

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212576Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	212576
Priority or Standard	Priority
Submit Date(s)	December 11, 2019
Received Date(s)	December 11, 2019
PDUFA Goal Date	August 11, 2020
Division/Office	Division of Hematologic Malignancies I/Office of Oncologic Diseases
Review Completion Date	July 7, 2020
Established Name	decitabine and cedazuridine
(Proposed) Trade Name	INQOVI
Pharmacologic Class	nucleoside metabolic inhibitor (decitabine) cytidine deaminase inhibitor (cedazuridine)
Applicant	Astex Pharmaceuticals, Inc.
Formulation(s)	Tablet
Dosing Regimen	One INQOVI (35 mg decitabine and 100 mg cedazuridine) tablet taken orally once daily on Days 1 through 5 of each 28-day cycle
Applicant Proposed Indication(s)/Population(s)	INQOVI is a combination of cedazuridine, a cytidine deaminase inhibitor, and decitabine, a nucleoside metabolic inhibitor, indicated for treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	INQOVI is a combination of decitabine, a nucleoside metabolic inhibitor, and cedazuridine, a cytidine deaminase inhibitor, indicated for treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS with the following French-

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	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.

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OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE=Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management
 IRT/QT=Interdisciplinary Review Team for QT Studies
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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT/SGPT	alanine aminotransferase
AML	acute myeloid leukemia
ANOVA	analysis of variance
AR	adverse reaction
AST/SGOT	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC ₀₋₈	area under the plasma concentration-time curve from time zero to 8 hours
AUC ₀₋₂₄	area under the plasma concentration-time curve from time zero to 24 hours
AUC _{0-inf}	area under the plasma concentration time curve from time zero extrapolated to infinity
AUC _{0-t}	area under the concentration-time curve from time 0 hours to the time of last measurable concentration
BLQ	below the limit of quantification
BM	bone marrow
BSA	body surface area
C1D1	Cycle 1 Day 1 (first study drug administration date)
CBC	complete blood counts
CDA	cytidine deaminase
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent clearance
CL _r	renal clearance
C _{max}	maximum measured concentration
CMC	chemistry, manufacturing, and controls
CMML	chronic myelomonocytic leukemia
CNS	central nervous system
CNT	concentrative nucleoside transporter
CR	complete response
CRCL	creatinine clearance
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
DEC	decitabine
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DMF	drug master files
DSRC	Data and Safety Review Committee

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ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
FAB	French-American-British
FDA	Food and Drug Administration
FDC	fixed-dose combination oral tablet of cedazuridine and decitabine
GCP	good clinical practice
gCV	geometric coefficient of variation;
Geo. LSM	geometric least squares mean
GI	gastrointestinal
GLP	good laboratory practice
HCT	hematocrit
HD	high dose
hERG	human ether à-go-go related gene
HEK	human embryonic kidney cells
HMA	hypomethylating agent
HI	hematologic improvement
HI-E	hematologic improvement-erythrocytes
HI-N	hematologic improvement-neutrophils
HI-P	hematologic improvement-platelets
IC ₅₀	half-maximal inhibition
ICH	International Council for Harmonization
IND	Investigational New Drug
Int-1	IPSS Intermediate-1 risk group
Int-2	IPSS Intermediate-2 risk group
IPSS	International Prognostic Scoring System
IPSS-R	International Prognostic Scoring System – Revised
IQR	inter-quartile range
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRC	Independent Review Committee
IV	intravenous
IWG	International Working Group
K-M	Kaplan-Meier
LD	low dose
LINE-1	long interspersed nucleotide element-1
LLOQ	lower limit of quantification
LOESS	locally estimated scatterplot
LSM	least squares mean
mCR	marrow complete response
MD	mid dose
MDS	myelodysplastic syndromes
MDS/MPN	myelodysplastic/myeloproliferative neoplasm

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M:E	myeloid:erythroid ratio
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network guidelines
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NOEL	no-observed-effect level
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAP	Pharmacometric Analysis Plan
PD	pharmacodynamics
PB	peripheral blood
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	by mouth
PopPK	population PK
PP	per protocol
PPI	proton pump inhibitor
PR	partial response
PRO	patient reported outcome
PS	performance status
PSUR	Periodic Safety Update report
PT	preferred term
QTc	heart rate-corrected QT interval
QWBA	quantitative whole-body autoradiography
RBC	red blood cell
R _{DDI}	ratio of AUC when administered with or without cedazuridine
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SEER	Surveillance, Epidemiology, and End Results
SOC	system organ class
t _{1/2}	terminal elimination half-life
TEAE	treatment emergent adverse event
TEAR	treatment emergent adverse reaction
TESAR	treatment-emergent serious adverse reaction

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TK	toxicokinetic
TI	transfusion independence
$t_{\max}$	time to reach maximum concentration
ULN	upper limit of normal
V/F	volume of distribution
WBC	white blood cells
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

Trade name:	Inqovi®
Established name:	decitabine and cedazuridine
Also known as:	ASTX727
Dosage form:	Tablets: 35 mg decitabine and 100 mg cedazuridine
Therapeutic class:	Antineoplastic
Chemical class:	Small molecule
Pharmacologic class:	nucleoside metabolic inhibitor (decitabine), cytidine deaminase inhibitor (cedazuridine)
Mechanism of action:	hypomethylating agent (decitabine) is antineoplastic agent

The Applicant submitted NDA 212576 for decitabine/cedazuridine tablet, also known as ASTX727, for the treatment of patients with previously treated and untreated myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML). Decitabine is a hypomethylating agent approved as the intravenous formulation for the same indication sought by the Applicant. Cedazuridine is a new molecular entity (NME) and is a cytidine deaminase inhibitor that prevents the rapid metabolism of decitabine in the gastrointestinal tract to allow for oral administration. The NDA provides for a fixed dose combination tablets of 35 mg of decitabine and 100 mg of cedazuridine which when given once daily for 5 days provides comparable cumulative exposure to the IV decitabine 5-day regimen of 20 mg/m² by intravenous infusion over 1 hour daily for 5 days. Decitabine/cedazuridine fixed dose tablet is administered one tablet daily on days 1-5 of a 28-day cycle until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review teams conclude that the information submitted by the Applicant has provided substantial evidence for the effectiveness of decitabine/cedazuridine for the treatment of adult patients with previously treated and untreated myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) and supports regular approval of this indication. This approval was based on the results of a phase 1/2 study (ASTX727-01) and a randomized phase 3 study (ASTX727-02). The recommendation is based on demonstration of equivalent exposure over 5 days and no erosion of efficacy compared to the 5-day IV decitabine dosing. The geometric mean ratio (90% CI) for the 5-day cumulative decitabine exposure between decitabine/cedazuridine and IV decitabine was 0.99 (0.93, 1.06). In the phase 2 study, the complete response (CR) rate was 18% (95% CI: 10, 28) with duration of response of 8.7 months (range: 1.1, 18.2). In the phase 3 study, the CR rate was 21% (95% CI: 15, 29) with duration of response of 7.5 months (range: 1.7, 17.5).

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Decitabine and cedazuridine tablets, also known as ASTX727, are a fixed-dose combination drug product that contains the active ingredients decitabine (35 mg) and cedazuridine (100 mg). Decitabine is a hypomethylating agent approved as intravenous formulation for the treatment of myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML). The oral bioavailability of decitabine is limited by degradation of decitabine by cytidine deaminase (CDA) enzyme activity present in the gastrointestinal tract and liver of humans. Cedazuridine is a CDA inhibitor, and oral administration of cedazuridine with decitabine enhances the oral bioavailability of decitabine. The proposed dose of decitabine and cedazuridine tablets provides systemic decitabine exposure comparable to the approved dose of intravenous decitabine.

MDS is a heterogeneous group of diseases characterized by ineffective, dysplastic hematopoiesis leading to cytopenias. Clinical presentation of MDS is a manifestation of cytopenias including fatigue, infections, and bleeding and risk of transformation to acute myeloid leukemia (AML) which is rapidly fatal without treatment. Patients with MDS have an increased risk of mortality. Current prognostic classification is the International Prognostic Scoring System-Revised (IPSS-R), and higher-risk MDS is classified as IPSS-R intermediate- (score >3.5), high-, or very high-risk MDS. Higher-risk MDS can be treated in the frontline setting with hypomethylating agents, azacitidine or decitabine. CMML is a related hematopoietic disorder characterized by peripheral blood monocytosis. CMML was previously classified as MDS and is currently classified as myelodysplastic/myeloproliferative neoplasm (MDS/MPN), and the treatment approach is similar to that for MDS.

Decitabine was approved as the intravenous formulation in 2006 for treatment of adult patients with previously treated and untreated, de novo and secondary MDS and CMML. In clinical studies leading to the approval of intravenous decitabine, the overall response rate (ORR) was 16-17% with complete response (CR) rate of 9-15%.

Because of extensive clinical experience with intravenous decitabine, the development of ASTX727 was designed such that oral administration of ASTX727 over 5 days would result in comparable exposure to intravenous decitabine administered daily for 5 days. The clinical program would then provide evidence of similar safety and efficacy profile compared to intravenous decitabine. The demonstration of comparable exposure, no erosion of efficacy, and similar safety profile was based on a phase 2 study (ASTX727-01-B) and a phase 3 study (ASTX727-02) in adult patients with MDS and CMML, for which intravenous decitabine is currently approved. Both studies were randomized, open-label, 2-sequence crossover studies where patients received either oral ASTX727 or intravenous decitabine in cycles 1 and 2 with two-way crossover,

and the remaining cycles were oral ASTX727. The primary endpoints for each study were 5-day cumulative exposure. Secondary endpoints included safety and efficacy including overall response rate and rates of transfusion independence. The acceptable response rate for MDS appropriate for regulatory decision-making is ORR defined as CR+PR responses. There were no PR responses on the Phase 2 or Phase 3 trials of ASTX727, and therefore, only CR responses were considered for demonstration of clinical benefit.

The geometric mean ratio for the 5-day cumulative decitabine exposure between decitabine/cedazuridine and IV decitabine was 0.99 (90% CI: 0.93, 1.06) in the phase 3 study. In study ASTX727-01-B in 80 patients, the CR rate was 18% (95% CI: 10, 28) with duration of response of 8.7 months (range: 1.1, 18.2). In study ASTX727-02 in 133 patients, the CR rate was 21% (95% CI: 15, 29) with duration of response of 7.5 months (range: 1.7, 17.5). Notably, the initial results from ASTX727-02 did not provide sufficient time on study resulting in low response rates and relatively short durability; however, a later data cutoff included at the 120-day safety update provided longer follow up. The CR responses were sufficiently durable to demonstrate clinical benefit in this patient population. The durability was slightly lower than with IV decitabine, however, the time on treatment was shorter and many of the responses were ongoing at the time of data cutoff, and thus, the median duration of CR would be expected to increase with longer follow-up. The CR benefit was supported by a transfusion benefit on both trials, which demonstrated that 49-53% of patients who were dependent on transfusions at baseline achieved at least 56 days transfusion independence post-baseline and 63-64% of patients who were independent of transfusions at baseline were able to maintain that transfusion independence for at least 56 days post-baseline.

Safety data was pooled across studies ASTX727-01-B and ASTX727-02 given the similar study designs and patient populations. Comparative review of safety between ASTX727 and IV decitabine was focused in the first cycle of therapy to avoid the possibility of overlapping toxicities between the first and second cycles of therapy. Evaluation of safety across all cycles included one cycle of IV decitabine, but because adverse reactions cannot be easily attributed to one cycle, the IV decitabine cycle was included in safety analysis. Overall, the adverse reactions appear to be more common in patients treated with ASTX727 compared to IV decitabine in the first cycle of therapy. This observation may have been due to imbalances in baseline demographics. It will be important for clinicians to closely monitor patients while on this oral form of decitabine given the possibility for significant cytopenias leading to increased risk of infection and bleeding. Despite this being an oral therapy that will allow patients to spend less time in the clinic, it will be important to have close follow-up for laboratory testing and clinical monitoring. The important risks of myelosuppression and embryo-fetal toxicity are unchanged from IV decitabine based on the data presented in the submission. Overall, given the historically poor outcomes of patients with MDS who are candidates for hypomethylating agent therapy, the level of toxicity observed with ASTX727 is acceptable for the clinical benefit observed.

In conclusion, the submitted clinical information from studies ASTX727-01-B and ASTX727-02 provided data for equivalent 5-day exposure of decitabine when administered as 35 mg decitabine and 100 mg cedazuridine tablets compared to the 5-day regimen of intravenous decitabine. Similar efficacy was demonstrated by CR rate and duration of CR supported by transfusion independence. The safety profile was also similar between oral ASTX727 and intravenous decitabine with small increase in myelosuppression which is manageable with monitoring and dose modification, if needed. While the treatment regimen evaluated included one cycle of IV decitabine for each patient, treatment with decitabine typically provides responses over several cycles of therapy, and the single IV cycle likely did not specifically contribute to efficacy of the oral regimen. Administering all cycles as oral decitabine and cedazuridine tablets is expected to have similar safety and effectiveness as intravenous decitabine. This provides for an oral route of administration of decitabine which may reduce time in clinic, and it will be important for prescribers to monitor compliance and adverse events closely.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• MDS is a heterogeneous group of diseases characterized by ineffective, dysplastic hematopoiesis leading to cytopenias • MDS is a serious and life-threatening disorder with complications related to cytopenias and transformation to AML resulting in decreased survival • MDS occurs in 4.5 per 100,000 persons, and is primary a disease of older adults with a median age at diagnosis of approximately 70 years • CMML is characterized by peripheral blood monocytosis • CMML was previously classified as MDS and the treatment approach is similar to that for MDS. • CMML occurs in 0.5 per 100,000 persons, and is primary a disease of older adults	MDS and CMML are serious diseases with a substantial risk of mortality. The FAB classification of MDS with refractory anemia with excess blasts in transformation (RAEB-T) was previously included in MDS but is currently categorized as AML and was excluded from the recommended indication. CMML was previous classified as MDS but is currently categorized as myelodysplastic/myeloproliferative neoplasm (MDS/MPN) and is a separate disease entity from MDS.
Current Treatment Options	• Decitabine is approved for treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts,	The hypomethylating agents, decitabine and azacitidine administered IV, are the only FDA approved therapies for higher-risk MDS (IPSS-R intermediate [score > 3.5], high, or very high or IPSS intermediate-2 or high risk). Despite the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups. ORR was 16-17% with CR rate of 9-15%. • Azacitidine is approved for treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). ORR was 14-16% with CR rate of 6%. • Lenalidomide is approved for treatment of adult patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Transfusion independence was seen in 99/148 (67%) patients.	differences in the wording of the approved indications, both are used interchangeably in the frontline setting for the treatment of patients with MDS, predominately in patients with higher-risk MDS. Lenalidomide is approved in patients with low-risk disease with deletion 5q and is not relevant to the population in which HMAs are used. Oral therapy would be of benefit, especially to elderly patients, to potentially decrease time needed for clinic visits due to IV infusions and treatment burden as treatment may continue for months to years if patients are deriving benefit.
Benefit	• Phase 2 and phase 3 studies were randomized open label randomized, open-label, 2-sequence crossover studies where patients received either oral ASTX727 or intravenous decitabine in cycles 1 and 2 followed by oral ASTX727 in subsequent cycles • The geometric mean ratio (90% CI) for the 5-day cumulative decitabine exposure between decitabine/cedazuridine and IV decitabine was 0.99 (0.93, 1.06) • Phase 2 study (ASTX727-01-B), the CR rate was 18% (95% CI: 10, 28) with duration of response of 8.7 months (range: 1.1, 18.2)	The basis of approval was demonstration of equivalent 5-day exposure to IV decitabine and no erosion of efficacy demonstrated by ORR and CR compared to IV decitabine. For MDS the acceptable response for regulatory decision making is overall response rate (ORR), defined as CR+PR responses. There were no PR responses on the Phase 2 or Phase 3 trials of ASTX727, and therefore, only CR with duration of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Phase 3 study (ASTX727-02), the CR rate was 21% (95% CI: 15, 29) with duration of response of 7.5 months (range: 1.7, 17.5)	CR was considered. Supportive evidence was provided by rates of transfusion independence. Notably the time on treatment was shorter in the phase 3 resulting in a shorter median duration of CR which could improve over time. The exposure on day 1 is lower for oral ASTX727 compared to IV decitabine, so while IV decitabine can be substituted for oral decitabine to complete a cycle, the converse is not necessarily true without lower exposure over the cycle.
Risk and Risk Management	- The most common grade 3-4 laboratory abnormalities ($\geq 50\%$) included neutropenia, thrombocytopenia, and anemia - The most common adverse reactions ($\geq 20\%$) were fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, leukopenia, cough, decreased appetite, upper respiratory infection, pneumonia, and transaminase increased - Serious adverse reactions ($>5\%$) included febrile neutropenia, pneumonia, and sepsis - Fatal adverse reactions included sepsis, septic shock, pneumonia, respiratory failure, and septic shock (1.4%), cerebral hemorrhage, and sudden death - Risk to fetus for decitabine was well described previously	Overall safety profile is acceptable for patients with MDS and CMML and similar to that described for IV decitabine. Prescribing information includes W&P for myelosuppression and embryo-fetal toxicity, consistent with IV decitabine. Slightly higher rate of cytopenias was observed with oral ASTX727 compared to IV decitabine in cycle 1; (b) (4) Post-marketing experience includes differentiation syndrome which occurred with IV decitabine but was not reported in clinical trials of decitabine/cedazuridine due to the limited patient experience.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	
☐	☐ Patient reported outcome (PRO)	
☐	☐ Observer reported outcome (ObsRO)	
☐	☐ Clinician reported outcome (ClinRO)	
☐	☐ Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	
☒	No patient experience data were submitted in the application.	

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NDA 212576, Original
INQOVI (decitabine and cedazuridine)

X

Lori Ehrlich, MD, PhD
Cross-Disciplinary Team Leader
OOD/DHM1

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Myelodysplastic syndromes (MDS) include a heterogeneous group of hematopoietic stem cell disorders characterized by dysplastic changes in myeloid, erythroid, and megakaryocytic progenitors and associated with cytopenias affecting one or more of the three lineages (Steensma 2018). Median age at diagnosis is approximately 70 years, and prognosis is generally poor with median survival times of 1.2 and 0.4 years in patients with intermediate (Int)-2 and high-risk MDS, respectively (Steensma 2018; Greenberg et al 1997). The disease affects more males than females, and among different racial groups, White individuals have the highest incidence (Garcia-Manero 2015; Ma et al 2007). MDS may evolve into acute myeloid leukemia (AML) in one-third of patients (Shukron et al 2012).

Chronic myelomonocytic leukemia (CMML) is characterized by a persistent peripheral blood monocytosis $\geq 1 \times 10^9/L$ with monocytes accounting for $\geq 10\%$ of white blood cells (WBCs) (Solary and Itzykson 2017). The condition is currently categorized by the World Health Organization (WHO) as a myelodysplastic/ myeloproliferative neoplasm (MDS/MPN) (Arber et al 2016). However, as CMML was previously classified as MDS, the treatment approach is similar to that for MDS.

According to the US-based Surveillance, Epidemiology, and End Results (SEER) program, a total of 28,138 new cases of MDS were diagnosed between 2012-2016 in the US, corresponding to an age-adjusted incidence rate of 4.5 per 100,000 persons. This estimate excluded a total of 2,961 cases of CMML, which corresponds to a CMML-specific age-adjusted incidence rate of 0.5 per 100,000. Between 2012 and 2016, 90% of cases in the US were diagnosed in patients ≥ 60 years of age (Howlader et al 2019).

Patients with MDS are at risk of complications of cytopenia and AML transformation. Functional defects or other comorbidities, such as cardiac or pulmonary conditions, may increase the risk of complications of anemia, iron overload due to transfusion, or bleeding due to thrombocytopenia (Steensma 2018). The main prognostic classification system for MDS is the International Prognostic Scoring System (IPSS), which was introduced in 1997 (Greenberg et al 1997) and revised in 2012 (IPSS-Revised [IPSS-R]) (Greenberg et al 2012). Both systems are widely used. The IPSS-R uses slightly different cytopenia cutoff points and incorporates the MDS cytogenetic score. Using IPSS criteria, expected median survival for Int-1, Int-2, and high risk MDS are 3.5, 1.2, and 0.4 years, respectively (Greenberg et al 1997). Using the comparable risk

groups in the IPSS-R, the expected median survival for intermediate, high risk, and very high risk groups are 3, 1.6, and 0.8 years, respectively ([Greenberg et al 2012](#)).

