heart rate for ASTX727 or IV decitabine. No signal of any effect was observed for atrioventricular conduction or cardiac depolarisation as measured by the PR and QRS interval durations for ASTX727 or IV decitabine. No clear effect on cardiac repolarisation was apparent as measured by the change from baseline to treatment for ASTX727 or IV decitabine.

There were 12 (9.2%) subjects with MDS/CMML treated with ASTX727 who had QTcF change from baseline >30 to 60 ms compared with 12 (9.3%) subjects treated with IV decitabine. There was no subject on ASTX727 and 1 subject on IV decitabine who had a QTcF>500 ms with ≤500 ms at baseline.

Phase 2 Study ASTX727-01-B (Subjects with MDS/CMML)

Clinically meaningful ECG findings were observed for 1 subject who had clinically significant sinus tachycardia (HR=115 bpm); this was reported as a non-serious TEAE and was not considered related to treatment.

Changes from baseline in QTcF that represented shifts of 2 or more CTCAE grades higher occurred in 2 subjects:

- One Subject had a shift from Grade 0 at baseline (402 msec) to Grade 2 on C3D1 (500 msec). By C6D1 the Grade had returned to 0 (446 msec). The subject had right bundle branch block. The subject received treatment with ASTX727 from Cycles 3-14; the only ECG TEAE that occurred was a Grade 1 TEAE of ECG QT prolonged on C13D10.
- One Subject had a shift from Grade 0 at baseline (439 msec) to Grade 3 at an unscheduled visit after Cycle 2 (523 msec; subject received ASTX727 in Cycle 2). This was attributed to possible left atrial enlargement and left bundle branch block. The subject received 1 additional cycle of ASTX727 with no ECG TEAEs.

Five subjects (6.3%) had 1 or more TEAEs of ECG QT prolonged, all of which occurred in ASTX727 cycles, none of which were serious or related to treatment, and all were CTCAE Grade 1 except for 1 subject. Only 2 of the 5 subjects had the event temporally associated with a treatment day (Day 1); for the other subjects the events occurred between Day 16 and Day 36 of the cycle. Although 3 of the 5 subjects had two occurrences of the event, all 5 subjects continued to receive subsequent ASTX727 cycles with no additional QT prolongation TEAEs (negative rechallenge).

3.5.9. Safety in special populations

The effect of intrinsic factors (age, sex, race, renal impairment, hepatic impairment, body surface area) on the safety of ASTX727 was discussed during assessment of the original MAA. No differences are expected between the AML and MDS/CMML populations in this respect.

In the two pivotal MDS/CMML studies, 82/208 subjects were ≥65 to< 75 years of age, and 74/208 were ≥75 years of age. The safety of ASTX727 in elderly patients is therefore well characterised.

3.5.9.1. Review of Safety for Subjects with MDS by IPSS-R Risk Score ≤3.5 and >3.5

In the integrated population, 175 subjects with MDS received ASTX727, 145 of whom had sufficient data to be reclassified using the IPSS-R. In reclassifying subjects by IPSS-R, the common practice of considering patients with IPSS-R scores >3.5 as higher-risk was followed for analysis purposes.

Subject disposition is shown in **Table *56***.

TEAEs by preferred term for ≥10% subjects with MDS and either IPSS-R scores of ≤3.5 or >3.5 are summarised in **Table *57***.

Table 56. Subject Disposition of the MDS Subjects in the Integrated Population by IPSS-R Score Category

Characteristic	IPSS-R≤3.5 (N=44) n (%)	IPSS-R>3.5 (N=101) n (%)	All Subjects (N=175) n (%)
Received Treatment, n (%)	44 (100.0)	101 (100.0)	175 (100.0)
At least 1 dose of ASTX727[a]	44 (100.0)	101 (100.0)	175 (100.0)
At least 1 dose of IV decitabine	43 (97.7)	98 (97.0)	169 (96.6)
Discontinued Treatment[b], n (%)	44 (100.0)	101 (100.0)	175 (100.0)
Adverse event	3 (6.8)	8 (7.9)	15 (8.6)
Death	0	13 (12.9)	18 (10.3)
Progressive disease	7 (15.9)	29 (28.7)	46 (26.3)
Alternative MDS/CMML therapy	0	2 (2.0)	2 (1.1)
Subject decision to permanently stop treatment	0	8 (7.9)	10 (5.7)
Bone marrow/stem cell transplant	6 (13.6)	25 (24.8)	36 (20.6)
Lost to follow-up	0	0	0
Other	28 (63.6)	16 (15.8)	48 (27.4)
Withdrawn from Study, n (%)	43 (97.7)	101 (100.0)	174 (99.4)
Death	10 (22.7)	63 (62.4)	92 (52.6)
Adverse event	0	0	1 (0.6)
Progressive disease	0	1 (1.0)	3 (1.7)
Withdrawal by subject	0	2 (2.0)	4 (2.3)
Lost to follow-up	0	0	0
Rollover to Study ASTX727-06	13 (29.5)	8 (7.9)	22 (12.6)
Study terminated by sponsor	16 (36.4)	18 (17.8)	37 (21.1)
Completed	2 (4.5)	2 (2.0)	4 (2.3)
Other	2 (4.5)	7 (6.9)	11 (6.3)
Reverse Kaplan-Meier Estimate of Duration of Follow-up, months[c]			
Median	29.8 (28.0, 32.2)	30.7 (29.3, 32.6)	30.4 (29.1, 31.1)
Continuing in Study, n (%)	1 (2.3)	0	1 (0.6)
Ongoing study treatment	0	0	0
On study for survival follow-up	1 (2.3)	0	1 (0.6)

[a] ASTX727 includes decitabine and cedazuridine as separate capsules and ASTX727 FDC tablets.
[b] Percentages are based on the number of subjects who received treatment.
[c] The length of follow-up is defined as number of months from the date of subject randomization to the date of death (regardless of cause) or to last known alive date.