There is no universally adopted risk classification system for CMML, but several classifications recognized the prognostic importance of total WBCs, thus differentiating dysplastic CMML (lower WBCs) from proliferative CMML (higher WBCs). More recently, the 2016 WHO classification defined 3 groups (CMML-0; CMML-1; and CMML-2) based on percentage blasts in peripheral blood and bone marrow ([Arber et al 2016](#)). Patients with CMML are generally diagnosed between age 65 and 75 years with a 2:1 male predominance ([Parikh and Tefferi 2012](#)). Similar to MDS, the main manifestations are those of the underlying cytopenia, including fatigue and dyspnea due to anemia, susceptibility to infections, and bleeding (although less common). Median survival ranges from approximately 9 to 20 months ([Parikh and Tefferi 2012](#)).

In conclusion, both MDS and CMML are serious and life-threatening myeloid malignancies with short median survival and life-threatening complications due to cytopenias and risk of transformation to AML.

The Regulatory Authorities' Assessment:

FDA agrees that both MDS and CMML are serious diseases with a substantial risk of mortality.

2.2. Analysis of Current Treatment Options

The only FDA-approved treatments for Intermediate and high-risk MDS and CMML are the hypomethylating agents azacitidine (Vidaza, FDA approved in 2004) and decitabine (Dacogen, FDA approved in 2006) (Table 1). Lenalidomide (Revlimid) is only approved in transfusion-dependent anemia in patients with low or intermediate-1 risk MDS with 5q deletion so it is not of relevance for patients with higher risk MDS or CMML.

Decitabine (Dacogen®) is administered as a 3-day regimen (15 mg/m² over a 3-hour intravenous [IV] infusion repeated every 8 hours for 3 days) or a 5-day regimen (20 mg/m² over a 1-hour IV infusion repeated daily for 5 days) ([Dacogen USPI 2019](#)). Based on published data, the 5-day regimen has been globally adopted as the standard regimen due to its improved convenience, better tolerability, lower total cycle dose (100 mg/m² compared with 135 mg/m²), and comparable benefit-risk profile compared with the 3-day regimen. Almost all current clinical studies of IV decitabine use the 5 day regimen. Azacitidine (Vidaza®) is administered daily for 7 days (starting dose of 75 mg/m² subcutaneous [SC] or IV) ([Vidaza USPI 2018](#)). Both drugs have improved the outcomes of intermediate- and high-risk MDS patients with a median survival time of 14 to 24 months ([Kantarjian et al 2006](#); [Fenaux et al 2009](#); [Zeidan et al 2018](#)).

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA and Health Canada Approved Treatments for MDS and CMML						
DACOGEN (decitabine)	MDS, CMML*	FDA: 2006 Type 1 NME Standard Review, Orphan Status 2010 5-day regimen approved Canada: 2019	<u>3-day:</u> 15 mg/m ² IV (3 hour) every 8 hours for 3 days	<u>3-day (N=89):</u> ORR (CR+PR): 17% CR: 9% Median duration of response (CR+PR): 288 days (116-388)	Delay and reduce dose for hematologic toxicity Fatal and serious myelosuppression occurs with treatment Can cause fetal harm	Repeat cycles every 6 weeks upon hematologic recovery for a minimum of 4 cycles
			<u>5-day:</u> 20 mg/m ² IV (1 hour) daily for 5 days	<u>5-day (N=99):</u> ORR (CR+PR): 16% CR: 15% Median duration of response (CR+PR): 443 (72-722)		Repeat cycles every 4 weeks upon hematologic recovery for a minimum of 4 cycles
VIDAZA (azacitidine)	MDS, CMML**	FDA: 2004 Type 1 NME Priority Review, Orphan Status Canada: 2010	<u>Starting Dose:</u> 75 mg/m ² SC or IV, daily for 7 days	Study 1 (N=99 or 89 without AML): Overall (CR+PR): 15.7% CR: 5.6% PR: 10.1% Study 2 (N=72) CR+PR (13.9%) Study 4 (N=179) Median OS 24.5 months vs 15 months for conventional care	Monitor for hematologic response and renal toxicities Causes anemia, neutropenia, thrombocytopenia Potentially hepatotoxic; increased risk for renal toxicity in patients with renal impairment	Increase dose to 100 mg/m ² if beneficial effect is not seen after 2 cycles and if no toxicity Repeat cycles every 4 weeks and treat for a minimum of 4-6 cycles

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Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				regimens		
Other Treatments						
Revlimid (lenalidomide)	Low or int-1 MDS with deletion 5q and transfusion-dependent anemia	FDA: 2005 Type 1 NME Priority Review, Orphan Status	10 mg orally once daily	RBC TI (N=148): 67%	Embryo-fetal toxicity Hematologic toxicity Venous and arterial thromboembolism	

CR=complete response; NME = new molecular entity; PR=partial response; ORR=overall response rate; RBC=red blood cell; TI=transfusion independence

* DACOGEN is indicated for treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

** VIDAZA is indicated for the treatment of patients with the following myelodysplastic syndrome (MDS) subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.

Source: USPIs for Dacogen, Vidaza, and Revlimid

The Applicant's Position:

Within the previous 15 years, agents approved for treatment of higher-risk MDS and CMML (decitabine, azacitidine) have improved patient outcomes ([Kantarjian et al 2006](#), [Fenaux et al 2009](#)) with higher response rates, hematological improvement, and higher transfusion independence than either best supportive care, or other conventional care regimens. Azacitidine also showed improved survival over conventional care regimens ([Fenaux et al 2009](#)). This is believed to be related to the prolonged treatment (median of 9 azacitidine cycles) in the AZA-001 study where azacitidine was given as long as the patient continues to benefit ([Fenaux et al 2009](#)). Decitabine MDS studies suffered from a design flaw where decitabine was only given for 2 cycles after achieving CR, or discontinued if a patient did not achieve at least partial response (PR) after 6 cycles. This resulted in a much shorter number of cycles in the decitabine study (median 3 cycles) ([Kantarjian et al 2006](#)). It is now globally acknowledged that both agents should be given continuously since stopping treatment is associated with quick relapse ([Cabrero et al 2015](#)), and that patients with stable disease and no objective response can still have a survival benefit ([Silverman et al 2011](#); [Papageorgiou et al 2018](#)). Both Dacogen and Vidaza USPIs recommend treatment for at least 4 to 6 cycles, and that treatment continues as long as the patient benefits.

The importance of treatment continuation for several months and sometimes years as long as the patient is benefitting results in significant burden on MDS patients. Patients with MDS are often over the age of 70 years and frequently have comorbidities or limited mobility that hinder their ability to attend daily hospital/clinic visits for multiple days each month to receive IV infusions or large volume subcutaneous injections, which can extend over several months or years, particularly in responding patients. This burden may ultimately lead to premature treatment discontinuation and put patients at risk of relapse, since HMA treatment must be continued for as long as the patient continues to benefit. At the same time complication of IV and subcutaneous administrations may result in infections and/or bleeding complications that may be serious in the context of severe neutropenia and thrombocytopenia that these patients often have.

An orally available hypomethylating agent (HMA) should substantially reduce the burden of treatment for patients and their caregivers. Identification of an orally bioavailable HMA agent has been challenging, primarily due to the rapid metabolism of nucleosides by cytidine deaminase (CDA) in the gastrointestinal (GI) mucosa and liver. High levels of CDA in the GI tract and liver rapidly degrade nucleosides upon oral administration and limit or prohibit their oral bioavailability. For example, to achieve even modest exposures of azacitidine requires administration of large doses, which are associated with Grade 3 and Grade 4 GI toxicity (e.g., nausea, vomiting, and diarrhea) and high variability in systemic exposures ([Garcia-Manero et al 2011](#)). The applicant believes that an oral HMA that provides equivalent systemic exposure to its parenteral form will alleviate the significant burden on MDS patients and their caregivers, and reduce utilization of hospital/clinic resources needed for parenteral administration. It also has the potential of achieving better long term treatment compliance, and fewer adverse

reactions related to multiple parenteral administrations.

The Regulatory Authorities' Assessment:

FDA agrees that current treatment options for MDS include decitabine, azacitidine, and lenalidomide, but that lenalidomide is only approved for patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities. Both decitabine and azacitidine are approved for patients with MDS, with slight differences in their indication statements, as outlined by the Applicant above. Of note, the azacitidine indication for the FAB subtypes of RA and RARS is limited to patients with neutropenia or thrombocytopenia or requiring transfusions, whereas this is not mentioned in the decitabine indication. Furthermore, the decitabine indication notes the inclusion of patients with de novo and secondary MDS, whereas this is not mentioned in the azacitidine indication statement. For decitabine, intermediate-1, intermediate-2, and high-risk IPSS is stipulated, whereas this is not mentioned in the indication statement for azacitidine. Lastly, the decitabine indication includes previously treated and untreated patients given that a subset of patients on the supportive trials received previous therapy for their MDS.

In practice, despite the small differences in the wording of the drug labels, both drugs are used interchangeably in the frontline setting for the treatment of patients with MDS, predominately in patients with higher-risk MDS (IPSS-R intermediate [score > 3.5], high, or very high or IPSS intermediate-2 or high risk) based on NCCN guidelines (NCCN 2020).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

ASTX727 is not currently marketed in the United States. ASTX727 fixed-dose combination (FDC) tablets are composed of 100 mg cedazuridine and 35 mg decitabine. Cedazuridine is a new molecular entity (NME). IV decitabine has been FDA approved for intermediate and high-risk MDS and CMML since 2006, and approved in the EU for previously untreated AML not candidates for intensive chemotherapy since 2012.

The Regulatory Authorities' Assessment:

FDA confirms the Applicant's assessment.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

The table below summarizes the key regulatory activities in the US and Canada for ASTX727.

The design of the Phase 3 study was discussed and agreed to with FDA at the End-of-Phase 2 (EOP2) Meeting held on 20 March 2017. The pharmacokinetic (PK) bridging approach to establish the effectiveness of ASTX727 FDC tablets (100 mg cedazuridine and 35 mg decitabine) compared to the 5-day regimen of IV decitabine (20 mg/m² Daily×5) was agreed to with the FDA at the ASTX727 EOP2 meeting on 20 March 2017. The pre New Drug Application (NDA) meeting to discuss the content of the ASTX727 NDA submission was held on 08 August 2019.

Scientific Advice was requested and received from the CHMP in July 2018. A Scientific Advice meeting with Health Canada was also held on 15 November 2018 between Otsuka Pharmaceutical Co., Ltd., Astex Pharmaceuticals, Inc., Taiho Pharma Canada Inc., and the Oncology Division 1 of the Bureau of Metabolism, Oncology and Reproductive Sciences to present and seek feedback on the clinical development and registration plan for ASTX727 in Canada. There was general agreement on the development program and the Phase 3 study design following consultation and advice from both CHMP and Health Canada.

Table 2. Summary of Key Health Authority Interactions Concerning ASTX727

Date	Major Interaction/Purpose
US Interactions	
29 November 2012	Type B Pre-IND meeting
18 December 2013	Original IND 116145 submission (Phase 1-2 Study ASTX727-01) IND for ASTX727 was opened in the US 21 Feb 2014, for treatment of MDS and CMML
20 March 2017	Type B End-of-Phase 2 meeting
May 2017	Initial pediatric study plan (waiver for the conduct of pediatric studies) submitted; agreement from the Agency November 2017. No pediatric studies are planned.
18 June 2018	Proprietary Name Conditionally Accepted
27 September 2018	FDA provided comments for the Pharmacometric Analysis Plan (PAP) for Study ASTX727-02
06 December 2018	Astex submitted the final PAP for Study ASTX727-02 to the Agency
23 May 2019	Orphan Drug Designation Application submission; Orphan Drug Designation granted 21 August 2019
31 May 2019	FDA provided preliminary responses to Type B CMC End of Phase 2 meeting questions
07 June 2019	Astex emailed responses to FDA's preliminary responses to Type B CMC End of Phase 2 meeting questions
08 August 2019	Type B Pre-NDA meeting
10 October 2019	Type B CMC Pre-NDA meeting
15 August 2019	Initial teleconference with FDA regarding Project Orbis participation. Astex confirmed interest in participation on 21 August 2019.
11 December 2019	Original ASTX727 New Drug Application (NDA: 212576, SN0001)
Interactions with Other Regulatory Authorities	
26 July 2018	Scientific Advice meeting with EMA (CHMP)
15 November 2018	Scientific Advice meeting with Health Canada
04 November 2019	Teleconference with Health Canada regarding Project Orbis and requirements/timing of NDS submission
11 December 2019	Initial teleconference with TGA Review Team regarding Project Orbis and requirements/timing of NCE submission
19 December 2019	NDS Submission to Health Canada completed
23 January 2020	NCE submission to Australia TGA completed

The Regulatory Authorities' Assessment:
 FDA confirms the Applicant's assessment.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted inspections for Studies ASTX727-01-B and ASTX727-02 at clinical sites in Nashville, TN (Vanderbilt-Ingram University Medical Center) and Houston, TX (MD Anderson Cancer Center). These sites had the highest accrual, greatest impact on the complete remission rate, (b) (4), (b) (6). Inspection review of both clinical sites determined that data derived from both sites were considered reliable. The classification for both sites was No Action Indicated.

The Applicant (Astex Pharmaceuticals, Inc.) was also audited. The classification for the Applicant inspection was also No Action Indicated. Based on these inspection results, the study data derived from the inspected clinical sites were considered reliable in support of the requested indication.

4.2. Product Quality

Decitabine and cedazuridine (Inqovi) is presented as a fixed-dose combination (FDC), biconvex, red, oval-shaped, film-coated tablet for oral use containing 35 mg of decitabine and 100 mg of cedazuridine. The tablets are plain-faced on one side and debossed with "H35" on the other side. Inactive ingredients include lactose monohydrate, hypromellose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The tablet coating includes polyvinyl alcohol- (b) (4) titanium dioxide, (b) (4) talc, and iron oxide red. All excipients are compendial-compliant. The drug product is supplied in a blister package formed by aluminum foil on foil lidding containing one tablet per cavity with an expiry of (b) (4) months when stored at USP controlled room temperature.

The Applicant indicated that the commercial tablet formulation (i.e., the final FDC) is similar to the early FDC clinical trial tablet formulation used in Study ASTX727-01-B, differing only in (b) (4), addition of the red film coat and debossing. The Phase 3 Study ASTX727-02 used the final FDC tablet formulation. Furthermore, decitabine and cedazuridine administered as separate capsules, used during the Dose Confirmation stage of the Phase 2 Study ASTX727-01-B, was found to have similar exposure to the early FDC and final FDC formulations. Based on the data submitted, the Biopharmaceutics reviewer concluded that the clinical trial and commercial formulations were comparable, so the data from Studies ASTX727-01-B and ASTX727-02 were acceptable for use in the assessment of efficacy and clinical safety.

There were no outstanding safety issues identified for the manufacturing process. Facilities

inspections have been completed. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment, and the claim was accepted under 21 CFR 25.31(b). No product quality concerns were identified on CMC review, and approval is recommended.

4.3. **Clinical Microbiology**

Not applicable.

4.4. **Devices and Companion Diagnostic Issues**

Not applicable. No devices or companion diagnostics are proposed for this application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

ASTX727 is an oral fixed-dose combination (FDC) drug product that contains the active ingredients decitabine and cedazuridine (E7727). Decitabine (Dacogen®) for injection is an approved nucleoside metabolic inhibitor; the oral bioavailability of decitabine is limited by cytidine deaminase (CDA) activity present in the gastrointestinal (GI) tract and liver of humans. CDA enzymatically deaminates cytidine analogs to generate pharmacologically inactive metabolites. Substrates of CDA include the cytidine analogs decitabine and gemcitabine. Cedazuridine is a CDA inhibitor, and oral administration of cedazuridine with decitabine enhances the oral bioavailability of decitabine. The proposed dose of ASTX727 provides systemic decitabine exposure comparable to the approved dose of decitabine for injection. While cedazuridine is not an anti-tumor drug, the combination of decitabine and cedazuridine as an FDC drug product is indicated to treat patients with cancer; thus, the nonclinical development program of cedazuridine will follow the recommendations in ICH S9 and ICH S9 Questions and Answers. A complete nonclinical program for cedazuridine is not necessary because of the combination and known toxicities associated with decitabine, for which the Applicant has the right of reference.

Cedazuridine inhibited the activity of human CDA in vitro ($IC_{50}=0.281 \mu\text{M}$) and improved the in vitro half-life of gemcitabine in the presence of human CDA from $t_{1/2} < 36$ minutes to $t_{1/2} > 66$ hours. Cedazuridine demonstrated negligible anti-proliferative activity in vitro at concentrations up to $10 \mu\text{M}$. The in vivo effect of cedazuridine on the antitumor activity of orally administered decitabine was assessed in the L1210 and KG-1 disseminated leukemia mouse models. In both mouse tumor models the dose of cedazuridine was varied (1 to 100 mg/kg, oral) while a fixed dose of decitabine was administered (0.3 or 0.4 mg/kg, oral). Control arms for oral cedazuridine monotherapy, oral decitabine monotherapy, and intravenous (IV) decitabine monotherapy were included. Decitabine was administered 30-40 minutes after cedazuridine to allow time-delay inhibition of CDA; contrariwise, cedazuridine and decitabine are delivered simultaneously in the ASTX727 FDC drug product. In both mouse tumor models oral cedazuridine administered in combination with oral decitabine conferred an increase in life span (31% to 88%, relative to vehicle control), but the effect was dose-dependent only in the L1210 disseminated tumor model. Neither oral cedazuridine nor oral decitabine monotherapy resulted in an increase in life span relative to vehicle control.

There were no cardiovascular or respiratory findings in a single-dose standalone safety pharmacology study in cynomolgus monkeys with oral doses of cedazuridine up to 200 mg/kg. In a 13-week toxicity study, cynomolgus monkeys were orally administered repeated doses of cedazuridine at up to 200 mg/kg/day with no remarkable electrocardiograph (ECG) findings. Neither cedazuridine nor its metabolites cross the blood brain barrier. No safety pharmacology

studies were conducted with ASTX727 or decitabine.

The intended pharmacologic effect of cedazuridine is to improve the oral bioavailability of decitabine; accordingly, the Applicant conducted a series of studies to evaluate the absorption, distribution, metabolism, and excretion (ADME) profiles of cedazuridine, decitabine, and ASTX727. Toxicokinetics (TK) were also evaluated as part of the general toxicology studies for cedazuridine (in mice and cynomolgus monkeys) and decitabine (in rats). Orally administered cedazuridine was rapidly absorbed in both species with a plasma T_{max} of ~1 hour in mice and ~2 hours in cynomolgus monkeys. In a time-delay study in cynomolgus monkeys 2-hour pretreatment with oral cedazuridine greatly enhanced exposure to subsequent orally administered decitabine (up to 17-fold increase in AUC_{0-t} , relative to oral decitabine monotherapy); concomitant oral administration of cedazuridine and decitabine resulted in a 6.4-fold increase in decitabine AUC_{0-t} , relative to oral decitabine monotherapy.

The distribution, metabolism, and excretion profiles of cedazuridine were evaluated in mass balance studies in mice and cynomolgus monkeys. In mice, orally administered [^{14}C]-cedazuridine distributed primarily into the metabolic/excretory and GI tissues and did not pass the blood brain barrier. The metabolite profile of [^{14}C]-cedazuridine was similar in mice and cynomolgus monkeys, which primarily consisted of unmodified cedazuridine and cedazuridine epimer, followed by less abundant metabolites resultant of dehydrogenation, oxidation, and urea conjugation. All significant human metabolites of cedazuridine were detected in mice and/or monkeys. In both mice and cynomolgus monkeys, the excretion profile of orally administered cedazuridine was primarily fecal, and some fecal excretion could be attributed to unabsorbed drug. In the general toxicology studies, cedazuridine (mice and cynomolgus monkeys) and decitabine (rats) were administered orally once daily for 5 to 7 days in 28-day cycles, similar to the clinical regimen. There were no sex-related differences in PK parameters or significant accumulation of cedazuridine or decitabine.

A series of studies were conducted to assess the toxicity of cedazuridine or decitabine monotherapy, or cedazuridine in combination with decitabine. A literature assessment submitted by the Applicant concluded that humans, mice, and cynomolgus monkeys have similar CDA tissue distribution and activity profiles, and CDA activity was notably absent in rats. The Applicant concluded mice and cynomolgus monkeys were the appropriate species to evaluate the toxicity of cedazuridine. Rats were chosen to evaluate the toxicity of oral decitabine given the relatively high oral bioavailability in this species. The pivotal studies were conducted under GLP-compliance, and the test articles were administered by the oral route following dosing regimens comparable to the planned clinical treatment cycle of 5 consecutive dosing days followed by 23 non-dosing days. Cedazuridine monotherapy was assessed in repeat-dose toxicity studies up to 13-weeks/4-cycles in duration in mice (up to 1000 mg/kg/dose) and cynomolgus monkeys (up to 200 mg/kg/dose). Findings in mice included bone marrow cytology changes, non-adverse changes in hematology parameters, increase in spleen

weight, and histopathologic changes in the bone marrow and spleen (hematopoiesis), small intestine (hyperplasia), and male (bilateral oligospermia of the epididymis) and female (follicular degeneration of the ovary) reproductive tracts. All findings were reversible following a 3-week recovery period; the testicular findings were partially recovered with a reduction in severity following the recovery period. Findings in cynomolgus monkeys were more limited and included bone marrow cytology changes, changes in hematology parameters (particularly red blood cell parameters), and histopathologic changes in the bone marrow (atypia) and GI tract (mitoses/single cell death and atypia), all of which were reversible following a 3-week recovery period.

Pivotal studies of oral decitabine monotherapy were limited to a 13-week/4-cycle study conducted in rats only (up to 7.5 mg/kg/dose). Observations in rats included changes in hematology parameters, bone marrow cytology changes, decreased thymus, spleen, testis and epididymis weights, and degenerative histopathological findings in the bone marrow, thymus, spleen, intestines, and male reproductive organs. Following the 3-week recovery period findings were reversible; the changes in the male reproductive organs persisted but showed reduced incidence and severity. The findings for orally administered decitabine were consistent with the known toxicological profile of IV administered decitabine.

The toxicologic profiling of cedazuridine in combination with decitabine was limited to a non-GLP 4-week/1-cycle study in cynomolgus monkeys. This study did not evaluate the ASTX727 FDC drug product; instead, monkeys were orally administered separate gelatin capsules containing cedazuridine (1, 3, or 6 mg/kg/day) and decitabine (2 mg/kg/day). This study did not identify any novel findings. TK analyses identified increased systemic exposure to decitabine with increasing doses of cedazuridine. Additional combination studies were not conducted due to the disparate toxic dose levels of decitabine and cedazuridine.

Cedazuridine was evaluated in a standard battery of GLP-compliant genotoxicity studies. Genetic toxicity studies for cedazuridine were not requested by the FDA because of the combination therapy that included a genotoxic drug. Cedazuridine was mutagenic in the Ames assay and genotoxic in the in vitro chromosome aberration assay, but not genotoxic in the in vivo micronucleus assay. The genotoxic potential of cedazuridine and decitabine will be described in the product label for ASTX727. Carcinogenicity studies were not conducted and are not warranted to support a marketing application for the proposed indication.

No stand-alone reproductive and developmental toxicology studies were conducted with cedazuridine or ASTX727. Decitabine is teratogenic, fetotoxic, and embryotoxic based on its mechanism of action and animal studies described in the product label for decitabine for injection; these risks will be described in the product label for ASTX727. In the repeat-dose toxicity study in mice cedazuridine caused adverse effects in male (bilateral oligospermia of the epididymis) and female (follicular degeneration of the ovary) reproductive tracts, but these were observed at exposures >100-fold the human exposures. A mouse fertility study described

in the product label for decitabine for injection and the repeat-dose toxicity study of oral decitabine in rats identified adverse effects in the male reproductive tract. Risks to fertility due to cedazuridine and decitabine will be described in the product label for ASTX727.

Due to the potential for ASTX727 to cause fetal harm, the use of effective contraception is recommended for female or male patients while receiving ASTX727 and for 6 or 3 months following the last dose, respectively. The recommendations for duration of contraception are based on the FDA guidance "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations".

There are no data on the presence of cedazuridine, decitabine, or their metabolites in human milk, the effects on the breastfed child, or on milk production. Because of the potential for serious adverse events in a breastfed child, the product label for ASTX727 recommends lactating women to avoid breastfeeding during treatment with ASTX727 and for at least 2 weeks after the last dose. The recommendation for the duration to avoid breastfeeding is consistent with the Dacogen label.

The Applicant proposed acceptance criteria of cedazuridine-related specified impurities in excess of the limits described ICH Q3A. These impurities were qualified in the monkey toxicology studies with safety factors of ^{(b) (4)} to greater than ^{(b) (4)} times the exposure at the proposed dose of ASTX727. The nonclinical pharmacology, ADME/TK, and toxicology data submitted to this NDA, in combination with the nonclinical data submitted to support the approval of decitabine for injection (NDA 21790), are adequate to support the approval of ASTX727 for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

This 505(b)(1) application relies on limited nonclinical data from the FDA's finding of safety for the listed drug, Dacogen[®] (decitabine) for Injection marketed by Otsuka America Pharmaceutical, Inc. under the approved NDA 21790. Reference is made to NDA 21790, which contains all FDA submissions and correspondence to Dacogen.

In addition, Table 3 lists the referenced Drug Master Files (DMFs) for one of the two drug substance components of the ASTX727 Tablets (decitabine), and for container closure components for ^{(b) (4)} blister configurations of ASTX727 tablets from ^{(b) (4)}.

Table 3. Referenced DMFs for Drug Substance Decitabine and Container Closure Components

Components	Drug Master File Name (Description)	Manufacturer	Drug Master File No.
	Decitabine (Drug Substance)		(b) (4)
			(b) (4)
Tablet Blister Components			(b) (4)

The Regulatory Authorities' Assessment:

We agree. Otsuka submitted a letter to NDA 21790 authorizing the FDA to reference the information in NDA 21790 to support NDA 212576 filed by Astex Pharmaceuticals.

5.3. Pharmacology

Primary pharmacology

The Regulatory Authority's Assessment:

Cedazuridine inhibited the recombinant human CDA-catalyzed deamination of cytidine in vitro ($IC_{50}=0.281 \mu M$). High levels of cedazuridine (0.39 mM) increased the in vitro half-life of gemcitabine in the presence of human CDA from $t_{1/2} < 36$ minutes to $t_{1/2} > 66$ hours; neither the effect of clinically-relevant levels of cedazuridine on the in vitro half-life of gemcitabine nor the effect of cedazuridine on the in vitro half-life of decitabine were assessed. A literature assessment submitted by the Applicant concluded that among common species used in nonclinical testing, mice and cynomolgus monkeys have CDA tissue distribution and activity profiles most similar to humans. CDA activity was notably absent in the rat. The human, mouse, and cynomolgus monkey CDA amino acid sequences are similar, but not identical. In vitro studies evaluating the effect of cedazuridine on mouse or cynomolgus monkey CDA were not submitted.

The effect of cedazuridine on the proliferation of eight human cancer cell lines, including two acute leukemia cell lines, was assessed in vitro; cedazuridine had no activity on the proliferation of tumor cells over the concentration range tested (3 to 10 μM) in the cell lines tested.

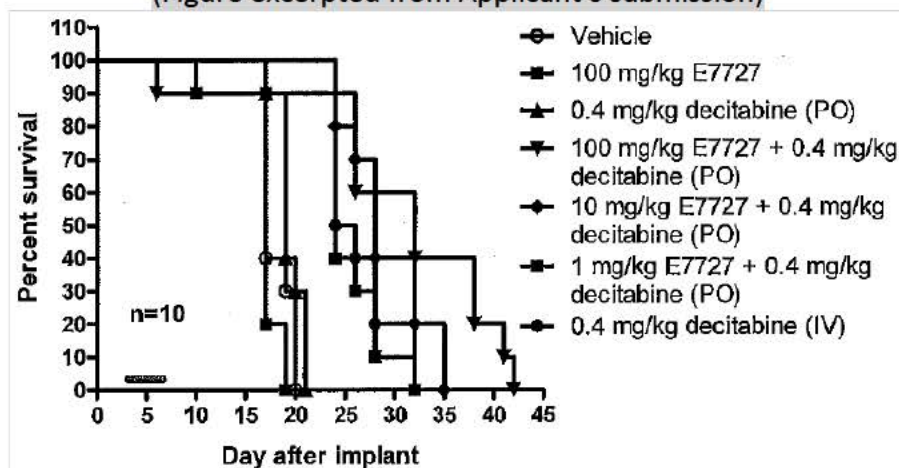
The effect of cedazuridine on the antitumor activity of decitabine was assessed in two

disseminated leukemia mouse models. In the L1210 disseminated tumor model CD2-F1 mice were inoculated with L1210 mouse ALL cells by IV injection. Three days after inoculation mice were treated orally with cedazuridine (1-100 mg/kg QDx5); 30-40 minutes later the same mice were treated orally with decitabine (0.4 mg/kg QDx5). In the KG-1 disseminated tumor model NSG mice were inoculated with KG-1 human AML cells by IV injection. Twenty-six days after inoculation mice were treated orally with cedazuridine (1-100 mg/kg QDx5); 30-40 minutes later the same mice were treated orally with decitabine (0.3 mg/kg QDx5). In the KG-1 model mice received two cycles of therapy separated by a 23-day non-dosing period. There were control arms for oral cedazuridine monotherapy, oral decitabine monotherapy, and IV decitabine monotherapy in both models. Antitumor activities of cedazuridine and/or decitabine were assessed by median survival time and the percentage increase in life span.

In the L1210 disseminated tumor model, oral cedazuridine treatment administered with a fixed oral dose of decitabine (0.4 mg/kg) resulted in a dose-dependent increase in life span (41-88%, $p \leq 0.0002$), relative to vehicle control (see Figure 1). Intravenous decitabine (0.4 mg/kg) monotherapy resulted in a 47% increase in life span ($p < 0.0001$) relative to vehicle control. Neither oral cedazuridine nor oral decitabine monotherapy resulted in a statistically significant increase in life span relative to vehicle control. The increased life span with the cedazuridine (100 mg/kg) and oral decitabine (0.4 mg/kg) combination relative to IV decitabine (0.4 mg/kg) monotherapy was statistically significant ($p < 0.0291$) and may be attributed to hepatic metabolism of IV administered decitabine.

Figure 1: Survival in the L1210 disseminated tumor mouse model

(Figure excerpted from Applicant's submission)

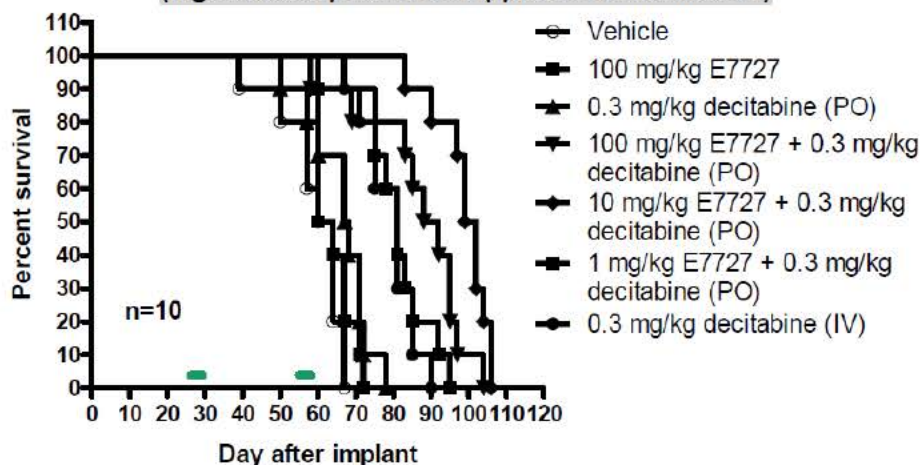


In the KG-1 disseminated tumor model, oral cedazuridine treatment administered with a fixed oral dose of decitabine (0.3 mg/kg) resulted in a non-dose dependent increase in life span (31-62%, $p < 0.0001$), relative to vehicle control (see Figure 2). Oral and IV decitabine (0.3 mg/kg) monotherapy resulted in a 9% ($p = 0.0142$) and 31% ($p < 0.0001$) increase in life span,

respectively, relative to vehicle control. Oral cedazuridine monotherapy did not result in a statistically significant increase in life span relative to vehicle control. The increased life span with the cedazuridine (10-100 mg/kg) and oral decitabine (0.3 mg/kg) combination relative to IV decitabine (0.3 mg/kg) was statistically significant ($p \leq 0.0165$) and may be attributed to hepatic metabolism of IV administered decitabine.

Figure 2: Survival in the KG-1 disseminated tumor mouse model

(Figure excerpted from Applicant's submission)



Secondary Pharmacology

Data:

No secondary pharmacodynamic (PD) studies have been conducted for cedazuridine.

The Applicant's Position:

No secondary PD studies have been conducted for cedazuridine, the new chemical entity component of ASTX727.

The Regulatory Authorities' Assessment:

Cedazuridine (1 and 10 μ M) was screened against a panel of 80 human cell receptors, ion channels, and transporters in the presence of reference compounds. Assay conditions varied depending on the target. Neither concentration of cedazuridine had a significant effect on reference compound binding under the conditions tested.

Safety Pharmacology

Data:

A. Cardiovascular

Safety pharmacology studies were conducted with cedazuridine to determine its in vitro effects on the human ether à-go-go related gene (hERG) potassium channel current in stably transfected human embryonic kidney (HEK293) cells (GLP Study/Report No. 100422.FJT) and on action potential parameters in isolated guinea pig papillary muscles (Report No. ER-849727-00). The cumulative data from these studies indicate that cedazuridine does not have any effect on the cardiovascular system as evidenced by an in vitro concentration giving half-maximal inhibition (IC₅₀) value of >300 µM for inhibition of hERG channel current and no effects on any action potential parameters in isolated papillary muscles from guinea pigs.

The potential in vivo effects of cedazuridine on the cardiovascular system and on respiratory function were evaluated in a stand-alone GLP-compliant study in conscious, naïve male cynomolgus monkeys using telemetry (Study/Report No. 20123940). Cedazuridine was orally administered as a single dose to male cynomolgus monkeys (n=4) at dose levels of 0, 20 and 200 mg/kg/day on Days 1, 3 and 10, respectively. Cedazuridine was well tolerated and had no effects on any cardiovascular parameters up to a single oral dose of 200 mg/kg [the no-observed-effect level (NOEL) in this study].

In addition, cardiovascular assessments included in a 7-day GLP toxicity study in rhesus monkeys (Study/Report No. LFA00080) and a 4-cycle GLP toxicity study in cynomolgus monkeys (Study/Report No. 20124863) showed no abnormalities in the electrocardiogram (ECG) data following repeat once-daily oral administrations of cedazuridine at doses of up to 200 mg/kg/day (the highest dose administered) for 7 consecutive days.

B. Respiratory

In a combination cardiovascular function and respiratory assessment study (details discussed above under “Cardiovascular”), a single oral dose of cedazuridine of up to 200 mg/kg was not associated with any effects on respiratory rate, tidal volume, or minute volume in conscious telemetered monkeys (Study/Report No. 20123940).

C. Central Nervous System (CNS)

Stand-alone nonclinical safety pharmacology assessment of ASTX727 (or cedazuridine or decitabine) on central nervous system (CNS) function has not been conducted. Cedazuridine and cedazuridine-derived entities do not show a strong tendency to distribute into tissues and, following oral administration, are primarily distributed into the GI tract and metabolic/excretory tissues (e.g., kidney or urinary bladder). Cedazuridine-derived entities do not cross the blood brain barrier (Study No. 17718; Report No. RPT04536).

The Applicant’s Position:

The results of safety pharmacology studies did not reveal adverse findings of concern regarding effects of cedazuridine on the cardiovascular system (based on in vitro hERG and actional potential assay data and on in vivo evaluations in monkeys) or the respiratory system (based on evaluations in conscious monkeys). Cedazuridine and cedazuridine-derived entities do not show a strong tendency to distribute into tissues and, following oral administration, are primarily distributed into the gastrointestinal tract and metabolic/excretory tissues (e.g., kidney or urinary bladder). CNS safety pharmacology studies were therefore not conducted. Thus, based on the results from the studies conducted with cedazuridine, no potential safety pharmacology concerns for ASTX727 attributable to cedazuridine have been identified.

The Regulatory Authorities' Assessment:

We agree with the Applicant's conclusions for the safety pharmacology studies conducted with cedazuridine. We note that no safety pharmacology studies were conducted with ASTX727 or decitabine.

5.4.ADME/PK

Data:

Absorption

Comparison of Pharmacokinetic Profiles of Decitabine and E7727 after Single Oral Administration of Two FDC Tablet Forms of ASTX727 using a Crossover Design (Study/Report No. APL-FFS-PK-20170522-01)

In this cross-over study, male cynomolgus monkeys were administered ASTX727 [100 mg cedazuridine (E7727) and 35 mg decitabine] as a fixed-dose combination (FDC) Tablet-A (earlier formulation used in the FDC stage of the Phase 2 clinical trial) or Tablet-B (new formulation, developed for the Phase 3 clinical trial). After a 6-day washout period, the ASTX727 formulation was reversed to complete the crossover. The results of this study indicate that both forms of FDC tablets showed similar PK profiles and exposures for decitabine and cedazuridine. Exposures for both decitabine and cedazuridine were higher on the second day of dosing compared to the first day on each week (i.e., Day 2 vs. Day 1 and Day 9 vs. Day 8). This effect was more pronounced for decitabine than for cedazuridine.

Pharmacokinetic Parameters for Decitabine and Cedazuridine in Male Cynomolgus Monkeys Administered ASTX727 in two Forms of FDC Tablets

Study Day	Analyte	FDC Tablet Form	AUC _{0-t} (ng*h/mL)	C _{max} (ng/mL)	t _{max} (h)	t _{1/2} (h)
Day 1/8 (first dose)	Decitabine	Tablet-A	121	64.1	2.25	0.700
		Tablet-B	80.5	55.6	1.83	0.832
	Cedazuridine	Tablet-A	6163	1285	3.17	4.00
		Tablet-B	6304	1244	2.75	4.02
Day 2/9 (second dose)	Decitabine	Tablet-A	291	156	1.92	0.782
		Tablet-B	226	127	1.92	1.15
	Cedazuridine	Tablet-A	7616	1472	3.00	5.10
		Tablet-B	8332	1772	2.67	5.06

AUC_{0-t} = area under the concentration-time curve from time 0 hours to the time of last measurable concentration; C_{max} = maximum measured concentration; FDC = Fixed-Dose Combination; t_{1/2} = terminal elimination half-life; t_{max} = time to reach maximum concentration

Distribution

Mass Balance, Radio-Pharmacokinetics in Male and Female CD-1 Mice and Tissue Distribution by Quantitative Whole Body Autoradiography in Female CD-1 and C57BL/6 Mice Following a Single Oral Administration of [¹⁴C]E7727
 (Study No. 17718; Report No. RPT04536)

In a quantitative whole-body autoradiography (QWBA) and mass balance study in female C57BL/6 and CD-1 mice, a single oral dose of 300 mg/kg (100 µCi/kg) [¹⁴C]-cedazuridine (E7727) was administered and the tissue distribution was profiled for up to 504 hours post-dose. Overall, cedazuridine did not show a strong tendency to distribute into tissues. The metabolic/excretory tissues (kidney, urinary bladder) as well as the tissues of the GI tract contained the highest distribution of [¹⁴C]-cedazuridine derived radioactivity. The tissues with lowest relative level of distributions in both strains of mice were brain, spinal cord, eye lens, and white fat, which were all below the quantifiable limit at all sampled time points. Based on a lack of distribution to the brain and spinal cord, it can be assumed that cedazuridine-related drug materials do not pass through the blood brain barrier. In addition, no significant distribution was noted in melanin-containing tissues such as pigmented skin and uveal tract, suggesting that [¹⁴C]-cedazuridine derived radioactivity was not preferentially associating with melanin.