Table 57. TEAEs Experienced by ≥10% of Subjects in Any IPSS-R Risk Score Subgroup of Subjects with MDS

MedDRA Preferred Term	IPSS-R ≤3.5 (N=44) n (%)	IPSS-R >3.5 (N=101) n (%)	All Subjects (N=175) n (%)
Total Number of TEAEs	1524	3525	5657
Number of subjects who reported at least one TEAE	44 (100.0)	101 (100.0)	175 (100.0)
Fatigue	22 (50.0)	55 (54.5)	90 (51.4)
Nausea	24 (54.5)	47 (46.5)	83 (47.4)
Anaemia	21 (47.7)	53 (52.5)	80 (45.7)
Constipation	17 (38.6)	49 (48.5)	79 (45.1)
Platelet count decreased	25 (56.8)	44 (43.6)	77 (44.0)
Diarrhoea	22 (50.0)	40 (39.6)	72 (41.1)
Dizziness	24 (54.5)	33 (32.7)	65 (37.1)
Neutrophil count decreased	20 (45.5)	36 (35.6)	65 (37.1)
Febrile neutropenia	17 (38.6)	31 (30.7)	60 (34.3)
Dyspnoea	20 (45.5)	32 (31.7)	58 (33.1)
Headache	13 (29.5)	37 (36.6)	56 (32.0)
Arthralgia	14 (31.8)	35 (34.7)	53 (30.3)
Cough	15 (34.1)	27 (26.7)	49 (28.0)
Decreased appetite	10 (22.7)	35 (34.7)	49 (28.0)
Oedema peripheral	10 (22.7)	28 (27.7)	47 (26.9)
Pyrexia	11 (25.0)	27 (26.7)	43 (24.6)
White blood cell count decreased	13 (29.5)	24 (23.8)	42 (24.0)
Pneumonia	9 (20.5)	23 (22.8)	38 (21.7)
Back pain	9 (20.5)	22 (21.8)	37 (21.1)
Muscular weakness	9 (20.5)	22 (21.8)	36 (20.6)
Neutropenia	9 (20.5)	20 (19.8)	35 (20.0)
Thrombocytopenia	9 (20.5)	23 (22.8)	35 (20.0)
Vomiting	10 (22.7)	21 (20.8)	35 (20.0)
Alanine aminotransferase increased	6 (13.6)	22 (21.8)	31 (17.7)
Hypokalaemia	4 (9.1)	25 (24.8)	31 (17.7)
Oropharyngeal pain	11 (25.0)	19 (18.8)	31 (17.7)
Contusion	12 (27.3)	12 (11.9)	28 (16.0)
Myalgia	7 (15.9)	17 (16.8)	28 (16.0)
Fall	9 (20.5)	16 (15.8)	26 (14.9)
Insomnia	6 (13.6)	18 (17.8)	26 (14.9)
Stomatitis	4 (9.1)	20 (19.8)	26 (14.9)
Blood creatinine increased	5 (11.4)	17 (16.8)	24 (13.7)
Hypocalcaemia	6 (13.6)	16 (15.8)	24 (13.7)
Upper respiratory tract infection	9 (20.5)	12 (11.9)	24 (13.7)
Hypoalbuminaemia	5 (11.4)	17 (16.8)	23 (13.1)
Pain in extremity	7 (15.9)	15 (14.9)	23 (13.1)
Abdominal pain	6 (13.6)	10 (9.9)	22 (12.6)
Aspartate aminotransferase increased	6 (13.6)	15 (14.9)	22 (12.6)
Hyponatraemia	3 (6.8)	16 (15.8)	22 (12.6)
Epistaxis	6 (13.6)	13 (12.9)	21 (12.0)
Hypomagnesaemia	6 (13.6)	10 (9.9)	21 (12.0)
Hypotension	7 (15.9)	11 (10.9)	20 (11.4)
Rash maculo-papular	4 (9.1)	13 (12.9)	20 (11.4)
Urinary tract infection	8 (18.2)	10 (9.9)	20 (11.4)
Blood bilirubin increased	1 (2.3)	16 (15.8)	19 (10.9)
Nasal congestion	7 (15.9)	8 (7.9)	19 (10.9)
Weight decreased	4 (9.1)	14 (13.9)	19 (10.9)
Hyperglycaemia	7 (15.9)	10 (9.9)	18 (10.3)
Rash	7 (15.9)	9 (8.9)	18 (10.3)
Chills	5 (11.4)	9 (8.9)	17 (9.7)
Blood alkaline phosphatase increased	1 (2.3)	13 (12.9)	15 (8.6)
Pruritus	1 (2.3)	11 (10.9)	15 (8.6)
Alopecia	5 (11.4)	9 (8.9)	14 (8.0)
Bone pain	6 (13.6)	7 (6.9)	14 (8.0)
Mouth ulceration	5 (11.4)	3 (3.0)	8 (4.6)

All subjects with IPSS-R ≤3.5 (N=44; 100.0%) reported at least one Grade ≥3 TEAE; 95 subjects (94.1%) with IPSS-R >3.5 reported at least one Grade ≥3 TEAE. Generally, Grade ≥3 TEAEs were myelosuppression and the consequences thereof (ie, infections).

Treatment-related SAEs occurred in 10 subjects (22.7%) with IPSS-R ≤3.5, and in 14 subjects (13.9%) with IPSS-R >3.5 (Table 37). Generally, SAEs and related SAEs were myelosuppression and the consequences thereof (ie, infections).

3.5.10. Long-term safety data

Study ASTX727-06 is an open-label, multicentre, extension study for subjects who participated in prior clinical studies of ASTX727. In the parent studies, among subjects with MDS/CMML, the median number of cycles received per subject was 8 cycles (duration of treatment 8 months) and for subjects with AML, 6 cycles (duration of treatment 6 months). After treatment in their parent study, subjects remained on treatment in the ASTX727-06 study for a median duration of 5 months. T

To assess the adverse event profile observed with continued use of ASTX727, the MAH made a comparison of TEAEs observed in the MDS/CMML population (N=208), the overall population of AML/MDS/CMML (N=288), and the ASTX727-06 extension rollover study (N=72). The comparison focussed on select anticipated events of myelosuppression, haemorrhage, and infection, and is presented in **Table *58***.

Overall, incidence of TEAEs for these anticipated events decreased substantially in the ASTX727-06 study. A large majority of the events occurring very commonly in the parent study only occurred commonly in the extension rollover study. Furthermore, many of the events observed in the integrated population have no longer been observed in the extension rollover study. This indicates an acceptable tolerability profile of ASTX727 for subjects who benefit from continued treatment.

The MAH concludes that long term use of ASTX727 did not result in higher observed rates of adverse events but that this evaluation is limited by the nature of the rollover study.

Table 58. Comparison of Select Anticipated Adverse Events of Interest Between Integrated Population and Extension Rollover Study

MedDRA System Organ Class MedDRA Preferred Term	MDS/CMML (N=208)	AML/MDS/CMML (N=288)	ASTX727-06 Extension Rollover Study (N=72)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anaemia	95 (45.7)	139 (48.3)	12 (16.7)
Febrile neutropenia	69 (33.2)	94 (32.6)	4 (5.6)
Leukopenia	12 (5.8)	17 (5.9)	1 (1.4)
Neutropenia	48 (23.1)	76 (26.4)	9 (12.5)
Thrombocytopenia	44 (21.2)	83 (28.8)	12 (16.7)
EYE DISORDERS			
Conjunctival haemorrhage	9 (4.3)	10 (3.5)	0
GASTROINTESTINAL DISORDERS			
Gastric haemorrhage	1 (0.5)	1 (0.3)	2 (2.8)
Gingival bleeding	7 (3.4)	9 (3.1)	1 (1.4)
Rectal haemorrhage	5 (2.4)	8 (2.8)	1 (1.4)
Gastrointestinal haemorrhage	5 (2.4)	7 (2.4)	0
Mouth haemorrhage	5 (2.4)	6 (2.1)	0
Melaena	2 (1.0)	5 (1.7)	0
Haematochezia	1 (0.5)	1 (0.3)	0
INFECTIONS AND INFESTATIONS			
Cellulitis	18 (8.7)	26 (9.0)	4 (5.6)
Pneumonia	40 (19.2)	59 (20.5)	7 (9.7)
Sepsis	18 (8.7)	21 (7.3)	0
Bacteraemia	4 (1.9)	6 (2.1)	2 (2.8)
Urinary tract infection	24 (11.5)	35 (12.2)	2 (2.8)
NERVOUS SYSTEM DISORDERS			
Cerebral haemorrhage	1 (0.5)	3 (1.0)	0
Cerebral haematoma	0	1 (0.3)	0
Subdural haematoma	3 (1.4)	4 (1.4)	0
Subdural haemorrhage	1 (0.5)	1 (0.3)	0
RENAL AND URINARY DISORDERS			
Haematuria	14 (6.7)	16 (5.6)	1 (1.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Epistaxis	27 (13.0)	34 (11.8)	3 (4.2)
Haemoptysis	5 (2.4)	5 (1.7)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDER			
Petechiae	18 (8.7)	20 (6.9)	0
Purpura	7 (3.4)	7 (2.4)	1 (1.4)
VASCULAR DISORDERS			
Haematoma	8 (3.8)	18 (6.3)	0

3.5.11. Adverse drug reactions for the label

Section 4.8 of the SmPC has been updated to include information from the MDS/CMML studies ASTX727-02 and ASTX727-01-8.

The ADR table in section 4.8 of the SmPC has been updated to reflect data from the MDS/CMML studies as well as the previous AML study. Due to the small number of patients in the AML study, the ADR table in the previously approved SmPC took into account also data for intravenous decitabine (Dacogen) in AML. The MAH has not proposed deletion or addition of any ADRs in the updated table, but have changed some of the frequency categories. This is made conservatively, so that the highest

reported frequency is described, regardless of whether it is calculated from the study of Inaqovi in AML, the studies of Inaqovi in MDS/CMML or from data for intravenous decitabine.

Other changes involve an update of the footnotes, mainly by addition of new preferred terms or specific reactions observed in the MDS/CMML studies to the description of the grouped terms used in the table.

The preferred term 'Differentiation syndrome' has been moved from SOC 'Neoplasms benign, malignant and unspecified (including cysts and polyps)' to SOC 'Blood and lymphatic system'.

Thus, the ADR table is proposed to be updated as show in **Table *59***.

Assessor's comment:

The ADR table in section 4.8 of the SmPC has been updated to reflect the data from the pivotal MDS/CMML studies (ASTX727-02, N=130 and ASTX727-01-B, N=78). The conservative approach in terms of frequency estimation is acknowledged. However, the footnote to the table, listing specific reactions reported within the grouped terms in the table, is considered too extensive and should be shortened.

Table 59. Proposed updates to the ADR table in section 4.8 (new text, ~~deleted text~~)

MedDRA SOC	MedDRA Term [a]	All CTCAE grades Frequency	CTCAE Grade 3-4 Frequency
Infections and infestations			
	All other infections (viral, bacterial, fungal) [b]	Very common	Very common
	Pneumonia (including fungal) [c]	Very common	Very common
	Sepsis [d]	Very common	Common
	Urinary tract infection [e]	Very common	Common
	Sinusitis (including fungal [f] and bacterial [g]) [f]	Common	Common [g]
Blood and lymphatic system			
	Leukopenia [h]	Very common	Very common
	Thrombocytopenia [h,i]	Very common	Very common
	Anaemia [h]	Very common	Very common
	Neutropenia [h,j]	Very common	Very common
	Febrile neutropenia	Very common	Very common
	Pancytopaenia [j,k]	~~Uncommon~~ [k] Common	~~Uncommon~~ [k] Common
~~**Neoplasms benign, malignant and unspecified (including cysts and polyps)**~~			
	Differentiation syndrome [l]	Not known	Not known
Metabolism and nutrition disorders			
	Hyperglycaemia [h,m]	Very common	Common
Nervous system disorders			
	Headache [n]	~~Common~~Very common	Common [n]
Cardiac disorders			
	Cardiomyopathy [o]	Uncommon	Uncommon
Respiratory, thoracic, and mediastinal disorders			
	Epistaxis [p]	~~Common~~Very common	Common [n]
	Interstitial lung disease [l]	Not known	Not known
Gastrointestinal disorders			
	Stomatitis [p]	Very common	Common
	Nausea [q]	Very common	Uncommon [q]
	Diarrhoea [r,q]	Very common	Common [r]
	Vomiting [q]	Very common	Common [q]
	Neutropaenic colitis [s,r]	Common [h]	Common [g]
Hepatobiliary disorders			
	Alkaline phosphatase increased [h,t]	Very common	~~Not applicable~~Common
	Alanine aminotransferase increased [h,u]	Very common	Common
	Aspartate aminotransferase increased [h,v]	Very common	Common
	Bilirubin increased [h,w,x]	Very common	~~Uncommon~~Common [f]
Skin and subcutaneous tissue disorders			
	Acute febrile neutrophilic dermatosis ~~(Sweet's syndrome)~~ [q]	Uncommon [q]	Not applicable [q]
General disorders and administration site conditions			
	Pyrexia [q]	Very common	Common