Concentrations of [¹⁴C]-Cedazuridine Derived Radioactivity in Plasma and Tissues with Highest Radioactivity in Mice Following a Single Oral Dose of [¹⁴C]-Cedazuridine

C57BL/6 Mice				CD-1 Mice		
Tissues/ Organs	C _{max} (µg equivalents/g)	t _{max} (h)	Tissue: Plasma ratio ^a	Tissues/ Organs	C _{max} (µg equivalents/g)	t _{max} (h)
Plasma	20.5	2.0	NA	Plasma	17.1	2.0
Urinary bladder wall	1444	1.0	25.04	Small intestine wall	272	2.0
Large intestine wall	286	4.0	47.36	Large intestine wall	67.5	8.0
Cecum mucosa	231	4.0	34.44	Cecum mucosa	241	2.0
Stomach wall glandular	96.1	1.0	2.44	Kidney medulla	27.0	2.0
Entire kidney	53.7	1.0	1.85	Entire kidney	25.2	2.0

C_{max} = maximum measured concentration; NA = not applicable; t_{max} = time to reach maximum concentration
 a. Only derived for C57BL/6 mice. Tissue to plasma ratios based on AUC_{0-t} (area under the concentration-time curve from time 0 hours to the time of last measurable concentration).

Metabolism

Based on the metabolite profile of cedazuridine in mice, monkeys, and humans, unchanged cedazuridine is the most abundant circulating entity followed by its epimer which is the most prominent circulating metabolite. Toxicological coverage for metabolites is available as all metabolites detected in vivo in humans were also present in mouse and monkey plasma.

Metabolite Radio-profiling and Identification in Female CD-1 Mice Following Single Oral Administration of [¹⁴C]-E7727

(Study No. 17755; Report No. RPT04528)

In this study, female CD-1 mice were administered a single oral gavage dose of 300 mg/kg (100 µCi/kg) of [¹⁴C]-cedazuridine (E7727).

Mean Radioactivity Contributions of Cedazuridine and Metabolites in Mice Following a Single Oral Administration of [¹⁴C]-Cedazuridine

Compound	Modification	Plasma (0 to 8 hours)	Urine (0 to 48 hours)	Feces (0 to 48 hours)	Total Urine + Feces
		% AUC _{0-8h} ^a	% Dose	% Dose	% Dose
Cedazuridine	Parent	50.4	6.36	37.8	44.2
M348/1-2 ^b	Sulfate conjugation				
Cedazuridine epimer	Epimerization	37.5	4.46	30.8	35.3
M266/1	Dehydrogenation	9.05	1.81	0.78	2.59
M284/1	Mono-oxidation	3.02	0.22	0.46	0.68
M310/1	Urea conjugation	ND	2.94	1.59	4.53
M310/2		ND	1.97	1.11	3.08
Total		100	17.8	72.5	90.3

AUC_{0-8h} = area under concentration-time curve from time 0 to 8 hours; ND = not detected

- a. Percent AUC_{0-8h} of total radioactivity
- b. Cedazuridine and M348/1-2 were co-eluted under method conditions, with cedazuridine being the major component.

Excretion

Mass Balance, Radio-Pharmacokinetics in Male and Female CD-1 Mice and Tissue Distribution by Quantitative Whole Body Autoradiography in Female CD-1 and C57BL/6 Mice Following a Single Oral Administration of [¹⁴C]E7727

(Study No. 17718; Report No. RPT04536)

The excretion profile of cedazuridine in mice and monkeys indicates that the majority of the administered oral dose is not absorbed and is excreted in the feces based on approximately 70% to 77% of the [¹⁴C]-cedazuridine dose recovered in feces over a 168-hour post-dose period in mass balance studies.

Mean [¹⁴C]-Cedazuridine Derived Radioactivity Recovery in Mice after a Single Oral Dose of [¹⁴C]-Cedazuridine

Time (Hours)	Urine (% Dose)		Feces (% Dose)		Cage ^a (% Dose)		Total (% Dose)	
	M	F	M	F	M	F	M	F
0 to 24	19.07	17.38	69.45	72.13	3.56	2.49	92.08	92.00
0 to 168	19.66	17.85	69.84	72.56	3.75	2.64	93.26	93.06

F = female; M = male

a. Cage rinse or cage rinse and wash

TK data from general toxicology studies

A Thirteen-Week/Four-Cycle Oral GLP Toxicity Study of E7727 in CD-1 Mice

(Study/Report No. 0862-16193)

Cedazuridine Toxicokinetics in Mice in a 13-week/Four-Cycle Oral Toxicity Study

Dose of Cedazuridine (mg/kg/day)	AUC _{0-24h} (ng*h/mL)		C _{max} (ng/mL)		t _{max} (h)		Accumulation Ratio ^a	
	M	F	M	F	M	F	M	F
Day 1								
100	29,100	28,400	11,600	10,100	1.0	1.0	NA	NA
300	98,000	104,000	12,100	14,700	1.0	0.50	NA	NA
1000	295,000	123,000	28,500	33,100	1.0	1.0	NA	NA
Day 63 (Day 7 of Dosing Cycle 3)								
100	62,900	46,600	10,400	9280	1.0	1.0	2.16	1.64
300	165,000	102,000	21300	17,500	1.0	1.0	1.68	0.98
1000	404,000	306,000	35000	40,600	1.0	1.0	1.37	2.49

AUC_{0-24h} = area under concentration-time curve from time 0 to 24 hours; C_{max} = maximum measured concentration; F = female; M = male; NA = not applicable; TK = toxicokinetic(s); t_{max} = time to reach maximum concentration

a. AUC_{0-24h} (Day 63) / AUC_{0-24h} (Day 1)

Cedazuridine Epimer Toxicokinetics in Mice in a 13-week/Four-Cycle Oral Toxicity Study

Dose of Cedazuridine (mg/kg/day)	AUC _{0-24h} (ng*h/mL)		% AUC _{0-24h} of Parent ^a		C _{max} (ng/mL)		t _{max} (h)		Accumulation Ratio ^b	
	M	F	M	F	M	F	M	F	M	F
Day 1										
100	18,800	19,500	65	69	8040	7540	1.0	1.0	NA	NA
300	69,300	39,800	71	38	10,200	11,400	1.0	1.0	NA	NA
1000	231,000	91,400	78	74	26,400	28,600	1.0	1.0	NA	NA
Day 63 (Day 7 of Dosing Cycle 3)										
100	42,100	31,000	67	67	7060	6390	1.0	1.0	2.24	1.59
300	112,000	68,300	68	67	15,000	12,500	1.0	1.0	1.62	1.72
1000	280,000	199,000	69	65	27,100	31,800	1.0	1.0	1.21	2.18

AUC_{0-24h} = area under concentration-time curve from time 0 to 24 hours; C_{max} = maximum measured concentration; F = female; M = male; NA = not applicable; TK = toxicokinetic(s); t_{max} = time to reach maximum concentration

a. Not reported in study report. Calculated manually as follows:
 $AUC_{0-24h}(\text{cedazuridine Epimer}) / AUC_{0-24h}(\text{cedazuridine}) \times 100$

b. $AUC_{0-24h}(\text{Day 63}) / AUC_{0-24h}(\text{Day 1})$

**A 92 Day Toxicity Study of E7727 Administered via Oral Gavage in Cynomolgus Monkeys
 Followed by a 21 Day Recovery**
 (Study/Report No. 20124863)

Cedazuridine Toxicokinetics in Monkeys in a 13-week/Four-Cycle Oral Toxicity Study

Dose of Cedazuridine (mg/kg/day)	AUC _{0-t} (ng*h/mL)		C _{max} (ng/mL)		t _{max} (h)		Accumulation Ratio ^a	
	M	F	M	F	M	F	M	F
Day 1								
20	8530	5830	1300	822	1.8	2.0	NA	NA
60	15,600	12,800	2430	1870	2.3	1.8	NA	NA
200	57,300	41,200	7250	5330	1.8	1.7	NA	NA
Day 63 (Day 7 of Dosing Cycle 3)								
20	11,400	8700	1760	1760	2.3	1.5	1.34	1.49
60	28,800	27,500	5050	4150	1.3	1.5	1.85	2.15
200	57,700	77,900	8670	10,600	1.3	1.2	1.01	1.89

AUC_{0-t} = area under the concentration-time curve from time 0 hours to the time of last measurable concentration; C_{max} = maximum measured concentration; F = female; M = male; NA = not applicable; t_{max} = time to reach maximum concentration

a. Calculated as: AUC_{0-t} (Day 63) / AUC_{0-t} (Day 1)

Cedazuridine Epimer Toxicokinetics in Monkeys in a 13-week/Four-Cycle Oral Toxicity Study

Dose of Cedazuridine (mg/kg/day)	AUC_{0-t} (ng*h/mL)		% AUC_{0-t} of Parent ^a		C_{max} (ng/mL)		t_{max} (h)		Accumulation Ratio ^b	
	M	F	M	F	M	F	M	F	M	F
Day 1										
20	4360	4390	51	75	816	789	1.8	2.0	NA	NA
60	9220	8790	59	69	1790	1680	1.8	1.6	NA	NA
200	27,300	27,300	48	66	3740	4310	1.9	1.7	NA	NA
Day 63 (Day 7 of Dosing Cycle 3)										
20	5530	5120	49	59	918	1420	2.0	1.3	1.27	1.17
60	8790	13,900	31	51	1400	2650	1.5	1.2	0.95	1.58
200	29,600	32,700	51	42	4270	4290	1.7	1.5	1.08	1.20

AUC_{0-t} = area under the concentration-time curve from time 0 hours to the time of last measurable concentration; C_{max} = maximum measured concentration; F = female; M = male; NA = not applicable; t_{max} = time to reach maximum concentration

a. Not reported in study report. Calculated manually as follows:

$$AUC_{0-t}(\text{cedazuridine Epimer}) / AUC_{0-t}(\text{cedazuridine}) \times 100$$

b. AUC_{0-t} (Day 63) / AUC_{0-t} (Day 1)

Decitabine: A 90-Day Multicycle Oral Repeated Dose Toxicity Study in Rats with a 59-Day Recovery Period (GLP)

(Study/Report No. T73417002-GN)

Decitabine Toxicokinetics in Rats in a 13-week/Four-Cycle Oral Toxicity Study

Dose of Decitabine (mg/kg/day)	AUC_{0-t} (ng*h/mL)		C_{max} (ng/mL)		t_{max} ^a (h)		$t_{1/2}$ (h)		Accumulation Ratio ^b			
									AUC_{0-t}		C_{max}	
	M	F	M	F	M	F	M	F	M	F	M	F
Day 1												
0.75	1450	1330	332	357	1.0	0.5	2.63	2.62	NA	NA	NA	NA
2.5	6290	6320	1060	1190	1.0	0.5	3.22	3.53	NA	NA	NA	NA
7.5	13,800	14,000	2180	2380	1.0	1.0	3.35	3.57	NA	NA	NA	NA
Day 61 (Day 5 of Dosing Cycle 3)												
0.75	3480	1920	531	454	0.75	0.75	3.55	3.09	2.40	1.47	1.60	1.32
2.5	8520	8060	1260	1280	1.0	0.5	3.55	3.44	1.36	1.28	1.20	1.10
7.5	17,100	18,000	2220	2350	1.0	1.5	3.58	3.40	1.24	1.28	1.02	0.99

AUC _{0-t} = area under the concentration-time curve from time 0 hours to the time of last measurable concentration; C _{max} = maximum measured concentration; F = female; M = male; NA = not applicable; t _{1/2} = apparent terminal elimination half-life; t _{max} = time to reach maximum concentration a. Median b. Day 61 / Day 1
TK data from reproductive toxicology studies None
TK data from Carcinogenicity studies None

The Applicant's Position:

The PK/TK profile of ASTX727 components cedazuridine and decitabine has been well characterized in various in vitro and in vivo nonclinical studies. There were no unexpected findings and the data from these studies are consistent with the pharmacological action of cedazuridine acting as an inhibitor of CDA as shown by significantly increased systemic exposures to decitabine following concomitant oral dosing of cedazuridine and decitabine at clinically relevant doses. Thus, the nonclinical PK/TK data support the clinical administration of ASTX727 on a schedule that involves daily administration for 5 days per dosing cycle (i.e., Days 1 to 5 of each 28-day cycle).

The Regulatory Authorities' Assessment:

The Applicant stated the nonclinical PK/TK data supported the ASTX727 clinical dosing schedule. The nonclinical PK/TK data did not directly contribute to the clinical efficacy or AUC equivalence data that supported the approval of NDA 212576. We have additional comments on the studies reviewed above and have reviewed additional ADME/PK data.

Absorption

In the comparative PK study evaluating FDC tablets of decitabine and cedazuridine in cynomolgus monkeys the t_{1/2} of cedazuridine was 4-5 hours. The higher exposures (AUC_{0-t} and C_{max}) of decitabine following the second day of dosing is consistent with the expected pharmacology of the FDC tablets of decitabine and cedazuridine.

The effect of oral cedazuridine followed by time-staggered oral decitabine on the PK profile of decitabine was evaluated in cynomolgus monkeys. Monkeys were administered a fixed oral dose of 1 mg/kg cedazuridine concomitantly with a fixed oral dose of 3 mg/kg decitabine, or following a 30-minute to 2-hour time-delay. Coadministration with cedazuridine resulted in higher plasma exposures (6.4-fold increase in AUC_{0-t}, 3.9-fold increase in C_{max}) of decitabine, relative to oral decitabine monotherapy. The plasma decitabine exposure increased further

with time delay; when administered 2 hours after cedazuridine, plasma decitabine AUC_{0-t} and C_{max} increased 17.0-fold and 13.2-fold relative to oral decitabine monotherapy, respectively.

Metabolism

The metabolite profile of cedazuridine in cynomolgus monkeys was evaluated as part of a mass balance and PK study. In this study, male and female cynomolgus monkeys were administered an oral dose of 20 mg/kg of [¹⁴C] cedazuridine; following a 2-week washout period the same monkeys were administered an IV dose of 2 mg/kg of [¹⁴C] cedazuridine. The overall metabolite profiles were similar for males and females following oral or IV administration. All significant human metabolites of cedazuridine were detected in mice and/or monkeys.

Excretion

The excretion profile of cedazuridine in cynomolgus monkeys was evaluated as part of the mass balance and PK study described above. The excretion profile of orally administered cedazuridine in monkeys was similar to that observed in mice, with the majority of the administered dose excreted in feces. The excretion profile of IV administered cedazuridine in monkeys was primarily urinary. It is unclear if the high fecal excretion of cedazuridine after oral administration could be attributed to unabsorbed drug.

TK data from general toxicology studies

There were no sex-related differences in TK parameters for cedazuridine or decitabine. There was also little to no accumulation of cedazuridine after once daily administration, which was the same as for the clinical regimen.

5.5. Toxicology

5.5.1. General Toxicology

Data:

Key toxicology findings from the following pivotal studies are summarized below:

- Cedazuridine (E7727): a 4-cycle GLP toxicology study in mice and 4-cycle GLP toxicology study in monkeys
- Decitabine: 4-cycle GLP toxicology study in rats
- Cedazuridine with decitabine (ASTX727): a 1-cycle (5 days of dosing) PK/PD study in monkeys

Study title/ Study number: A Thirteen-Week/Four-Cycle Oral GLP Toxicity Study of E7727 in CD-1 Mice (Study/Report No. 0862-16193).

Key Study Findings

- Bone marrow cytology findings: dose levels of 1000 mg/kg/dose were associated with “mildly higher” myeloid:erythroid (M:E) ratios in females and “minimally lower” M:E ratios in males; reversibility in these effects was noted in both sexes following a 3-week recovery period;
- Hematopoiesis in spleen and sternal bone marrow that appeared to be consistent with a regenerative response to a reduction in circulating leukocyte counts; reversibility in these effects was noted following a 3-week recovery period; and
- Adverse histopathology findings in the male and female reproductive tracts that showed partial recovery in males and full reversibility in females at the end of a 3-week recovery period. It is worth noting that full recovery of all spermatogenic stages is expected to take longer than the 35-day period of a full spermatogenic cycle and, therefore, the partial recovery noted in males suggests progression to recovery of these findings.

Conducting laboratory and location (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing: Cedazuridine (E7727): 0 (control), 100, 300, or 1000 mg/kg/day
4 dosing cycles, with each complete cycle consisting of 7 days of dosing followed by a 21-day non-dosing period for a total of 28 days per cycle.
A recovery period of 3 weeks was included at the end of the 4th dosing cycle.

Route of administration: Oral (gavage)

Formulation/Vehicle: 0.5% methylcellulose

Species/Strain: Mouse/Hsd:ICR (CD-1[®])

Number/Sex/Group: Main study: 22 animals/sex/group;
Recovery phase: 6 animals/sex/group

Age: 6-8 weeks (prior to first dose)

Satellite groups/ unique design: An additional 9 animals/sex/group were used for hematology evaluations on Days 8 and 28 (these evaluations were considered to be exploratory in nature and the mean data were not presented in the study report) and an additional 39 animals/sex/group (and

9/sex/group in the vehicle control group) were used for TK evaluations.

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No test article-related deaths. Oral gavage error-related deaths: 1 control male and 3 control females, 2 LD males and 2 LD females, and 1 MD male
Clinical Signs	No test article-related adverse effects
Body Weights	No test article-related adverse effects
Ophthalmoscopy	No test article-related adverse effects
Hematology	No test article-related adverse effects
Clinical Chemistry	No test article-related adverse effects
Gross Pathology	No test article-related adverse effects
Organ Weights	HD: Slight ↑ in the absolute and relative (to body and brain) spleen weights in females that correlated with more severe cases of ↑ splenic myelopoiesis; findings reversible following the 3-week recovery period.
Histopathology	At all test article dose levels: <u>Spleen and sternal bone marrow:</u> Hematopoiesis in both organs that appeared to be consistent with a regenerative response to a reduction in circulating leukocyte counts. The relative lack of red cell precursors in the bone marrow was reflected in the reductions in circulating red cells and reticulocytes. Evidence of ongoing loss of all lineages of hematopoietic marrow tissue (specifically, focally ↑ adipocytes and/or macrophage aggregates associated with cell debris) was noted in a few HD females. A ↓ in lymphocyte counts was noted in the mesenteric lymph node (possibly reflecting oral administration) and in the splenic white pulp in MD and HD females and in 2 HD males. At the end of the recovery period, the spleen and bone marrow hematopoietic changes were fully reversible. <u>Male reproductive tract:</u> Bilateral oligospermia within the epididymis of HD animals, accompanied by the presence of cell debris within the epididymal lumen and degenerative changes (necrosis of single or small groups of germ cells, epithelial vacuolation, and/or germ cell depletion) in the testicular seminiferous epithelium. There was a reduction in severity of the testicular findings at the end of the recovery period, suggesting partial recovery. <u>Female reproductive tract:</u> Follicular degeneration, characterized by pale, enlarged, and degenerating granulosa cells in HD animals; full reversibility noted in females at the end of the recovery period.
Other evaluations	<u>Bone marrow cytology findings:</u> “mildly higher” M:E ratio in HD females and a “minimally lower” M:E ratio in HD males. Mild to marked ↓ in lymphocyte percentages and mild ↓ in mean peripheral lymphocyte counts also were noted in both sexes. Reversibility of these bone marrow cytology findings in both sexes at the end of the recovery period.

HD = high dose; LD = low dose; M:E =myeloid:erythroid; MD = mid dose.

Study title/ Study number: A 92 Day Toxicity Study of E7727 Administered via Oral Gavage in Cynomolgus Monkeys Followed by a 21 Day Recovery (Study/Report No. 20124863).

Key Study Findings

- Hematology findings consisting of minimally decreased RBC mass [hemoglobin, RBC count, and hematocrit(HCT)] with associated increases in reticulocytes, and a concomitant minimal to mild increase in red cell distribution width; recovery noted for RBC mass (both sexes), reticulocytes (both sexes), and red cell distribution width (females only) at the end of the 21-day recovery period;
- Mild morphologic changes in the erythroid lineage at the low- and mid-dose levels of 20 and 60 mg/kg/day and marked morphologic changes in the myeloid and erythroid lineages at the high dose level of 200 mg/kg/day; all bone marrow cytology changes were reversible following the 21-day recovery period; and
- Histopathology findings in the bone marrow and GI tract in high-dose animals (200 mg/kg/day); all changes were reversible following the 21-day recovery period.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:

Cedazuridine (E7727): 0 (control), 20, 60, or 200 mg/kg/day
4 dosing cycles, with each complete cycle consisting of 7 days of dosing followed by a 21-day non-dosing period for a total of 28 days per cycle.
A recovery period of 21 days was included at the end of the 92-day study period (i.e., following administration of the last dose in the 4th cycle).