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

[b] Grouped terms include anal abscess, abscess fungal, anorectal infection, aspergillus infection, bacteraemia, bacterial infection, bacterial test positive, bronchopulmonary aspergillosis, candida infection, catheter site cellulitis, cellulitis, cellulitis staphylococcal, corona virus infection, coronavirus test positive, cytomegalovirus infection, ear infection, enterobacter infection, enterococcal bacteraemia, enterococcal infection, enterocolitis viral, erythema, escherichia bacteraemia, escherichia infection, folliculitis, fungal foot infection, fungal infection, fungal oesophagitis, fungal skin infection, furuncle, gingival swelling, gingivitis, herpes virus infection, ~~infection,~~ herpes zoster, influenza, influenza like illness, klebsiella bacteraemia, laryngitis, nasal congestion, nasal herpes, nasopharyngitis, ~~oral~~noninfective gingivitis, oesophageal candidiasis, oral candidiasis, oral herpes, oral infection, oropharyngeal candidiasis, otitis externa, otitis media, parainfluenzae virus infection, periodontal disease, periodontitis, perirectal abscess, peritonsillitis, pharyngeal erythema, pharyngitis, polyserositis, pseudomonal bacteraemia, respiratory syncytial virus infection, respiratory tract infection, rhinovirus infection, skin candida, skin infection, soft tissue infection, staphylococcal bacteraemia, staphylococcal infection, streptococcal bacteraemia, ~~respiratory tract infection, skin infection,~~ subcutaneous abscess, tonsillitis, tooth abscess, tooth infection, upper respiratory tract infection, varicella, viral infection, viral upper respiratory tract infection, varicella zoster virus infection

[c] Grouped terms include atypical pneumonia, bronchitis, ~~pneumonia~~lower respiratory tract infection, pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia fungal, pneumonia pseudomonal

[d] Grouped terms include bacterial sepsis, candida sepsis, hepatosplenic candidiasis, neutropenic sepsis, pulmonary sepsis, sepsis, septic shock, systemic candidiasis, urosepsis

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

[f] Grouped terms include sinusitis, sinusitis aspergillus, sinusitis fungal, sinus congestion, sinus pain

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

[g] CIOMS frequency captures the more conservative occurrence of the adverse drug reaction in either the N=80 AML or the N=208 MDS/CMML populations

[h] Based on laboratory values

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

~~[j] Neutrophils decreased (n=79)~~

[j] Grouped terms include myelosuppression, pancytopenia

[k] ~~Pancytopaenia, including fatal~~Fatal events~~, was~~ of pancytopaenia were not observed ~~in the clinical trial~~ with Inaqovi, however ~~it was~~they were observed in in clinical trials with ~~IV~~intravenous decitabine ~~at a frequency of uncommon (< 1%)~~

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

~~[m] Hyperglycemia (n=72)~~

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

[m] Grouped terms include headache, migraine, sinus headache

[n] CIOMS frequency captures the more conservative occurrence of the adverse drug reaction with the use of intravenous decitabine

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

[p] Grouped terms include abscess oral, aphthous ulcer, glossitis, lip ulceration, mouth swelling, mouth ulceration, mucosal infection, mucosal inflammation, oral discomfort, oral mucosal blistering, oral mucosal erythema, oropharyngeal discomfort, oropharyngeal pain, pharyngeal ulceration, stomatitis, tongue ulceration, toothache

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

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

[s] Grouped terms include diarrhoea, faeces soft

[t] 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~~intravenous decitabine

~~[u] Aspartate aminotransferase increased (n=72)~~

~~[v] Alanine aminotransferase increased (n=73)~~

~~[w] Alkaline phosphatase increased (n=71)~~

~~[x] Bilirubin increased (n=73)~~

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

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

[aa] Grouped terms include chills ~~and~~, pyrexia

CTCAE= Common Terminology Criteria for Adverse Events

3.5.12. Post-marketing data

The most recent Development Safety Update Report (DSUR) for ASTX727 is based on a reporting period from 07 July 2022 to 06 July 2023. No new information from the post-marketing setting was obtained during the reporting period for ASTX727 that changes the benefit-risk profile of ASTX727.

3.5.13. Discussion on clinical safety

The original MAA for ASTX727 in the treatment of AML was primarily based on a PK bridge, demonstrating similar systemic exposure to decitabine following administration of ASTX727 and intravenous (IV) decitabine (Dacogen).

With the current application, Inaqovi is proposed for treatment of MDS/CMML. This indication is not previously approved in the EU for IV decitabine, and the PK bridge to IV decitabine is therefore not relevant for the current application. The safety assessment, thus, primarily needs to be made based on the two pivotal studies with ASTX727 in MDS/CMML (Studies ASTX727-02-NA and ASTX727-01-B, n=208). The data from the AML study (Study ASTX727-02-EU, n=80) is considered supportive.

The data from the three main ASTX727 studies (total n=288) were discussed already in the original MAA, but with focus on the AML population and the comparison with IV decitabine. Therefore, the pivotal data for the assessment of the safety profile of ASTX727 in MDS/CMML has been presented again in this assessment report.

In addition, the MAH presented data from the roll-over, extension study ASTX727-06, for subjects who participated in the prior clinical studies of ASTX727.

The study design of the three main studies was a crossover, in which subjects took IV decitabine followed by ASTX727 (or vice versa) in Cycles 1 and 2 and then ASTX727 thereafter. During the original MAA for the AML indication, it was concluded that the safety profiles with the two treatments were similar and that cedazuridine in ASTX727 did not add any new toxicity. Therefore, safety data for ASTX727 is not considered confounded by subjects having received IV decitabine in either Cycle 1 or Cycle 2. From a safety perspective, the studies are assessed as single-arm trials.

In the parent studies, among subjects with MDS/CMML, the median number of cycles received per subject was 8 cycles (duration of treatment 8 months) and for subjects with AML, 6 cycles (duration of treatment 6 months). The median duration of follow-up (using reverse Kaplan-Meier) was 30.2 months (95% CI: 29.0 to 30.7) for the 208 subjects with MDS/CMML and 24.0 months (95% CI: 20.5 to 24.5) for the 80 subjects with AML. After treatment in their parent study, some subjects (n=72) remained on treatment in the ASTX727-06 extension study for a median duration of 5 months.

The overall adverse event profile observed in the three main studies with the five-day dosing regimen of ASTX727 in AML or MDS/CMML patients (n=288) was as expected with a myelotoxic treatment and as could be expected in these patient populations, with haematological neoplasms and a median age of 71 years and 76 years in the MDS/CMML and AML populations, respectively. Thus, haematologic suppression and different types of infections were commonly reported (about 70-85% of patients). Many of these events were of CTCAE Grade ≥3. Based on single-arm trials it cannot be assessed whether these events are attributed mainly to the underlying disease or to treatment with ASTX727.

The rate of reported AEs within the SOCs Blood and lymphatic disorders and Infections was slightly higher in the AML patients (85%) than in MDS/CMML patients (75%). On the other hand, haematological deviations based on laboratory data (SOC Investigations) were much more commonly recorded in MDS/CMML than in AML patients (72% vs. 45%).

Also for other SOCs, except Blood and lymphatic disorders and Infections, the rate of reported AEs within each SOC was generally higher in MDS/CMML patients than in AML patients.

Gastrointestinal disorders were reported in 87% of MDS/CMML patients and 55% of AML patients. Most of the gastrointestinal AEs were of Grade 1-2. Further, in MDS/CMML patients, AEs were commonly reported (>60%) within the SOCs General disorders (e.g. fatigue and peripheral oedema), Metabolism and nutrition disorders, Musculoskeletal disorders (e.g. arthralgia) and Respiratory disorders (e.g. dyspnoea).

The SmPC recommends that myelosuppression should primarily lead to dose delays (delay the next cycle), while persistent myelotoxicity after a dose delay should lead to dose reductions in subsequent cycles. This is in line with the guidance for dose modifications provided in the study protocols. An additional dose reduction step, as compared with the guidance in the protocols, was added to the SmPC, as investigators found additional dose reductions to be necessary in some study patients. The rate of dose modifications (interruptions or reductions) was largely similar between the MDS/CMML and the AML groups (52% of patients with MDS/CMML, 48% in patients with AML). Myelotoxicity and its complications were the most common reasons for dose modifications. The rate of treatment-related AEs leading to discontinuation of treatment was, however, low in both groups and lowest in the MDS/CMML group (1.9% in MDS/CMML patients and 3.8% in AML patients). This indicates that toxicity

could generally be managed by dose modifications and that ASTX727 treatment was not less well tolerated in the MDS/CMML group than in the AML group.

Most cases of death due to AEs during the treatment period (n=34) in the integrated population (n=288) were not considered related to treatment with ASTX727. Fatal AEs were most commonly reported within SOC Infection (n=21), including the fatal AEs that were considered treatment-related by both investigator and MAH (n=4). Infections were also the most commonly reported SAEs (reported in 36% and 51% of MDC/CMML and AML patients, respectively) followed by febrile neutropenia (33% and 34% respectively). The pattern of fatal adverse events and SAEs is not unexpected in the study populations.

The MAH has made a subgroup comparison of adverse event rates in MDS patients at lower risk (IPSS-R ≤3.5; N=44) and higher risk (IPSS-R >3.5; n=101). The differences between the groups were small and do not affect the overall safety assessment for these two subgroups.

Data from the extension study ASTX727-06 indicated that the incidence of anticipated events (myelosuppression, haemorrhage, infection) decreased compared with the parent studies, indicating an acceptable tolerability profile of ASTX727 for subjects who benefit from continued treatment.

In conclusion, the safety profile for ASTX727 in MDS/CMML is as expected for a cytotoxic treatment in this patient population. There was a high rate of dose modifications (interruptions or reductions) in the ASTX727 studies, but the rate of discontinuations due to treatment-related AEs was relatively low. Therefore, the toxicity seems to be largely manageable with dose modifications. Provided that a patient population can be identified where efficacy can be established and the clinical benefit outweighs the common cytotoxic side effects, from a safety perspective there would be no major objections to the approval of ASTX727.

Summary of product Characteristics

Section 4.8 of the SmPC has been updated to include information from the MDS/CMML studies ASTX727-02-NA and ASTX727-01-B. The ADR table in the previously approved SmPC took into account data from Study ASTX727-02-EU in AML (n=80) and data for intravenous decitabine (Dacogen) in AML. The MAH has not proposed deletion or addition of any ADRs in the updated table but some of the frequency categories have been changed. This is done conservatively, so that the highest reported frequency is described, regardless of whether it is calculated from the study of Inaqovi in AML, the studies of Inaqovi in MDS/CMML or from data for intravenous decitabine. Further, in the footnote to the table, the MAH has added new preferred terms/specific reactions observed in the MDS/CMML studies.

3.5.1. Conclusions on clinical safety

The safety profile for ASTX727 in MDS/CMML at the proposed 5-day regimen is as expected for a cytotoxic treatment and acceptable in the proposed treatment niche (provided that efficacy is established). The toxicity seems to be largely manageable with dose modifications.

3.5.2. 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.