Route of administration:

Oral (gavage)

Formulation/Vehicle:

0.5% methylcellulose

Species/Strain:

Monkey/Cynomolgus

Number/Sex/Group:

Main study: 6 animals/sex/control, MD, HD groups and 4 animals/sex/LD group;

Age:

Recovery phase: 2 animals/sex/control, MD, HD groups
2.3 to 5.0 years (at initiation of dosing)

Satellite groups/ unique design:

None

Deviation from study protocol

No

affecting interpretation of results:

Observations and Results: changes from control

Parameters	Major findings
Mortality	No deaths
Clinical Signs	No test article-related adverse effects
Body Weights	No test article-related adverse effects
Ophthalmoscopy	No test article-related adverse effects
ECG	No test article-related adverse effects
Hematology	HD: minimally ↓ RBC mass (hemoglobin, RBC count, and HCT) on Days 15 and 71 (for females) and on Day 71 (for males), with associated ↑ in reticulocytes at these time points. By Day 91, reticulocytes were moderately to markedly ↓ for both sexes. A concomitant minimal to mild ↑ in red cell distribution width was noted at all time points between Days 15 and 91. Recovery noted for RBC mass (both sexes), reticulocytes (both sexes), and red cell distribution width (females only) on Day 111 (i.e., the end of the 21-day recovery period)
Clinical Chemistry	No test article-related adverse effects
Urinalysis	No test article-related adverse effects
Gross Pathology	No test article-related adverse effects
Organ Weights	No test article-related adverse effects
Histopathology	<u>Bone marrow</u>: HD: Minimal to marked atypia of the hematopoietic cells (correlating with morphologic changes in bone marrow cytology and characterized by atypia in the erythroid lineage and, at higher severities, atypia in the myeloid lineage) and mild to moderate ↓ in bone marrow cellularity (characterized by ↓ overall cellularity of the erythroid lineage and, to a lesser extent, the myeloid lineage); <u>GI tract</u>: HD: Minimal to mild ↑ in mitoses/single cell death of the mucosal epithelial cells of the esophagus and tongue and minimal to marked atypia of the mucosal epithelial cells in the stomach, duodenum, jejunum, ileum, cecum, colon, and rectum (changes characterized by variable severity of one or more of the following: ↑ single cell death, ↑ mitotic figures, atypical mitotic figures, loss of cellular polarity, disorganization, crowding and piling of cells, variation in nuclear size, multiple prominent nucleoli, karyomegaly, cytomegaly, villous blunting and fusion, and crypt collapse). In 1 HD male, changes were noted in the adrenal gland (minimal cortical neutrophilic infiltrates), prostate gland (mild atypia of the glandular epithelium), lymph node (mild ↑ in cellularity), optic nerve (minimal, perivascular mixed cell infiltrates), spleen (mild ↑ in cellularity), and salivary gland (mild zymogen gland depletion) and, in another HD male, changes were noted in the kidneys (aggregates of mononuclear cells and myeloid hematopoietic precursors with occasional mitotic figures within the renal interstitium). All histopathology changes reversible following the 21-day recovery period.

Other evaluations	<u>Bone marrow cytology findings:</u> Mild morphologic changes in the erythroid lineage for individual animals in LD and MD groups and generally marked morphologic changes in the myeloid and erythroid lineages in the HD group that indicated abnormal cell maturation and were associated with correlating histopathology. Mildly ↑ numbers of metarubricytes with lobulated or mildly lobulated nuclei for individual animals in the LD and MD groups, rarely accompanied by ↑ cell size. Bone marrow changes in the HD group consisted of the following: • In the myeloid lineage: Variable proportions of giant band neutrophils, segmented neutrophils, eosinophils, and basophils (in addition to earlier stage myeloid progenitors for some animals), frequently with abnormal nuclear morphology; and • In the erythroid lineage: Generally, marked ↑ in the numbers of late stage erythroid progenitors (rubricytes and metarubricytes) with abnormal nuclear morphology consisting of variably sized (often large) lobulated, irregularly shaped, and/or fragmented nuclei. Erythroid lineage cells frequently exhibited asynchronous maturation, generally reflected by ↑ cytoplasmic volume and hemoglobinization relative to the maturational stage of the nucleus. These changes correlated with histopathology findings in the bone marrow of minimal to marked atypia in one or more hematopoietic lineages. All bone marrow cytology changes reversible following the 21-day recovery period.

HCT = hematocrit; HD = high dose; LD = low dose; MD = mid dose; RBC = red blood cell

Study title/ Study number: Decitabine: A 90-Day Multicycle Oral Repeated Dose Toxicity Study in Rats with a 59-Day Recovery Period (GLP) (Study/Report No. T73417002-GN)

Key Study Findings

- Hematology findings consisting of decreases in RBC and WBC parameters at all treatment dose levels and decreases in platelet counts only at the 7.5 mg/kg/day (high dose) level; changes reversible at the end of a 59-day recovery period;
- Bone marrow changes consisting of mild to moderate decreases in the M:E ratio in low-dose animals and minimal to marked increases in the M:E ratio in mid- and high-dose animals; changes reversible at the end of a 59-day recovery period; and
- Histopathology effects consisting of degenerative changes in the bone marrow, thymus, spleen, intestines, and male reproductive organs.

Conducting laboratory and location: [REDACTED] (b) (4)

[REDACTED]

GLP compliance: Yes

Methods

Dose and frequency of dosing: Decitabine: 0 (control; water for injection), 0.75, 2.5, or 7.5 mg/kg/day
 4 dosing cycles, with each complete cycle consisting of 5 days of dosing followed by a 23-day non-dosing period for a total of 28 days per cycle.
 A recovery period of 59 days was included following completion of the dosing phase of the 4th dosing cycle.

Route of administration: Oral (gavage)

Formulation/Vehicle: Water for injection

Species/Strain: Rat/Sprague-Dawley

Number/Sex/Group: Main study: 15 animals/sex/group;
 Recovery phase: 5 animals/sex/group

Age: 8 weeks (at start of dosing)

Satellite groups/ unique design: An additional 5 animals/sex/group were used for hematology evaluations at various timepoints during the in-life period, and an additional 4 animals/sex/group were used for TK evaluations.

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No deaths
Clinical Signs	↓ testis size at all dose levels (observed after completion of the 2 nd dosing cycle; reversible at the end of the 59-day recovery period in LD but not MD or HD males.
Body Weights	No test article-related adverse effects
Ophthalmoscopy	No test article-related adverse effects
Hematology	<u>RBC parameters</u> : Statistically significant ↓ in RBCs, HCT, and hemoglobin at all dose levels and in reticulocytes in MD and HD males and at all dose levels in females. Statistically significant ↑ in MCV in MD and HD males and females and in MCH in treated males and in MD and HD females. <u>Platelets</u> : Statistically significant ↓ in platelet counts in HD animals. <u>WBC parameters</u> : Statistically significant ↓ in WBCs and lymphocytes at all dose levels in males and in HD females, in neutrophils and monocytes at all dose levels, in eosinophils in MD and HD males, and in basophils in LD and HD males. All hematology changes reversible at the end of the 59-day recovery period.
Clinical Chemistry	No test article-related adverse effects
Urinalysis	↓ urinary sperm in HD males on Day 90 and in MD and HD males at the end of the 59-day recovery period.

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Gross Pathology	↓ thymic size at all dose levels, ↓ testicular size in MD and HD males, and ↓ epididymal size in HD males; the thymic change was almost fully reversible at the end of the recovery period while the testicular and epididymal changes were still present.
Organ Weights	↓ organ weights: thymus (absolute and relative; statistically significant at all dose levels), spleen (absolute and relative; at all dose levels in males), testis (absolute and relative; statistically significant at all dose levels), and epididymis (absolute and relative; statistically significant at HD level). Reversibility noted in the spleen weights (all groups) and thymus weights (LD males and all females) at the end of the recovery period; effects on thymus weights in MD and HD males and the effects on testicular and epididymal weights persisted.
Histopathology	<u>Terminal necropsy</u> : ↓ bone marrow cellularity at all dose levels; thymic lymphoid depletion at all dose levels; splenic lymphoid depletion in HD males and at all dose levels in females; intestinal single cell necrosis/ apoptosis in MD and HD males and at all dose levels in females; testicular degeneration/atrophy, Sertoli cell vacuolation, and Leydig cell hyperplasia in MD and HD males; epididymal oligospermia at all dose levels, epididymal cell debris in MD and HD males, and epididymal single cell necrosis/apoptosis in HD males. <u>Recovery necropsy</u> : Full/approaching full reversibility in effects in spleen, intestine, thymus and bone marrow; changes in the male reproductive organs were not recovered except for the epididymal single cell necrosis/apoptosis. In addition, testicular degeneration/atrophy, Sertoli cell vacuolation, and epididymal oligospermia appeared at the LD level.
Other evaluations	<u>Bone marrow cytology findings</u> : Mild to moderate ↓ in the M:E ratio in LD animals and minimal to marked ↑ in the M:E ratio in MD and HD animals (consistent with the hematology changes); effects reversible at the end of the recovery period.

HCT = hematocrit; HD = high dose; LD = low dose; M:E =myeloid:erythroid; MD = mid dose; RBC = red blood cell; WBC = white blood cell

Study title/ Study number: A Pharmacokinetic/Pharmacodynamic and Safety Evaluation Study in Cynomolgus Monkeys following Concomitant Repeat-Dose Oral Administration of E7727 and Decitabine (Study/Report No. 031554).

Key Study Findings

- Hematology findings of anemia and leucopenia in treated animals; generally reversible following a 23-day non-dosing period; and
- Bone marrow cytology findings of higher M:E ratios among the different groups of treated males (based on higher mean total myeloid cell counts and lower mean total erythroid cell counts); reversible following a 23-day non-dosing period.

Conducting laboratory and location (b) (4)
 GLP compliance: No

Methods

Dose and frequency of dosing: Cedazuridine (E7727): 1, 3, or 6 mg/kg/day; and Decitabine (fixed dose): 2 mg/kg/day
 Once-daily for 5 consecutive days; administration of cedazuridine immediately followed by administration of decitabine.
 Non-dosing period: 23 days following the last dose

Route of administration: Oral

Formulation/Vehicle: Gelatin capsule

Species/Strain: Monkey/Cynomolgus

Number/Sex/Group: Main study: 3 animals/sex/group

Age: 3 to 6 years

Satellite groups/ unique design: None

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No deaths
Clinical Signs	No test article-related adverse effects
Body Weights	No test article-related adverse effects
Hematology	↓ in mean RBC and WBC counts, hemoglobin and HCT levels, and levels of reticulocytes, neutrophils, lymphocytes, monocytes, eosinophils, and basophils; “slight recovery” reported for the red cell indices and for most white cell indices by Day 15 and mean reticulocyte counts peaked at Day 15, reflecting active regeneration. Reversibility in these effects (with the exception of neutrophil counts), noted following the 23-day non-dosing period.
Clinical Chemistry	No test article-related adverse effects

Gross Pathology	No test article-related adverse effects
Organ Weights	No test article-related adverse effects
Histopathology	Minimal microscopic hepatocellular centrilobular vacuolation, morphologically consistent with fat, in one HD female (considered non-adverse and a possible test article-related effect).
Other evaluations	<u>Bone marrow cytology findings:</u> Higher mean total myeloid cell counts, lower mean total erythroid cell counts, and higher M:E ratios were noted between the different groups of treated males (dose related)

HCT = hematocrit; HD = high dose; LD = low dose; M:E =myeloid:erythroid; MD = mid dose; RBC = red blood cell; WBC = white blood cells

The Applicant’s Position:

In summary, the main repeat-dose toxicity findings from studies conducted in mice, rats, and monkeys were characterized by reversible myelosuppression (leukopenia, neutropenia, lymphopenia, and/or decreased platelet counts) due to decitabine, or both (ASTX727), reversible reproductive tract effects due to cedazuridine, and thymic lymphoid depletion (cedazuridine, reversible) and testicular effects (partially reversible) due to decitabine.

The Regulatory Authorities’ Assessment:

We agree with the Applicant’s overall conclusions for the 13-week studies of cedazuridine in mice and cynomolgus monkeys. There were similar cedazuridine-related hematology findings observed in both mice and monkeys, although in mice the magnitude of the findings was not adverse and not included in the Applicant’s review. In both species, the hematology findings correlated with histopathologic findings in the spleen and/or bone marrow. The Applicant’s review also captured histopathology findings in the GI tract of monkeys but did not describe similar findings in mice. Findings in the GI tract of monkeys were generally described as atypia (including increased single cell death and increased mitoses) while findings in mice were described as hyperplasia and not adverse. Hyperplasia in mice may have been indicative of a regenerative response subsequent to necrosis, and thus the etiology of the findings in mice and monkeys may be similar. The lack of ECG findings in the 13-week monkey study were consistent with the absence of findings in the stand-alone safety pharmacology study in cynomolgus monkeys.

The Applicant evaluated the toxicology of orally administered decitabine in the rat. The oral bioavailability of decitabine is relatively high in rats, which is likely attributed to low CDA activity in this species. We agree the rat is a relevant species to evaluate the toxicology of orally administered decitabine. We agree with the Applicant’s overall conclusions for the 13-week study of oral decitabine in rats; the results were similar to those after IV administered decitabine, which was reviewed to support the approval of decitabine for injection (NDA 21790).

The toxicologic profiling of the cedazuridine and decitabine combination was limited to a 1-cycle study in cynomolgus monkeys. Additional combination studies were not conducted or deemed necessary.

General toxicology; additional studies

Data:

No additional general toxicology studies have been conducted.

The Applicant’s Position:

Not applicable.

The Regulatory Authorities’ Assessment:

We agree that no additional general toxicity studies were conducted or are needed to support the approval of NDA 212576.

5.5.2. **Genetic Toxicology**

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Data:

Study title/ number: E7727: Reverse Mutation Assay in Bacteria (Study/Report No. 963133)

Key Study Findings:

- Cedazuridine (E7727) was mutagenic in *Salmonella typhimurium* strain TA1535 both in the presence and absence of external metabolic activation, but only at the highest tested concentration of 5000 µg/plate, and was non-mutagenic in *Salmonella typhimurium* strains TA98, TA100, and TA1537 and in *E. coli* strain WP2 *uvrA* (pKM101) both in the presence and absence of external metabolic activation.

Metabolic Activation	Test Article	Conc (µg/plate)	Revertant Colony Counts (Mean)				
			TA98	TA100	TA1535	TA1537	WP2 <i>uvrA</i>
With Activation	Cedazuridine	0 (vehicle control)	53	152	28	20	81
		1250	48	180	30	15	84
		1768	44	158	33	14	70
		2500	49	181	34	17	73
		3536	40	182	52	24	71
		5000	42	153	63^a	18	76

Conc = concentration

a. Substantial increase in revertant colony counts.

GLP compliance: Yes

Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2 uvrA (pKM101) were incubated with cedazuridine both in the presence and absence of S9 at the following concentrations: 0 (control), 313, 625, 1250, 2500, or 5000 µg/plate (initial test) and 0 (control), 1250, 1768, 2500, 3536, or 5000 µg/plate (confirmatory test).

The Applicant's Position:

It is worth noting that the standard OECD-compliant Ames assay recommends the use of *S. typhimurium* strains TA100 and TA1535 (OECD 1997a). While these strains both contain the same base pair mutation (adenine-thymine to guanine-cytosine), they differ only in that TA100 contains a pKM101 plasmid which is reported to make it more sensitive than TA1535 in detecting bacterial mutagens (Prival and Zeiger 1998). According to Prival and Zeiger (1998), analysis of the data on the 36 chemical substances that were judged to be mutagenic in TA1535 and non-mutagenic or equivocal in TA100 indicates that the absolute increases in revertant colony counts in TA1535 were so small that they could have been missed if the same increases had occurred in a strain with a higher spontaneous background revertant colony count (i.e., TA100). The findings from the Ames assay with cedazuridine reflect the analysis from Prival and Zeiger (1998) in that the increases in the revertant colony counts in TA1535 noted in both the initial and confirmatory tests were only just doubled at 5,000 µg/plate compared to colony counts in TA1535 controls and that such increases were absent in the more sensitive TA100 (Intertek 2018). Thus, the positive findings that were noted only at the highest tested concentration in strain TA1535 are difficult to interpret given the absence of response in the more sensitive strain TA100.

The Regulatory Authorities' Assessment:

Cedazuridine (5000 µg/plate) was mutagenic in *S. typhimurium* strain TA1535 in the presence of external metabolic activation (2.3-fold increase in mean revertants). In the absence of external metabolic activation (data not shown) cedazuridine (5000 µg/plate) was mutagenic in strain TA1535 in the initial test (2.2-fold increase in mean revertants), but in the confirmatory test the 1.5-fold increase in mean revertants did not meet the prespecified evaluation criteria (≥2 times the concurrent vehicle control).

In Vitro Assays in Mammalian Cells

Data:

**Study title/ number: E7727: Chromosome Aberration Study in Human Lymphocytes
 (Study/Report No. 963134)**

Key Study Findings:

- Cedazuridine was genotoxic in a chromosome aberration assay in human lymphocytes both in the presence and absence of external metabolic activation.
- Cytotoxic effects: Significant cell toxicity (indicated by a decrease in relative mitotic index) noted at the highest tested concentrations, as follows:
 - 36% relative mitotic index for the 4-hour incubation (-S9), corresponding to 64% cytotoxicity;
 - 34% relative mitotic index for the 4-hour incubation (+S9), corresponding to 66% cytotoxicity; and
 - 19% relative mitotic index for the 21-hour incubation (-S9), corresponding to 81% cytotoxicity.

Metabolic Activation	Test Article	Conc (µg/mL)	Cytotoxicity ^a (% of control)	% Aberrant Cells (excluding gaps)	Total Polyploid Cells
4-Hour treatment with 17-hour recovery					
Without Activation	Cedazuridine	0 (vehicle control)	100	1.0	1
		75.0	151	1.5	1
		150	120	3.0	0
		300	36	17.0***	0
With Activation	Cedazuridine	0 (vehicle control)	100	1.0	1
		150	77	1.0	0
		300	87	9.5***	0
		600	34	29.0***	0
21-Hour treatment					
Without Activation	Cedazuridine	0 (vehicle control)	100	1.0	0
		18.8	83	1.0	1
		37.5	83	1.0	0
		75.0	19	8.0***	0

*** - $p \leq 0.001$ (Fisher's)

a. Based on mitotic indices.

GLP compliance: Yes

Test system: Primary cultures of human peripheral blood lymphocytes were treated with cedazuridine for 4 hours in the presence of S9 [+S9; 0 (control), 150, 300, or 600 $\mu\text{g}/\text{mL}$], absence of S9 [-S9; 0 (control), 75, 150, or 300 $\mu\text{g}/\text{mL}$], and for 21 hours in the absence of S9 [-S9; 0 (control), 18.8, 37.5, or 75 $\mu\text{g}/\text{mL}$].

The Applicant's Position:

The positive genotoxicity findings in the human lymphocytes were generally only observed in the presence of significant cell toxicity (as indicated by a decrease in the relative mitotic index compared to concurrent controls) at the highest tested concentrations. All other test article concentrations in all test conditions caused lesser degrees of cytotoxicity (as indicated by relative mitotic indices of $\geq 77\%$) and, with one exception, did not cause increases in the percentage of aberrant cells. Given that the positive genotoxicity results in this study were noted mainly at test article concentrations that caused cytotoxicity levels in excess of the current OECD-recommended maximum of $55 \pm 5\%$ of the concurrent negative controls (OECD 2016), according to the OECD guideline, care should be taken in interpreting the positive results.

The Regulatory Authorities' Assessment:

Cedazuridine was genotoxic in the in vitro chromosome aberration assay under the conditions tested. There was a concentration-dependent increase in percent aberrant cells and in the 4-hour treatment with activation, the statistical increase in the aberrant cells occurred at a cedazuridine concentration that did not cause significant cell toxicity (<55% of concurrent vehicle control).

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Data:

Study title/ number: E7727 Mammalian Erythrocyte Micronucleus Test in Mouse (Study/Report No. 9800434)

Key Study Findings:

- Cedazuridine was non-genotoxic in this in vivo mouse bone marrow micronucleus assay.

GLP compliance: Yes

Test system: Cedazuridine was administered orally (by gavage) to male Crl:CD1(ICR) mice (5/group) at dose levels of 0 (control), 500, 1000, or 2000 mg/kg as 2 doses at 0 and 24 hours.

NDA Multi-disciplinary Review and Evaluation
NDA 212576, Original
INQOVI (decitabine and cedazuridine)

The Applicant's Position:

Cedazuridine was non-genotoxic in the in vivo mouse bone marrow micronucleus assay.

The Regulatory Authorities' Assessment:

We agree with the Applicant's conclusion that cedazuridine was not genotoxic in the in vivo mouse bone marrow micronucleus assay under the conditions tested. We note cedazuridine did not cause notable bone marrow toxicity under the conditions tested. Results of the QWBA and 13-week repeat-dose toxicity studies indicated cedazuridine was distributed to the bone marrow and there were cedazuridine-related histopathology findings in the bone marrow.

Other Genetic Toxicity Studies

Data

No other genetic toxicity studies have been conducted.

The Applicant's Position:

Not applicable

The Regulatory Authorities' Assessment:

We agree that no additional genetic toxicity studies are needed to support the approval of NDA 212576. Of note, decitabine was determined to be genotoxic in studies reviewed to support the approval of decitabine for injection (NDA 21790).

5.5.3. Carcinogenicity

Data:

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

The Applicant's Position:

Based on its positive genotoxicity, decitabine may be expected to have carcinogenic potential. As such, there is a carcinogenic risk associated with exposure to ASTX727.

The Regulatory Authorities' Assessment

Per ICH S9, we agree that carcinogenicity studies are not needed to support the approval of ASTX727 for the proposed indication.

5.5.4. Reproductive and Developmental Toxicology

Data:

No stand-alone reproductive and developmental toxicity studies have been conducted with ASTX727 or with its active components, cedazuridine and decitabine.

The Applicant's Position:

Based on its mechanism of action, decitabine is expected to result in adverse reproductive effects. The US prescribing information for decitabine ([Dacogen USPI 2019](#)) includes information on the effect of decitabine on postnatal development and reproductive capacity. Histopathology findings in the male and female mouse reproductive tract following administration of cedazuridine were previously described above (in the General Toxicology section) and support potential adverse reproductive effects. Thus, there is a risk of reproductive and developmental toxicity associated with exposure to ASTX727.

The Regulatory Authorities' Assessment:

Cedazuridine and decitabine are genotoxic, and decitabine targets rapidly dividing cells in general toxicology studies; per ICH S9, reproductive and developmental toxicity studies are not needed for this class of drugs. These drugs are expected to cause malformation or embryofetal lethality.

5.5.5. **Other Toxicology Studies**

Data:

No additional data.

Applicant's Position:

There were no other toxicity studies conducted with ASTX727 or with its components, cedazuridine and decitabine.

The Regulatory Authorities' Assessment:

We agree.

X	X
Michael Manning, PhD Primary Reviewer OOD/DHOT	Brenda Gehrke, PhD Acting Team Leader OOD/DHOT

6 Clinical Pharmacology

6.1. Executive Summary

The Regulatory Authorities' Assessment:

The Applicant seeks approval of INQOVI (ASTX727: decitabine and cedazuridine) for the treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk one International Prognostic Scoring System groups. The proposed INQOVI dosing regimen is one tablet (35 mg decitabine and 100 mg cedazuridine) taken orally once daily, on an empty stomach, on first five consecutive days of each 28-day cycle. Patients should avoid food 2 hours before and 2 hours after each INQOVI dose.

The Clinical Pharmacology section of the NDA is supported by the evaluation and analysis of comparative pharmacokinetics (PK) and pharmacodynamics (PD) of INQOVI versus IV decitabine, multiple dose PK of decitabine and cedazuridine, and exposure-response relationships for efficacy and safety.

Based on the efficacy and safety results in the Phase 2 and Phase 3 studies in patients with MDS and the comparative PK and PD assessment of INQOVI and IV decitabine in the Phase 3 study, the proposed INQOVI dosing regimen of 35 mg decitabine and 100 mg cedazuridine as a single tablet administered orally once daily for Days 1-5 of each 28-day cycle with the dose modification schema is acceptable. The geometric mean ratio (90% CI) for the 5 day cumulative decitabine exposure between INQOVI and IV decitabine was 0.99 (0.93, 1.06). The high 5-day cumulative decitabine exposure was associated with a higher likelihood of adverse reactions, including any grade neutropenia and thrombocytopenia, that were mostly managed by dose delays and dose reductions.

Analysis of the data provided by the Applicant showed that an increase in cumulative decitabine exposure with decrease in body surface area or body weight was not clinically meaningful. The cumulative decitabine exposures between INQOVI and IV decitabine were comparable for patients with mild to moderate renal impairment, mild hepatic impairment, and in the presence or absence of proton pump inhibitors. No dose adjustment is recommended for patients based on body size or in patients with mild to moderate renal impairment, mild hepatic impairment, and concomitant use of proton pump inhibitors. The results of the food-effect study were found to be unreliable, and the QT-concentration assessment did not adequately characterize the effect of cedazuridine on QT/QTc interval prolongation and post marketing clinical studies will be needed to address these issues.

Recommendations

The proposed INQOVI dosing regimen of 35 mg decitabine and 100 mg cedazuridine as a single tablet orally once daily for the first 5 consecutive days of each 28-day cycle in patients with MDS with the dose modification schema in the event of adverse reactions is acceptable. From a Clinical Pharmacology standpoint, the NDA is approvable provided the Applicant and the FDA reach an agreement regarding the labeling language.

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☐ PMC ☒ PMR	Determination of an appropriate INQOVI dose for patients with moderate and severe hepatic impairment.	Decitabine is excreted mainly via the hepatic route. Patients with moderate and severe hepatic impairment may have higher decitabine exposure than patients with normal hepatic function that may increase the risk of toxicity.	Multiple dose INQOVI in patients with moderate and severe hepatic impairment compared to patients with normal function.
☐ PMC ☒ PMR	Determination of an appropriate INQOVI dose for patients with severe renal impairment and end stage renal disease (ESRD).	Cedazuridine is mainly excreted renally, and an increase in its exposure can increase decitabine exposure. Patients with severe renal impairment or ESRD may have higher cedazuridine exposure resulting in increased decitabine exposure than patients with normal renal function, that may increase the risk of toxicity.	Multiple dose INQOVI in patients with severe renal impairment and ESRD compared to patients with normal function.
☐ PMC ☒ PMR	Determination of an effect of cedazuridine on cardiac repolarization.	A delay in cardiac repolarization favors the development of cardiac arrhythmias, and can be measured as prolongation of the QT interval. The impact of cedazuridine exposures on prolongation of QT interval in patients has not been adequately established.	Thorough QT study of cedazuridine in healthy subjects.
☒ PMC ☐ PMR	Determination of PK and safety of INQOVI when administered with food.	The effect of food on decitabine exposure following administration of INQOVI has not been adequately characterized. The data provided presents conflicting results that	Pharmacokinetic trial in patients to determine the effect of food on decitabine and cedazuridine exposure when administered with INQOVI.

		indicate a pronounced food effect or a lack of food effect. Data is needed to be able to provide instructions to patients and present the risk of taking INQOVI with food if there is an effect, or provide flexibility to patients to take INQOVI without regard to food, increasing dosing compliance and providing a less complicated strategy when taken with other drugs, if there is no effect	

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Mechanism of Action:

ASTX727, a combination of cedazuridine (new molecular entity) and decitabine, is an oral hypomethylating agent (HMA).

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. When administered orally, decitabine is degraded by cytidine deaminase (CDA) and has limited oral bioavailability.

Cedazuridine (E7727) is a competitive inhibitor of CDA with a concentration giving half-maximal inhibition (IC₅₀) value of 281 ± 58 nmol/L. The potency of the E7727-epimer to inhibit CDA is only 1/10th of E7727.

Oral administration of cedazuridine with decitabine enhances the oral bioavailability of decitabine via inhibition of first pass metabolism of decitabine in the gut and liver by CDA.

Pharmacodynamics:

- Administration of ASTX727 transiently increased plasma concentrations of cytidine as expected for the CDA inhibitor, cedazuridine.
- Administration of ASTX727 resulted in a similar reduction in long interspersed nucleotide element-1 (LINE-1) DNA methylation in peripheral blood mononuclear cells to that of

administration of IV decitabine 20 mg/m². At the recommended ASTX727 dose, a maximal of near maximal pharmacodynamic effect of LINE-1 demethylation was observed over the range of decitabine systemic exposures, based on PK-PD modeling.

- The potential for QT prolongation effect of ASTX727 was evaluated in the Phase 3 study by performing limited electrocardiogram (ECG) assessment before and after dosing at the expected t_{max} of both decitabine and cedazuridine. No large mean changes (i.e., >10 msec) in the heart rate-corrected QT interval (QTc) interval were observed. An exposure-QTc analysis suggested no concentration-dependent QTc interval prolongation for either decitabine or cedazuridine.

General Pharmacokinetics

- Cedazuridine exposures were dose proportional across the dose range of 40 to 100 mg.
- Decitabine 5-day AUC_{0-t} over the dosing range of 20 to 40 mg was dose proportional.
- Both cedazuridine and decitabine reach steady-state on Day 2 of administration of ASTX727, with low accumulation ratios (1.3 to 1.6 for cedazuridine and 1.7 to 1.8 for decitabine).
- Steady-state concentrations of decitabine were reached on Day 1 of dosing with IV decitabine 20 mg/m².

AUC equivalence:

The Phase 3 study showed that the extent of absorption (total cycle 5-day AUC₀₋₂₄) of decitabine from oral dosing with ASTX727 was equivalent to IV administration of decitabine (Table 4).

Table 4. Comparison of Decitabine 5-day AUC₀₋₂₄ Between ASTX727 and Intravenous Decitabine (Phase 3 Study ASTX727-02)

Treatment	N	Decitabine 5-day AUC ₀₋₂₄ Geometric LSM	Percentage Ratio (%) (Oral/IV) of Geometric LSM (90% CI)
Oral ASTX727	123	855.69	98.93 (92.66, 105.6)
IV Decitabine	123	864.94	

AUC₀₋₂₄=area under the plasma concentration-time curve from time zero to 24 hours; CI=confidence interval; CSR=clinical study report; LSM=least squares mean; IV=intravenous; N=number of subjects.

Source: CSR ASTX727-02, Table 22

Absorption:

- Following oral administration of ASTX727, cedazuridine was rapidly absorbed and the median time to maximum plasma concentration (t_{max}) was 3 hours (range, 0.52 to 7.9 hours). Approximately 47.5% of an oral dose of cedazuridine was absorbed and the oral bioavailability of cedazuridine was 20.7%.
- Following oral administration of ASTX727, decitabine was rapidly absorbed and t_{max} was 1 hour (range, 0.3 to 3). The t_{max} with IV administration was at the end of the infusion.
- When coadministered, cedazuridine (40, 60, or 100 mg) increased the oral bioavailability of decitabine (20, 30, or 40 mg) compared to that of oral decitabine alone by (R value) 3.68-12.0-fold.
- While administration of ASTX727 with a high-fat, high-calorie meal (approximately 800-1000 calories, with approximately 150 calories from protein, approximately 250 calories from carbohydrates, and approximately 500-600 calories from fat) had little effect on cedazuridine and cedazuridine-epimer exposures, decitabine exposure parameters were approximately 40% (AUC) to 54% (maximum plasma concentration [C_{max}]) lower compared to those following administration under fasted conditions. Administration with food delayed cedazuridine t_{max} slightly but had little effect on systemic exposures.

Distribution

- Cedazuridine was approximately 35% bound to human plasma proteins in vitro. The geometric mean (coefficient of variation [CV]) of apparent volume of distribution (V/F) for cedazuridine was 296 L (51%).
- Decitabine was approximately 5% bound to human plasma proteins in vitro. After administration of ASTX727, the geometric mean (CV) of decitabine V/F at steady state was 417 L (54%).

Elimination (Metabolism and Excretion)

Metabolism:

- The primary metabolic pathway for cedazuridine was conversion to the epimer. There was also some dehydrogenation and some conjugation with urea.

Elimination:

- Renal clearance was the main route of excretion of orally absorbed cedazuridine and the cedazuridine-epimer.
- After oral administration of [^{14}C]-cedazuridine, 17.1% (range, 12.0% to 24.1%) of the administered dose was excreted in the urine as unchanged cedazuridine within 75 hours. The cedazuridine-epimer excreted in the urine was 17.5% of the orally administered cedazuridine dose.

- After IV administration of [¹⁴C]-cedazuridine, 80.9% (range, 73.5% to 88.4%) of the total radioactivity was recovered in the urine and 0.6% was recovered in the feces within 72 hours.
- After oral administration of [¹⁴C]-cedazuridine, the mean total recovery was 96.9% (range, 93.2% to 100.2%) over the 120-hour collection interval with the majority of radioactivity recovered in urine and feces in the first 72 hours postdose (92.2%). The renal clearance (CL_r) was 4.46 L/h (range, 3.01 to 5.47 L/h).
- The major elimination pathway for decitabine is metabolic, by CDA, and physico-chemical degradation at physiological conditions.
- Following a single oral dose of ASTX727, the mean (CV) terminal elimination half-life (t_{1/2}) of cedazuridine was 6.3 hours (18%). The apparent clearance (CL/F) of cedazuridine was 30.6 L/h at Day 1 and 30.3 L/h at steady state.
- Following a single oral dose of ASTX727, the mean t_{1/2} (CV) of decitabine was 1.2 hours (23%) compared to 1.0 hours (47%) for IV decitabine. After administration of ASTX727, decitabine CL/F was 342 L/h at Day 1 and 197 L/h at steady state.

Specific Populations

- Age, sex, body weight, or mild to moderate hepatic impairment (by NCI criteria) did not have a clinically meaningful effect on the PK of decitabine or cedazuridine after administration of ASTX727. Mild or moderate renal impairment (NCI criteria) had an effect on cedazuridine exposures, but based on the relatively small magnitude of the effect this was considered not clinically meaningful.
- The effect of severe hepatic impairment or of severe renal impairment on the PK of decitabine and cedazuridine is unknown.

Drug-Drug Interactions

- The exposure of cedazuridine was unaffected by coadministration with decitabine.
- Model-based analyses of proton pump inhibitor (PPI) coadministration showed that PPI had no effect on the PK of decitabine or cedazuridine.
- Cedazuridine is a potent inhibitor of CDA, so it would affect the metabolism and exposure of any coadministered drug that is metabolized via this enzyme.
- In vitro, cedazuridine did not induce CYP1A, CYP2B6, CYP2C9, and CYP3A and did not inhibit any of the CYP isoforms tested (i.e., CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A).
- Cedazuridine was not an inhibitor of P-gp, BCRP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, CNT1, ENT1, or ENT2. A weak inhibition of CNT2 and CNT3 was observed, but only at the highest concentration tested.
- In in vitro studies, cedazuridine was not metabolized by human liver S9 fraction or liver cytosol and was not a substrate for the majority of transporters. Although cedazuridine was transported by CNT1, CNT3, and ENT2, the potential for drug-drug interactions with co medications is low.

- Decitabine is not a substrate for CYP enzymes, and the plasma protein binding of decitabine is negligible. Decitabine is unlikely to inhibit or induce CYP enzymes.

Exposure-adverse event analysis:

- Model-based analyses of exposure-safety relationships using pooled data of Phase 2 part of Study ASTX727-01 and from Study ASTX727-02 (Phase 3) focused on mainly hematological parameters such as neutropenia and thrombocytopenia determined that none of the trends in these analyses were significant, suggesting a similar risk of thrombocytopenia or neutropenia with oral versus IV decitabine within or across exposure ranges and weight groups (quartiles) and that no dose adjustment is needed based on the subject's weight.

The Regulatory Authorities' Assessment:

Refer to Table 5 in Sections 6.3.1.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The selection of the dose and regimen is based on the decitabine 5-day AUC equivalence of ASTX727 with IV decitabine (20 mg/m² Daily×5). Dose levels for the combination to achieve total cycle AUC that match the IV were confirmed in the Phase 2 study (Table 12 and Table 13) and the full AUC equivalence was established in the Phase 3 study (Table 6). In addition, ASTX727 treatment at the recommended dose and regimen achieved almost identical demethylation to IV decitabine, as measured by %LINE 1 demethylation (Table 8, Table 9, and Figure 3). Likewise, the safety data from the Phase 2 and Phase 3 studies largely mirrors the expected safety profile of IV decitabine in the same patient population.

Administration of ASTX727 with food (high-fat, high-calorie meal) had little effect on cedazuridine and cedazuridine epimer exposures; however, decitabine exposure parameters were approximately 40% (AUC) to 53.5% (C_{max}) lower compared to those following administration under fasted conditions (Table 16).

See Section 6.3.1 for more details.

The Applicant's Position:

The recommended dose of ASTX727 is 1 tablet containing 100 mg cedazuridine and 35 mg decitabine taken orally once daily on Days 1 through 5 of each 28-day cycle for a minimum of 4 cycles. ASTX727 tablets should be taken with water on an empty stomach. (b) (4)

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's position regarding the proposed dose of one ASTX727 (35 mg decitabine and 100 mg cedazuridine) tablet once daily for first the 5-days of each 28-day cycle under fasted conditions, based on the demonstration of comparable PK and PD in Study ASTS727-02 between ASTX727 and IV decitabine and efficacy in Study ASTX727-01-B and Study ASTS727-02. FDA agrees with the Applicant's proposed strategy for dose modification for hematological toxicity, including the proposed schema for dose reductions.

FDA does not agree with the Applicant's position regarding the food effect due to inconsistency in the PK results in Study ASTX727-04 (refer to Section 6.3.2.4). There is inadequate data evaluating the effect of food on ASTX727. Additional data regarding the effect of food on ASTX727 is needed as a post-marketing commitment. FDA recommends that patients should avoid taking food 2 hours before and 2 hours after administration of ASTX727, consistent with the fasted conditions followed in Studies ASTX727-01-B and ASTX727-02.

6.2.2.2. Therapeutic Individualization

Data:

Exploratory subgroup analyses by age (32 to 90 years), sex, body weight (41 to 158 kg), or mild to moderate hepatic impairment (total bilirubin > upper limit of normal [ULN] up to $\leq 3 \times$ ULN) did not have a clinically meaningful effect on the PK of decitabine or cedazuridine after administration of ASTX727. Mild or moderate renal impairment (creatinine clearance [CRCL] ≥ 20 to 59 mL/min/1.73m²) had an effect on cedazuridine exposures, but this was not considered to be clinically meaningful. The effects of severe hepatic impairment or severe renal impairment on the PK of decitabine and cedazuridine is unknown.

Drug-drug interaction studies have not been conducted with cedazuridine or decitabine. In vitro studies indicate that neither cedazuridine nor decitabine is likely to inhibit or induce major human cytochrome P450 enzymes. Neither cedazuridine nor decitabine is an inhibitor or a substrate of major human drug transporters. Cedazuridine is an inhibitor of CDA.

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

The Applicant's Position:

In regards to drug-drug interactions (DDIs), the following are recommended:

- **Drugs metabolized via CYP450 pathways:** no modification
- **Drugs metabolized by CDA:** avoided concomitant use
- **Proton Pump Inhibitors (or other gastric pH modifying agents):** no modification needed

In regards to special populations, the following are recommended:

- **Renal Impairment:** no modification needed for patients with mild to moderate impairment. No data on patients with severe impairment
- **Hepatic Impairment:** [REDACTED] (b) (4)
[REDACTED] No data on patients with severe impairment

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's position of no dose modifications based on age (32 to 90 years), sex, body weight (41 to 158 kg), body surface area, mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min), mild hepatic impairment (total bilirubin $> \text{ULN}$ to $1.5 \times \text{ULN}$, or $\text{AST} > \text{ULN}$). The FDA agrees with the Applicant's position that no dose modifications are necessary for the concomitant use of CYP modulators and that the concomitant use of drugs that are metabolized by CDA should be avoided. FDA agrees that no dosing modifications are needed with concomitant use of PPIs or other gastric pH modifying agents.