4. Risk management plan

The MAH submitted an updated RMP version 1.1 with this application. The main proposed RMP changes were the following:

- Addition of two new indications: Chronic myelomonocytic leukemia (CMML) and Myelodysplastic syndrome (MDS).

An updated version 1.2 was submitted with the response to RSI.

Part I Product overview

Information regarding the proposed indications has been added to the table in part I. The new information included is acceptable.

Part II Safety specification

Module SI – Epidemiology of the indication and target population

New information regarding the proposed changes to the indication has been added to the module. The information is considered sufficient and the module is acceptable.

Module SII – Nonclinical part of the safety specification

New information regarding the central nervous system and phototoxicity has been added to the module. The new information included is considered acceptable.

Module SIII – Clinical trial exposure

The cut-off day of the data presented from clinical trial exposure to oral decitabine and cedazuridine has been altered from 10 Sep 2021 to 25 May 2023. The exposure numbers for the indication AML have been updated according to the cut-off date which is considered acceptable.

Module SIV – Populations not studied in clinical trials

The new proposed indications MDS and CMML have been added in table 2.4.1-1 in the module as part of the clinical study ASTX727-02. This is considered acceptable.

Module SV – Post-authorisation experience

Method used to calculate exposure

Estimates of patient exposure are based on the availability of monthly sales and "free goods" distribution figures per product. Due to the limitations of this approach, it is not possible to estimate reliably the number of patients treated with marketed oral decitabine and cedazuridine, nor to estimate exposure by indication. The trade name of oral decitabine and cedazuridine being marketed in the US, Canada, and Australia is INQOVI for Myelodysplastic Syndrome (MDS). The cumulative estimates have been calculated to 30 Jun 2023.

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

- The Average Defined Dose (ADD) for oral decitabine and cedazuridine is 1 dose pack containing 5 tablets. One (1) tablet contains 35 mg of decitabine and 100 mg cedazuridine and is taken orally once daily on day 1 through 5 of each 28-day cycle.
- Each patient received the ADD of 1 dose pack (5 tablets).
- Each patient received this dose for 4 cycles of treatment.

- Each patient received a total dose of 4 dose packs (20 tablets).

Sales figures for oral decitabine and cedazuridine were received from 07 Jul 2020 to 30 Jun 2023.

It is difficult to determine the number of patients treated with oral decitabine and cedazuridine during the post marketing experience. Therefore, the number of patients exposed is an estimation based on these sales data.

Exposure

The estimated cumulative number of patients treated with marketed oral decitabine and cedazuridine worldwide as of 30 Jun 2023 was approximately 9,934.

Assessor's comments

The presentation of the post-authorisation exposure has been updated with a new cut-off date from 16 January 2022 to 30 June 2023. Hence, the new exposure data presented is covered by the period 07 July 2020 to 30 June 2023. The update is considered acceptable.

Module SVI – Additional EU requirements for the safety specification

Not applicable.

Module SVII – Identified and potential risks

Module SVII.1 reflects the initially approved RMP.

In module SVII.2, the MAH provided a justification of the statement that there are no new safety concerns or reclassified risks related to the proposed indication: higher-risk MDS with Revised International Prognostic Scoring System greater than 3.5 (IPSS-R >3.5).

Hence, no update of module SVII.3 is needed.

Module SVIII – Summary of the safety concerns

The following summary table of safety concerns is included in the RMP.

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

Part III Pharmacovigilance plan (including post-authorisation safety studies)

The Pharmacovigilance plan is unchanged, except for a few editorial changes This is agreed.

Part IV Plans for post-authorisation efficacy studies

Not applicable.

Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

As there are no new safety concerns, Part V is unchanged.

Part VI Summary of the risk management plan

The editorial changes made to Part VI regarding the proposed indications are acceptable.

Part VII

The annexes are unchanged and acceptable.

4.1. Overall conclusion on the RMP

☒The changes to the RMP version 1.2 with data lock point of 25-05-2024 and final sign off date of 07-08-2024 are acceptable.

5. Changes to the Product Information

As a result of this variation, sections 4.1, 4.8 and 5.1 of the SmPC are being updated to reflect the new indication and data from the MDS/CMML studies. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

5.1.1. User consultation

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Inaqovi, EMEA/H/C/005823/0000 (Key safety messages) and Reblozyl, EMEA/H/C/004444/0000 (Description of Myelodysplastic syndromes (MDS)).

Assessment of the Bridging proposed by the applicant is attached in Appendix I.

The bridging report submitted by the applicant has been found acceptable.

6. Benefit-Risk Balance

6.1. Therapeutic Context

6.1.1. Disease or condition

Following the first RSI the MAH's presently proposed indication for Inaqovi is "as monotherapy for the treatment of adult patients with myelodysplastic syndromes (MDS) and a risk score of >3.5 according to the revised international prognostic scoring system (IPSS-R)."

6.1.2. Available therapies and unmet medical need

The treatment of MDS is based on the patient's risk category and cytogenetic profile. Higher-risk MDS carries a major risk of progression to AML and short survival, and treatment should aim to modify the

disease course, with options including allo-SCT, HMAs and, less frequently, ChT (mainly intensive anthracycline-cytarabine combinations).

In the EU, azacitidine (Vidaza) is approved for the treatment of patients not eligible for HSCT with intermediate-2 and high-risk MDS according to the IPSS and CMML with 10% to 29% marrow blasts without myeloproliferative disorder (Vidaza® SmPC).

There is an unmet need for effective disease modifying agents with impact on progression to AML/mortality.

6.1.3. Main clinical studies

Two clinical studies have been performed to support the new indication, ASTX727-02 NA and ASTX727-01-B.

ASTX727-02 NA

A Phase 3, Randomized, Open-Label, Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) versus IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML) (randomized n=138, treated n=133).

The primary objective was to establish bioequivalence between Inacovi, oral decitabine/cedazuridine tablets 100/35 mg on days 1–5 vs. IV decitabine 20 mg/m2 on days 1–5. Patients were randomised 1:1 to either tablets or IV for the first cycle. For cycle 2 patients were crossed over to the other alternative. From cycle 3 and onwards, all patients received tablets.