There was only one patient with severe renal impairment (creatinine clearance 15 to < 30 mL/min) in the Phase 2 and 3 studies, and hence there is insufficient data to reliably demonstrate the effect of severe renal impairment on the PK and safety of ASTX727. Therefore, additional information regarding the exposure and safety of ASTX727 in patients with severe renal impairment and end-stage renal disease will be needed as a post-marketing requirement.

We disagree with the Applicant's position on therapeutic individualization in patients with moderate hepatic impairment. There were only 3 patients with moderate hepatic impairment and no patients with severe hepatic impairment in the clinical studies. Hence, there is insufficient data to reliably demonstrate the effect of moderate and severe hepatic impairment on the PK and safety of ASTX727. Additional information regarding the exposure and safety of ASTX727 in patients with moderate and severe hepatic impairment will be needed as a post-marketing requirement.

6.2.2.3. Outstanding Issues

Data:

The studies included in the PopPK analysis (the Phase 2 parts of Study ASTX727-01 and the Phase 3 Study ASTX727-02) did not include subjects with severe renal impairment or with severe hepatic impairment. These studies also did not have sufficient racial diversity to inform potential correlations with regard to race or ethnicity. ECG evaluations with time-matched PK

were included in Phase 3 but were limited to single tracing before treatment and another post-treatment at the expected t_{max} of decitabine and cedazuridine on Day 3 of Cycle 1 and 2. This was due to already demanding PK assessments in the study design to support the primary endpoint of the trial.

A thorough QT study was not conducted with ASTX727 as these studies are challenging to conduct in this disease population with advanced age and often cardiac comorbidities and use of concomitant medications. (b) (4)

[Redacted]

The Applicant's Position:

Neither race nor ethnicity is expected to affect the clinical pharmacology of ASTX727, but this has not been verified.

The effects of severe renal impairment or severe hepatic impairment on the clinical pharmacology of ASTX727 are unknown at this time.

[Redacted] (b) (4)

Regulatory Authorities' Assessment:

- FDA disagrees with the Applicant's assessment of the QT prolongation risk. FDA notes that the PK and ECG data from ASTX727-02, used in the Applicant's QT risk assessment, are not sufficient to adequately characterize the effect of cedazuridine from ASTX727 on the QTc interval (refer to 6.3.2.5 for details). Evaluation of the QT prolongation potential of cedazuridine will be required. This will need to be assessed as a post-marketing requirement.
- There is insufficient data to assess the exposure and safety of ASTX727 in patients with moderate or severe hepatic impairment (refer to 6.3.2.3 for details). This will need to be assessed as a post-marketing requirement.
- There is insufficient data to assess the exposure and safety of ASTX727 in patients with severe renal impairment and end-stage renal disease (refer to 6.3.2.3 for details). This will need to be assessed as a post-marketing requirement.
- The results in Study ASTX727-04 do not permit for an adequate assessment of the effect of food on the pharmacokinetics of ASTX-727 (refer to 6.3.2.4 for details). There is no data to adequately describe and label the effect of food on the pharmacokinetics of ASTX727. This will need to be evaluated as a post-marketing commitment.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Regulatory Authorities' Assessment:

The information in Table 5 below.

Table 5. Summary of General Pharmacology and Pharmacokinetic Characteristics of ASTX727 (decitabine and cedazuridine)

Pharmacology	
Mechanism of Action	Decitabine is a nucleoside metabolic inhibitor. Cedazuridine is a competitive inhibitor of CDA with an IC ₅₀ of 281 nmol/L
Active Moieties	Cedazuridine and decitabine
QT Prolongation	The effect of cedazuridine on the QTc interval has not adequately characterized.
General Information	
Bioanalysis	Validated bioanalytical assays (LC-MS/MS) methods to determine concentrations of decitabine, cedazuridine, and cedazuridine-epimer.
Healthy vs. Patients	Clinical studies of ASTX727, IV decitabine, or decitabine in combination with cedazuridine were conducted only in patients. Single oral 100 mg cedazuridine: CL/F (L/hr): 28 (22, 48) vs. 31 (9-90) (subjects vs. patients).
Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	At steady state following once daily dosing with ASTX727: • Mean decitabine (%CV) AUC_{tau} was 178 (53%) ng•h/mL, and C_{max} was 145 (55%) ng/mL. • Mean cedazuridine AUC_{tau} was 3291 (45%) ng•h/mL and C_{max} was 371 (52%) ng/mL.
Dose Proportionality	C _{max} and AUC _{tau} of decitabine at 20 to 40 mg once daily in combination with 100 mg cedazuridine, and cedazuridine at 40 to 100 mg once daily in combination with 20 mg decitabine were approximately dose proportional.
Accumulation	The accumulation ratios based on AUC _{tau} for decitabine was 1.7 (42%) and cedazuridine was 1.1 (63%).
Variability	Decitabine geometric CV was 53% to 56% for AUC _{tau} and 52% to 66% for C _{max} . Cedazuridine geometric CV was 46 to 47% for AUC _{tau} and 49% to 54%. for C _{max} .
Absorption	
Median T_{max}	Decitabine: 1 hour (0.3, 3) Cedazuridine: 3 hours (1.5 to 6.1)
Food effect (Fed/fast)	The effect of food on the PK of ASTX727 has not been adequately assessed.
Distribution	

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Volume of Distribution	Decitabine V/F at steady state is 417 L (54%) Cedazuridine V/F at steady state is 296 L (51%)
Plasma Protein Binding	Fraction unbound for decitabine is 96% (4%) at 17 ng/mL to 94% (2%) at 342 ng/mL, and for cedazuridine is 66% (6%) at 1000 ng/mL to 62% (2%) at 50000 ng/mL.
Blood to Plasma Ratio	0.622 to 1.07 (cedazuridine)
As Substrate of Transporters	In vitro, cedazuridine was not a substrate for P-gp (up to 1000 μ M), ENT1/4, MATE1/2-K, OAT1/3, OATP1B1/2B1, OCT1/2 (up to 50 μ M). Although cedazuridine is transported by CNT1, CNT3, and ENT2, the potential for drug-drug interactions with comedications is low.
Elimination	
Terminal Elimination Half-Life	After administration of ASTX727 in the Phase 3 study, the mean $T_{1/2}$ at steady state of decitabine was 1.5 (27%) hours and cedazuridine was 6.7 (19%) hours.
Metabolism	
Fraction Metabolized (% dose)	Cedazuridine accounted for 59% of total drug-related material in plasma. Cedazuridine-epimer and M266/1 metabolite accounted for 31% and 10%, respectively, of total drug-related material in plasma.
Primary Metabolic Pathway(s)	Decitabine is mainly metabolized via deamination by CDA found in the liver, and also in granulocyte, intestinal epithelium, and whole blood, and degradation via hydrolytic ring-opening. The primary metabolic pathway for cedazuridine is physiochemical conversion to its epimer.
Excretion	
Primary Excretion Pathways (% dose) $\pm$SD	Primary route of elimination of cedazuridine is renal: 99% in urine following IV dose. After an oral dose, 46% (21% unchanged) of the orally administered dose was recovered in the urine and 51% (27% unchanged) in feces.
Interaction liability (Drug as Perpetrator)	
Inhibition/Induction of Metabolism	Cedazuridine is an inhibitor of CDA. In vitro, cedazuridine is not an inducer of CYP1A, CYP2B6, CYP2C9, or CYP3A (up to 400 μ M) or inhibitor of CYP1A, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A (IC_{50} >400 μ M).
Inhibition/Induction of Transporter Systems	Cedazuridine was not an inhibitor of P-glycoprotein (P-gp), BCRP, MATE1/2-K, OAT1/3, OATP1B1/2B1, OCT2, CNT1 & ENT1/2 (up to 300 μ M), and a weak inhibitor of concentrative nucleoside transporter (CNT)2 and CNT3 with ~30% inhibition at 300 μ M.

AUC_{tau} = area under concentration-time curve during the dosing interval; CDA=cytidine deaminase; C_{max} =maximum plasma concentration; IC_{50} =concentration giving half-maximal inhibition; $t_{1/2}$ =elimination half-life; t_{max} =time to maximum plasma concentration; CL/F=clearance; V/F=apparent volume of distribution.

Note: PK parameters are presented as geometric mean (%CV) or median (minimum, maximum) unless otherwise noted

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Yes. Supportive evidence of effectiveness is provided based on PK assessments in the Phase 2 (ASTX727-01-B) and the Phase 3 pivotal study (ASTX727-02) and based on pharmacodynamic effects in the Phase 2 and 3 studies.

Pharmacology

In vitro, cedazuridine was a potent inhibitor of CDA (IC_{50} of 0.281 μ M) and was able to increase the $t_{1/2}$ of the CDA-mediated metabolism of gemcitabine from ≤ 36 minutes to ≥ 66 hours.

Pharmacokinetic Equivalence

In the Phase 3 Study ASTX727-02, ASTX727 administered Daily $\times 5$ was compared with IV decitabine 20 mg/m² Daily $\times 5$. The primary analysis of the primary study endpoint showed that the 5-day AUC_{0-24} 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 (Table 6).

Results of the secondary analyses further supported the primary analysis AUC_{0-24} (Table 7) in that all analyses show that 90% CI for the oral/IV ratio are contained entirely between 80% and 125%. The range of decitabine exposures after oral ASTX727 at the recommended doses (100 mg cedazuridine and 35 mg decitabine) largely overlapped with the range of exposures after IV decitabine at 20 mg/m² (Figure 1).

Table 6. ASTX727-02 Phase 3: Equivalence Analysis for Comparison of Decitabine AUC Exposures Between ASTX727 and Intravenous Decitabine – Primary Endpoint and Sensitivity Analyses

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 ₀₋₂₄	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

ANOVA=analysis of variance; AUC=area under the plasma concentration-time curve; AUC₀₋₂₄=area under the plasma concentration-time curve from time zero to 24 hours; CI=confidence interval; CSR=clinical study report; CV=coefficient of variation; Geo. LSM=geometric least squares mean; IV=intravenous; 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).

Source: CSR ASTX727-02, Table 22.

Table 7. ASTX727-02 Phase 3: Comparison of Decitabine AUC Exposures Between ASTX727 and Intravenous Decitabine – Secondary Analysis

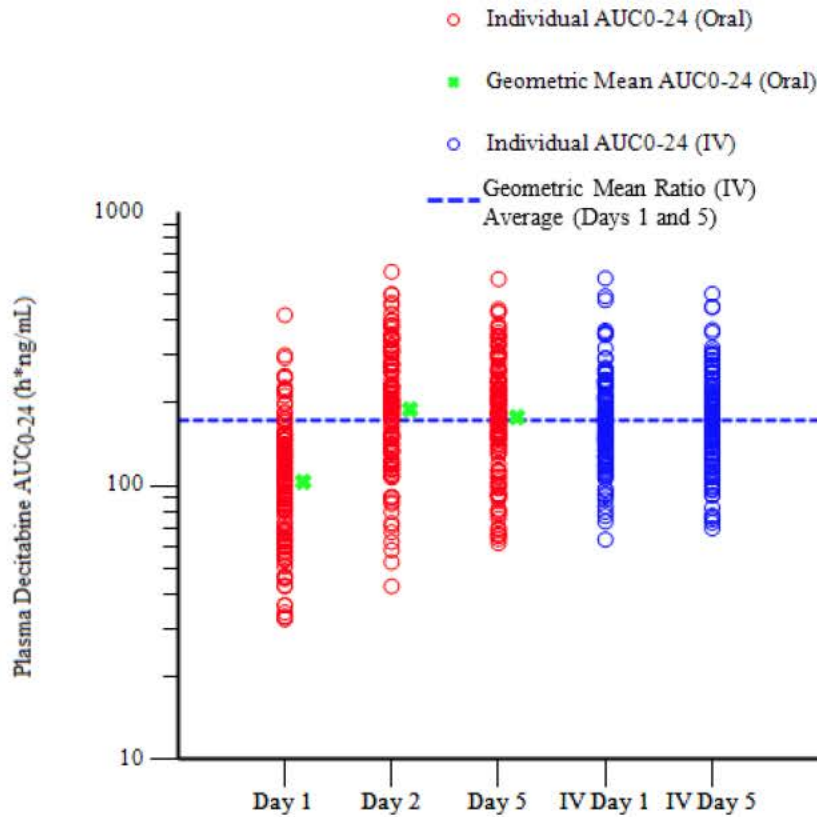
Analysis		AUC Parameter (ng•h/mL)	IV Decitabine		Oral ASTX727		Percentage Ratio (%) of Geo. LSM (90% CI)		Intrasubject Variability (CV, %)
			N	Geo. LSM	N	Geo. LSM			
Secondary	Paired	5-day AUC _{0-inf}	123	866.75	123	849.39	98.00	(91.79, 104.6)	31.7
Sensitivity	Unpaired	5-day AUC _{0-inf}	131	867.62	128	842.46	97.10	(91.02, 103.6)	32.1
	Paired	5-day AUC _{0-inf}	128	871.72	128	844.34	96.86	(90.77, 103.4)	32.1
Secondary	Paired	5-day AUC _{0-t}	124	853.34	124	837.19	98.11	(91.88, 104.8)	31.9
Sensitivity	Unpaired	5-day AUC _{0-t}	131	859.82	128	831.36	96.69	(90.62, 103.2)	32.2
	Paired	5-day AUC _{0-t}	128	863.86	128	833.23	96.45	(90.38, 102.9)	32.2
Secondary	Paired	5-day AUC ₀₋₈	124	856.95	124	839.17	97.93	(91.74, 104.5)	31.7
Sensitivity	Unpaired	5-day AUC ₀₋₈	131	863.45	128	833.38	96.52	(90.49, 102.9)	32.0
	Paired	5-day AUC ₀₋₈	128	867.52	128	835.27	96.28	(90.25, 102.7)	32.0

ANOVA=analysis of variance; AUC=area under the plasma concentration-time curve; AUC₀₋₈=area under the plasma concentration-time curve from time zero to 8 hours; AUC_{0-inf}=area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC_{0-t}=area under concentration-time curve from time zero to the last measurable concentration; CI=confidence interval; CSR=clinical study report; CV=coefficient of variation; Geo. LSM=geometric least squares mean; IV=intravenous; 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).

Source: CSR ASTX727-02, Table 23.

Figure 1. ASTX727-02 Phase 3: Individual Patients Decitabine Exposures (AUC₀₋₂₄) after ASTX727 (oral) and IV decitabine



Biomarker Response

In the Phase 3 Study ASTX727-02, the difference between maximum percent LINE-1 demethylation was <1% between ASTX727 and IV decitabine 20 mg/m² (Table 8).

Table 8. ASTX727-02 Phase 3: Comparison of LINE-1 Demethylation Between ASTX727 and Intravenous Decitabine

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

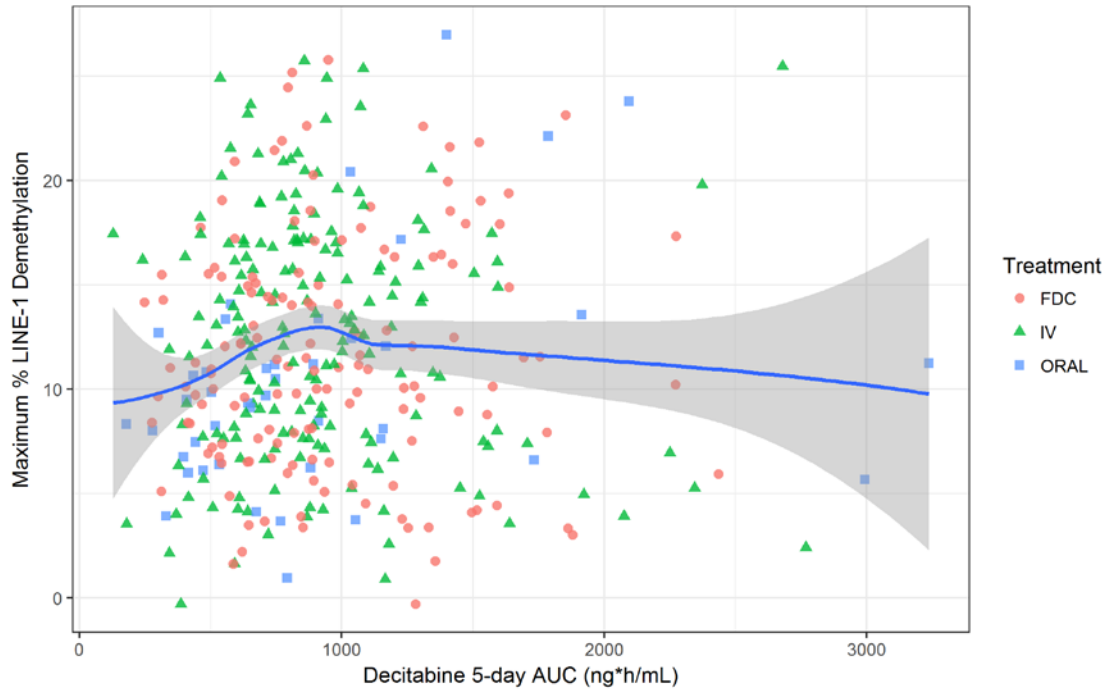
ANOVA=analysis of variance; CI=confidence interval; CSR=clinical study report; IV=intravenous; LINE-1=long interspersed nucleotide element-1; LSM=least squares mean; n=number of subjects.

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

Source: CSR ASTX727-02, Table 28.

A PK/PD analysis of the relationship between maximum LINE-1 demethylation and 5-day decitabine AUC found that there appeared to be a saturable positive PK/PD relationship, with little further increase in response with higher exposures (Figure 2). This suggests that a maximal drug effect was achieved over the range of decitabine exposures in the Phase 2 parts of Study ASTX727-01 and in Study ASTX727-02.

Figure 2. Relationship Between Maximum LINE-1 Demethylation and 5-Day Decitabine AUC by Treatment (Studies ASTX727-01 and ASTX727-02)



AUC=area under the plasma concentration-time curve; CI=confidence interval; FDC=fixed dose combination oral tablet of cedazuridine and decitabine ; IV=intravenous; LINE-1=long interspersed nucleotide element-1; LOESS=locally estimated scatterplot; ORAL=oral cedazuridine and decitabine capsules given together. Note: The blue line represents the LOESS smooth regression line for maximum LINE-1 demethylation across decitabine 5-day AUC and the gray-shaded area is the 95% CI; circles, triangles, and squares are the observed data.

Source: Modeling Report ASTX-PMX-DECITABINE-1414, Figure 2.

Phase 1 Study:

Decitabine administration had no effect on plasma cytidine levels in Study ASTX727-01.

As expected, on days when cedazuridine was administered in Cycle 1 of Study ASTX727-01, a consistent increase in plasma cytidine levels was observed. This appeared to be modest (approximately 2-fold) and transient, as evidenced by the trend of recovery toward baseline by 24 hours, and full recovery as seen at predose on Cycle 2 Day -3.

Phase 2 Study:

The results of the primary PD endpoint (LINE-1 demethylation) are presented below (Table 9 and Figure 3). There was no significant difference between the PD effect on DNA methylation measured by LINE-1 between oral and IV in Cycles 1 or 2.

Table 9. ASTX727-01 Phase 2: Maximum % LINE-1 Demethylation

Study Stage	Course	N	Treatment	Mean Baseline	Maximum %LINE-1 Demethylation		Difference ^a	
					Least Squares Mean ^b	95% CI	Estimate	95% CI
Phase 2 Overall	1	40	Cedazuridine + Oral Decitabine 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	Cedazuridine + Oral Decitabine 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)		

For Course 1, baseline is the last available value on or before C1D1.

For Course 2, baseline is the value on C2D1.