ASTX727-01-B

A Phase 1-2 Pharmacokinetic Guided Dose-Escalation and Dose-Confirmation Study of ASTX727, a Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine in Subjects with Myelodysplastic Syndromes (MDS). This first-in-human trial, ASTX727-01, had 3 stages: Phase 1 Dose Escalation, Phase 2 Dose Confirmation, and Phase 2 fixed dose combination (FDC). Focus here are the Phase 2 parts i.e., the Dose Confirmation Stage and FDC Stage of study ASTX727-01 (randomized n=86, treated n=80).

The primary objective was to establish bioequivalence between Inacovi, oral decitabine/cedazuridine tablets 100/35 mg on days 1–5 vs. IV decitabine 20 mg/m2 on days 1–5. Patients were randomised 1:1 to either tablets or IV for the first cycle. For cycle 2 patients were crossed over to the other alternative. From cycle 3 and onwards, all patients received tables.

The key clinical outcome of these studies is Complete Responses (CR), which are not anticipated to occur without active treatment (as illustrated by the control group trial of Dacogen that was pivotal to its approval for MDS in the US). The following is the definition of Responses in the ASTX727-02 NA and ASTX727-01-B (IWG2006):

Complete Response (CR): the following for at least 4 weeks		
Peripheral: normal peripheral counts with persistent granulocyte count ≥1.0 x 10^9/L, platelet ≥100 x 10^9/L, and Hgb ≥11 g/dL. **Marrow:** normal bone marrow with persistent marrow blasts ≤5%; persistent dysplasia will be noted.		
Partial Response (PR): the following for at least 4 weeks		
Peripheral: normal peripheral counts with granulocyte count ≥1.0 x 10^9/L, platelet count ≥100 x 10^9/L, and Hgb ≥11g/dL. **Marrow:** normal bone marrow and marrow blasts >5% but were reduced by 50% or more.		
Marrow Complete Response (mCR): the following at least for 4 weeks		
Reduction of bone marrow blasts to ≤5% and decrease by 50% or more with or without normalization of peripheral counts.		
Hematological Improvement (HI): lasts at least 8 weeks		
Erythroid Response (HI-E):	Major Response:	Hemoglobin increase ≥1.5 g/dL in the absence of RBC transfusions.
Platelet Response (HI-P):	Major Response:	Absolute increase of platelet count from <20 to >20 X 10^9/L and by at least 100%, or if more than 20 x 10^9/L, by an absolute increase of at least 30 x 10^9/L in the absence of platelet transfusions.
Neutrophil Response (HI-N):	Major Response:	granulocyte increase ≥100%, and by an absolute increase ≥0.5 x 10^9/L.
[a] Abnormal baseline counts should be assessed within one week prior to therapy, not influenced by transfusions (no transfusion for at least 1 week).		

6.2. Favourable effects

The geometric mean ratio (GMR) of 5-day total decitabine AUC0-24hr between Inaqovi and IV decitabine was 99% for patients with MDS/CMML and 100% for patients with AML (90% confidence interval [CI] 93% - 106% and 91% - 109% for MDS/CMML and AML, respectively).

Thus, similar exposure for 5-Day AUC0-24 between oral and IV decitabine was convincingly demonstrated. AUC0-24 for day 1 is lower for oral compared to IV treatment and Cmax is also lower following oral treatment (22-28% lower on day 5).

In ASTX727-02 NA CR was observed in 23.9% (n=16/67; 95% CI 14.3, 35.9) of all treated subjects with IPSS-R >3.5.

For patients with IPSS-R >3.5 and BM blasts >5% CR was observed in 17.1% (n=7/41; 95% CI 7.2, 32.1). The overall response (CR+Cri and PR) was 59.4% n=82/138; 95% CI 50.7, 67.7)). Median duration of complete response was 14.1 months (95% CI 8.3 to 18.1) for patients with IPSS-R >3.5.

In ASTX727-01-B 14 16.7% (n=6/36) achieved a complete response (CR) (95% CI: 6.4, 32.8) for patients with IPSS-R >3.5.

For patients with IPSS-R >3.5 and BM blasts >5% CR was observed in 16.7% (n=4/24; 95% CI 4.7, 37.4). Median duration of complete response was 4.7 months (95% CI 1.1, NE) for patients with IPSS-R >3.5.

From both ASTX727-02 NA and ASTX727-01-B a total of 36 patients that did not fulfil any of the IWG2023 CR response criteria at baseline, i.e. patients with tri-linage cytopenia and >5% BM blasts. In this population did 8 patients achieve CR and 13 mCR, 22.2% and 36.1% respectively.

6.3. Uncertainties and limitations about favourable effects

The evaluation of efficacy of Inaqovi in studies ASTX727-02 NA and ASTX727-01-B is limited due to the single arm design, with no statistical inference on clinical outcomes. While complete responses are

not anticipated in the absence of therapy, and demonstrate the activity of Inaqovi, time to event endpoints is not fit for efficacy assessments since drug effects cannot be isolated. No conclusions can be drawn regarding the impact of Inaqovi on time to AML and OS.

Marrow responses indicate the direct effect of decitabine on the tumour and are a key part of the definition of complete response. However, the clinical benefit of achieving CR has not been justified. In addition, the reported CR rates contain patients already fulfilling part of the CR criteria already at baseline. In total 36 patients were identified from both studies that did not fulfil any IWG2023 CR criteria at baseline. This is a very limited, post hoc defined population to determine established efficacy based on CR.

No data to support treatment of patients intended for allo-SCT has been provided.

6.4. Unfavourable effects

The safety of ASTX727 in MDS/CMML patients is primarily assessed based on the two main studies, ASTX727-02-NA and ASTX727-01B (total n=208), with supportive data from the study in AML (ASTX727-02-EU; n=80).

The safety profile for ASTX727 in MDS/CMML was as expected for a cytotoxic treatment. Thus, AEs related to 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 CTCAE Grade 3 or higher in the MDS/CMML population, including SAEs and fatal events. AEs within SOC Blood and lymphatic disorders were overall reported in 75% of MDS/CMML patients, and the frequencies of Grade 3 or higher of PT anaemia, febrile neutropenia, thrombocytopenia and neutropenia were 40.4%, 33.2%, 19.7% and 20.2% respectively. The frequency of AEs in the SOC infections and infestations overall was 69% and the frequency of Grade 3 or higher was 38.9%.

The events within SOC Gastrointestinal disorders (reported in 87% of patients) were in general of CTCAE Grade 1-2, and about half of these events were not considered treatment-related by the investigator.

The most commonly reported laboratory deviations in MDS/CMML patients were platelet count decreased (all events 43%, Grade ≥3 events 38%), neutrophil count decrease (all events 38%, Grade ≥3 events 36%), and white blood cell decrease (all events 24%, Grade ≥3 events 21%).

There rate of dose modifications (interruptions or reductions) was high, about 50%, in the MDS/CMML study, but the rate of discontinuations due to AEs was lowest in MDS/CMML patients, 6.3% overall and 1.9% due to AEs that were considered treatment-related. Therefore, the toxicity seems to be largely manageable with dose modifications.

Data from an extension study (n=72) indicated that the incidence of anticipated events (myelosuppression, haemorrhage, infection) decreased compared with the parent studies.

6.5. Uncertainties and limitations about unfavourable effects

The most commonly reported AEs, including fatal events, in the MDS/CMML and AML patient populations, haematologic suppression and its consequences, might be due to the underlying disease as well as to ASTX727 treatment. An adequate rate estimation for ASTX727 cannot be made based on OS metrics, as the pivotal studies are basically single-arm trials.

6.6. Effects Table

Table 3. Effects Table for Inaqovi - indicated for the treatment of adult patients with myelodysplastic syndromes (MDS) with IPSS-R >3.5 (data cut-off Database lock**: 07 June 2021 (ASTX727-02 NA), 16 Sep 2020 (ASTX727-01-B)>**

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
CR	IPSS-R>3.5	N, (%) (95% CI)	22, (21.4%) (13.9, 30.5)	N/A	N=103 No control arm Patients already fulfilling criteria for CR at baseline	ASTX727-02-NA +ASTX727-01-B
DoCR	Median duration of CR	Months (95% CI)	12.9 (5.5, 16.2)	N/A	Small number of patients	ASTX727-02-NA +ASTX727-01-B
CR	IPSS-R>3.5 and >5% BM blasts at inclusion	N, (%) (95% CI)	11, (16.9%) (8.8, 28.3)	N/A	N=65 No control arm A proportion of patients did already at baseline fulfil criteria for haematological parameters included in CR	ASTX727-02-NA +ASTX727-01-B
DoCR	IPSS-R>3.5 and >5% BM blasts at inclusion	Months (95% CI)	14.1, (8.3, 18.1)	N/A	Small number of patients	ASTX727-01-B +ASTX727-01-B

Unfavourable Effects

Effect	Description	Subjects with AE (%)	Treatment	Control	Uncertainties/ Strength of evidence	References
SOC Blood and Lymphatic disorders		75%	ASTX727 (35 mg decitabine + 100 mg cedazuridine) x 5 days per 28-day cycle + one cycle of IV decitabine 20 mg/m^2 x 5 days	N/A	No control arm	Pooled data from Studies ASTX727-02 NA and ASTX727-01-B N=208

SOC Infections and Infestations		87%	"	"	"	"
SOC Gastroin-testinal disorders		69%	"	"	"	"
Treatment-related Grade ≥3 AEs	Treatment-relatedness as assessed by investigator	66%	"	"	"	"
Treatment-related SAEs	Treatment-relatedness as assessed by investigator	17%	"	"	"	"
Discon-tinuation due to treatment-related AE	Treatment-relatedness as assessed by investigator	1.9%	"	"	"	"
Fatal treatment-related AE	Treatment-relatedness as assessed by investigator	2.4%	"	"	"	"

Abbreviations:

Notes:

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

Decitabine is not approved for MDS in the EU. Therefore, a PK bridging approach is not possible; rather, clinical benefits need to be inferred directly from the Inaqovi program.

In the US, decitabine is indicated for treatment of adult patients with myelodysplastic syndromes (MDS) with refractory anemia and/or with intermediate-1, intermediate-2, or high-risk International Prognostic Scoring System groups. This was based on an RCT versus no active treatment, which showed a 17% complete response rate for decitabine, compared to none for best supportive care.

The primary endpoint of the pivotal trial for Inaqovi was the similarity of AUC between oral decitabine (35 mg decitabine in combination with 100 mg cedazuridine) and for decitabine given IV at 20 mg/m2 per day for 5 consecutive days per 28-day cycle. Since this was reached, it can be inferred that the efficacy of ASTX727 at the proposed dose is similar to that of IV decitabine at this dose.

The fact that AUC was similar for the i.v. decitabine and Inaqovi, allows for the treatment of this study, with a PK cross-over design, as a single arm trial isolating the effect of Inaqovi in terms of CR.

CR reflects near-normalized haematological parameters in the bone marrow with <5% blasts. Such normalisation is not anticipated without treatment. However, many patients in the IPSS-R >3.5 population fulfilled parts of the criteria for CR already at baseline precluding the use of CR in the whole population to isolate drug effect. Furthermore, the clinical benefit of achieving BR in this IPSS-R >3.5 patient population need to be justified. Patient level surrogacy as claimed by the applicant do not

separate the prognostic and predictive value of achieving CR. This cannot support an efficacy claim as it does not isolate Inaqovi treatment as cause of the claimed survival benefit.

For high-risk MDS patients the only potentially curative option is allo-SCT. No data to support treatment of patients intended for allo-SCT has been provided. Hence, B/R for patients intended for allo-SCT cannot be determined.

The safety profile for ASTX727 in MDS at the proposed 5-day regimen is as expected for a cytotoxic treatment and is acceptable in the proposed treatment niche, provided that efficacy can be established.

6.7.2. Balance of benefits and risks

The benefit risk balance of Inaqovi is negative since efficacy for the sought indication is presently not considered established.

6.7.3. Additional considerations on the benefit-risk balance

A request for a SAG-O meeting has been discussed by the CHMP on the proposal from the Rapporteur but not further pursued.

6.8. Conclusions

The overall B/R of Inaqovi is negative.