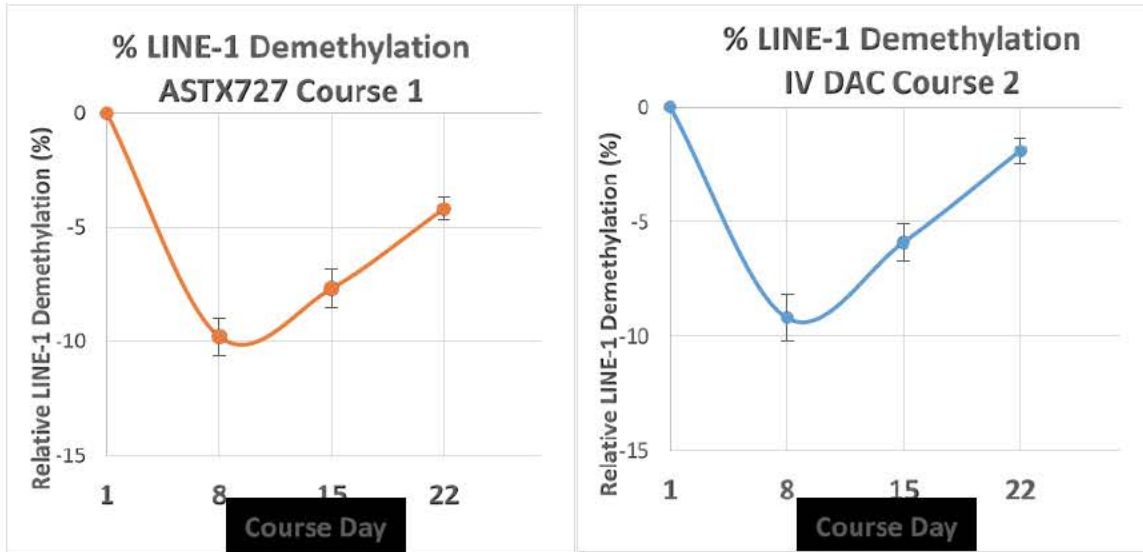
^a The 95% CIs for the difference (oral – IV) of mean maximum %LINE-1 demethylation between ASTX727 and IV decitabine were generated using an ANOVA model separately for Cycle 1 and Cycle 2.

^b LSM=Least Squares Mean of maximum %LINE-1 methylation change from baseline.

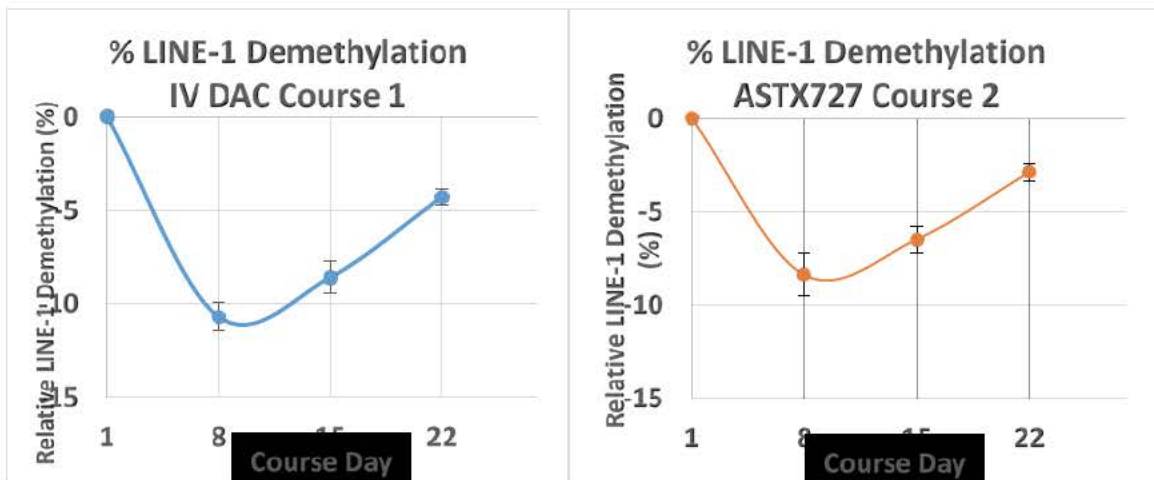
Source: ASTX727-01-B CSR Table 14.5.3.1

Figure 3. ASTX727-01 Phase 2: LINE-1 Methylation

Sequence A



Sequence B



N=78. Sequence A = ASTX727 in Course 1; IV decitabine in Course 2. Dosing was on Days 1-5 of each 28-day Course. DAC=IV decitabine. Error bars are SEM.

NOTE: Course 1 assessments at baseline (i.e., latest available value on or before C1D1) and on Days 8, 15, 22.

Course 2 assessments at baseline (C2D1) and on Days 8, 15, 22.

Sources: ASTX727-01-B CSR Table 14.5.1.2 and Table 14.5.2.2

The Applicant's Position:

Yes.

The demonstration of equivalent decitabine exposures between ASTX727 and IV decitabine based on total cycle AUC_{0-24} supports the PK bridging approach. Decitabine plasma AUC exposures are largely considered to be the principal PK determinant of both biological and clinical activity of decitabine and the ASTX727 5-day AUC was equivalent to the IV decitabine 5-day AUC (Table 6). Decitabine exerts its hypomethylating activity after incorporation into DNA during the S-Phase of the cell cycle, and AUC exposures would be consistent with driving decitabine activity as more cells enter into the S-Phase over the exposure window represented by AUC. This is also supported by similar PD effect of LINE-1 demethylation between oral ASTX727 and IV decitabine over the treatment cycle in Phase 3 (Table 8).

The PK/PD analysis demonstrated that a maximal drug effect of LINE-1 demethylation was achieved for ASTX727 and IV decitabine 20 mg/m² over the range of decitabine exposures in the Phase 2 parts of Study ASTX727-01 and in Study ASTX727-02 (Figure 2).

Overall, the PK and biomarker response were similar between ASTX727 and IV decitabine 20 mg/m², supporting the conclusion that ASTX727 has the same effectiveness as IV decitabine 20 mg/m².

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's position on the effectiveness of ASTX727 tablet (35 mg of decitabine and 100 mg of cedazuridine) when administered orally, once daily for the first 5 days of each 28-day cycle under fasted conditions, i.e., 2 hours before and 2 hours after dosing. The Phase 3 study demonstrated comparable 5-day cumulative decitabine exposure (primary PK endpoint) between ASTX727 and IV decitabine as shown in Table 6, and that the 90% confidence intervals of the geometric mean ratio were within bioequivalence limits of 80% and 125%.

Comparison of daily decitabine exposures (Table A) demonstrated that following the first dose of ASTX727, the Day 1 exposure compared to IV decitabine was 40% lower. However, following 5 consecutive once daily doses of ASTX727, the Day 5 decitabine exposure was comparable between ASTX727 and IV decitabine. Also, the decitabine exposures at Day 2 and Day 5 were comparable, indicating attainment of steady state at Day 2 for ASTX727. Nonetheless, the lower Day 1 exposure for ASTX727 is not likely to affect the efficacy, as

- decitabine requires at least 4 cycles to show response per the Dacogen USPI, with a median time to CR+PR response of 162 days,
- the efficacy of ASTX727 in the Phase 2 study were comparable to those of Dacogen (see Sections 8.1.2 and 8.1.4), and
- maximum LINE-1 demethylation was observed at Day 8 suggesting a cumulative effect of exposure.

Table A: Comparison of Decitabine Exposures in Study ASTX727-02

COMPARISON*		N	GMR	90% CI
ASTX vs. IV	5-day AUC†	109	0.98	0.92, 1.05
ASTX vs. IV	Day 1 AUC _{24h}	115	0.60	0.55, 0.65
ASTX vs. IV	Day 5 AUC _{24h}	112	1.06	0.98, 1.14
ASTX	AUC _{24h} : Day 1 vs. Day 5	122	0.58	0.55, 0.62
ASTX	AUC _{24h} : Day 2 vs. Day 5	124	1.07	1.02, 1.13
IV	AUC _{24h} : Day 1 vs. Day 5	111	1.03	0.98, 1.07

†only patients with Day 1, 2, and 5 AUC for ASTX727, and Day 1 and 5 AUC for IV decitabine.

*paired analysis.

Source: Reviewer analysis

The PD endpoint, i.e., the maximum long interspersed nucleotide element 1 (LINE-1) demethylation was comparable between ASTX727 and IV decitabine in the Phase 3 study (Table 8). The results are presented as comparison for each cycle, as recovery of baseline methylation was not complete at the end of Cycle 1. A sensitivity analysis using ln-transformed data indicated that the point estimates of decitabine after ASTX727 administration were similar for Cycle 1, and within 15% for Cycle 2 and while the lower limit of the 90% confidence interval was lower 0.8, the confidence interval included 1 (Table B).

Table B: Comparison of Maximum LINE-1 demethylation in Study ASTX727-02

N	COMPARISON		GMR	90% CI
62	ASTX vs. IV	Cycle 1	0.86	0.73, 1.03
63*	ASTX vs. IV	Cycle 2	0.98	0.80, 1.19

* Patient (b) (6) on IV decitabine excluded due to a positive change in baseline in the untransformed data. Presented by cycle, due to carryover effects of LINE-1 methylation from Cycle 1 to 2. Maximum LINE-1 demethylation is represented as maximum percent change from baseline. Source: Reviewer analysis

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

Dose Selection Rationale

The decitabine AUC_{0-t} after the single oral dose of decitabine alone on Day -3 of Study ASTX727-01 was lower than that for IV decitabine 20 mg/m² at all oral doses tested in Phase 1 (20, 30, and 40 mg; Table 10). The oral bioavailability was consistently low. Decitabine exposures increased dramatically when administered orally with cedazuridine (Days 2 and 5 of Phase 1 Study ASTX727-01-A) compared with Day -3. The magnitude of increase in AUC_{0-t} ranged from approximately 4- to 7-fold on Day 2 (first dose with the combination) and from 7- to 12-fold on Day 5 (Table 11).

In the Phase 2 study (ASTX727-01-B), the selection of cedazuridine and decitabine doses of

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INQOVI (decitabine and cedazuridine)

100 mg and 35 mg, respectively was confirmed to produce an oral/IV AUC ratio of ~94% in the Dose Confirmation stage using separate capsules (Table 12) and ~98% in the FDC stage using the FDC tablet (Table 13).

Table 10. ASTX727-01 Phase 1: 5-Day Decitabine AUC_{0-t}

Cohort	Oral Dose (mg)		N	AUC _{0-t} by Day (ng•h/mL) Geometric Mean (gCV, %)				5-Day Total AUC _{0-t} (ng•h/mL)		% of 5-Day IV AUC (Oral/IV)
	Decitabine	Cedazuridine		Day -3* (oral decitabine alone)	Day 2*	Day 5*	IV Day 1	Oral	IV (N=41)	
1	20	40	5	7.90 (58)	29.0 (45)	53.6 (40)	138 (41)	243	821	30
2	20	60	6	7.49 (52)	30.5 (62)	68.9 (44)	170 (39)	306		37
3	20	100	6	7.90 (147)	53.5 (44)	94.8 (46)	192 (47)	433		53
4	40	100	6	29.8 (100)	167 (45)	221 (74)	153 (50)	1050		128
5	30	100	18	15.3 (92)	81.7 (59)	146 (50)	166 (41)	667		81

AUC_{0-t}=area under the plasma concentration-time curve from time zero to the time of the last measurable plasma concentration; gCV=geometric coefficient of variation; IV=intravenous.

* Decitabine oral dose alone was administered on Day -3, combination (decitabine + cedazuridine) was administered on Days 2-5 and compared with IV decitabine given on Day 1

Source: CSR ASTX727-01-A CSR Table 18.

Table 11. ASTX727-01 Phase 1: Mean decitabine Oral Bioavailability and Increase in Decitabine AUC_{0-t} from cedazuridine/decitabine given together (Days 2-5) Compared with oral decitabine alone on Day -3

Cohort	Oral Dose (mg)		N	Geometric Mean (gCV, %)		
	Decitabine	Cedazuridine		F, %	R _{DDI} (AUC _{0-t}) _{Day 2}	R _{DDI} (AUC _{0-t}) _{Day 5}
1	20	40	5	11.3 (61)	3.68 (55)	6.79 (51)
2	20	60	6	9.16 (56)	4.07 (72)	9.21 (51)
3	20	100	6	7.81 (65)	6.77 (123)	12.0 (133)
4	40	100	6	18.8 (63)	5.60 (60)	7.42 (77)
5	30	100	18	13.1 (77)	5.34 (94)	9.55 (77)

AUC_{0-t}=area under the plasma concentration-time curve from time zero to the time of the last measurable plasma concentration; F=bioavailability when decitabine was dosed alone; gCV=geometric coefficient of variation; IV=intravenous; R_{DDI}=ratio of AUC when administered with or without cedazuridine.

Source: CSR ASTX727-01-A CSR Table 20.

Table 12. ASTX727-01 Phase 2: Plasma Decitabine Results for AUC Assessment – Dose Confirmation Stage

Parameter	N	IV Geometric LSM	Oral Geometric LSM	Percentage Ratio of Geometric LSM, %	(80% CI)	(90% CI)	Intrasubject Variability (CV, %)
5-day AUC _{0-t} , ng•h/mL	40	802.81	750.82	93.52	(82.10, 106.5)	(79.02, 110.7)	47.0
5-day AUC ₀₋₂₄ , ng•h/mL	36	789.03	760.51	96.39	(84.99, 109.3)	(81.90, 113.4)	42.5
5-day AUC _{0-inf} , ng•h/mL	34	785.56	743.16	94.60	(82.78, 108.1)	(79.59, 112.4)	43.7

AUC₀₋₂₄=area under the plasma concentration-time curve from time zero to 24 hours postdose; AUC_{0-inf}=area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC_{0-t}=area under the plasma concentration-time curve from time zero to the time of the last measurable plasma; CI=confidence interval; CV=coefficient of variation; IV=intravenous; LSM=least squares mean.

Source: ASTX727-01-B CSR Table 19.

Table 13. ASTX727-01 Phase 2: Plasma Decitabine Results for AUC Assessment – Fixed-Dose Combination Stage

Parameter	N	IV Geometric LSM	Oral Geometric LSM	Percentage Ratio of Geometric LSM, %	(80% CI)	(90% CI)	Intrasubject Variability (CV, %)
5-day AUC _{0-t} , ng•h/mL	24	745.26	727.29	97.59	(80.48, 118.3)	(75.96, 125.4)	53.8
5-day AUC ₀₋₂₄ , ng•h/mL	19	762.56	823.06	107.93	(85.48, 136.3)	(79.61, 146.3)	57.3
5-day AUC _{0-inf} , ng•h/mL	19	763.25	822.08	107.71	(85.33, 136.0)	(79.48, 146.0)	57.2

AUC=area under the plasma concentration-time curve; AUC₀₋₂₄=area under the plasma concentration-time curve from time zero to 24 hours postdose; AUC_{0-inf}=area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC_{0-t}=area under the plasma concentration-time curve from time zero to the time of the last measurable plasma; CI=confidence interval; CV=coefficient of variation; IV=intravenous; LSM=least squares mean..

Source: ASTX727-01-B CSR Table 24.

The final confirmation of the dose selection came from the PK equivalence primary endpoint analysis in the pivotal Phase 3 study presented above in Table 6 (primary analysis), and Table 7 (sensitivity and secondary analyses). In addition, the levels and range of decitabine exposures after oral ASTX727 recommended dose largely overlapped with the range of exposures after IV decitabine standard dose (Figure 1).

Exposure-Safety

An exposure-safety analysis was performed on exposure and adverse event (AE) data from the Phase 2 part of Study ASTX727-01 and from Study ASTX727-02 (Phase 3). There was no statistically significant difference in the risk of thrombocytopenia or neutropenia with oral versus IV decitabine.

The tables and figures below show model-based predictions of probability or the incidence of the most common adverse events of neutropenia and thrombocytopenia over a range of decitabine 5-day AUC exposures.

Table 14. Phase 2 and 3: Decitabine Model-predicted Probability of Worst Grade Neutropenia ≥ 3 over a Range of Decitabine Exposures

Route	DEC 5-day AUC (ng*hr/mL)	Predicted Probability ^a
ORAL	175	0.0444
ORAL	930	0.181
ORAL	1700	0.280
ORAL	2450	0.354
ORAL	3200	0.413
INTRAVENOUS	175	0.0820
INTRAVENOUS	930	0.137
INTRAVENOUS	1700	0.163
INTRAVENOUS	2450	0.181
INTRAVENOUS	3200	0.195

^a Predicted at reference values for baseline weight (80 kg), baseline neutrophil count ($1.5 \times 10^9/L$), and ECOG=0.

DEC=decitabine

Source: AXP0205F-Report-Exp-AE Table 51

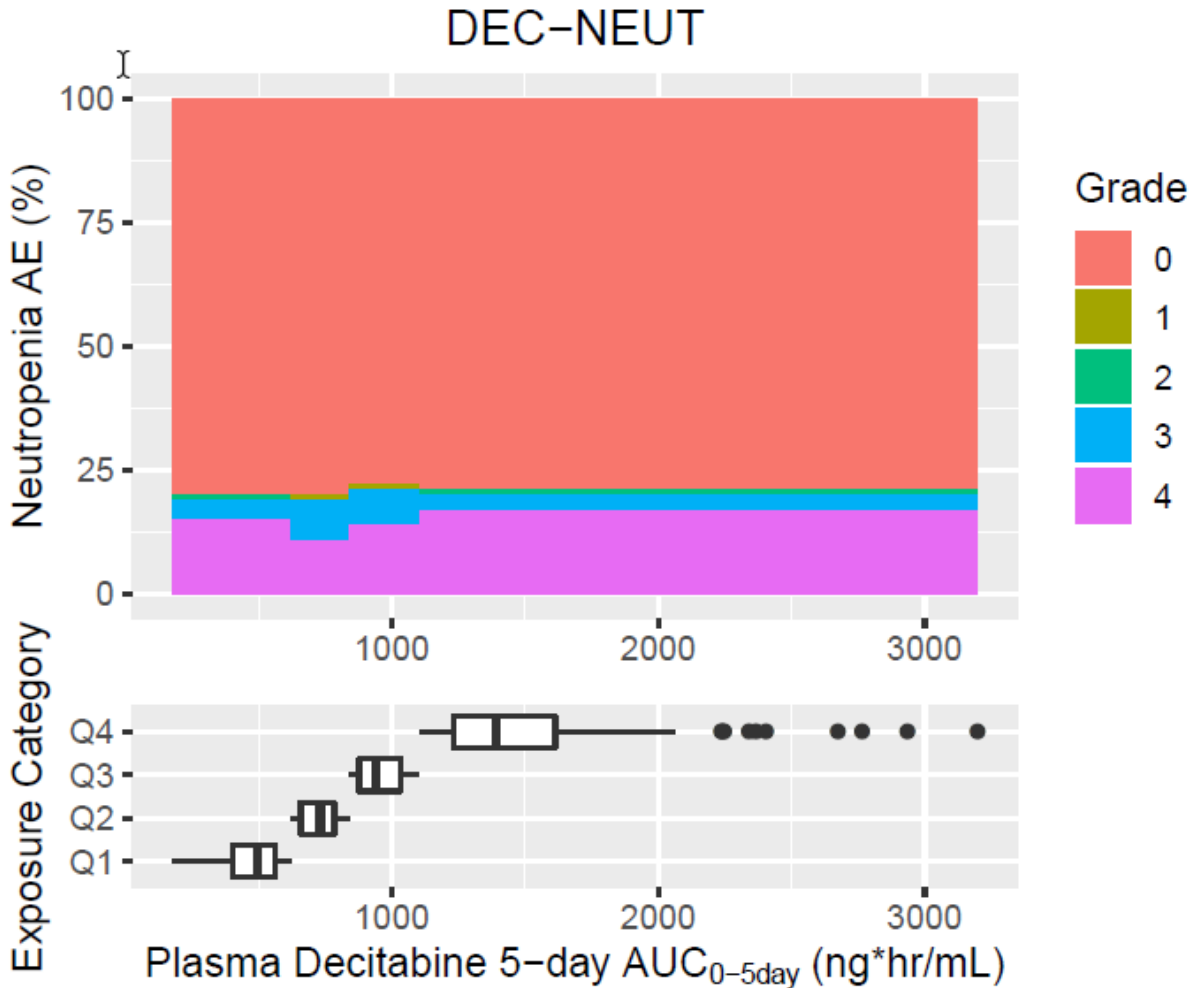
Table 15. Phase 2 and 3: Decitabine Model-predicted Probability of Worst Grade Thrombocytopenia ≥ 3 over a Range of Decitabine Exposure

Route	DEC 5-day AUC (ng*hr/mL)	Predicted Probability*
ORAL	175	0.111
ORAL	930	0.124
ORAL	1700	0.130
ORAL	2450	0.133
ORAL	3200	0.136
INTRAVENOUS	175	0.0734
INTRAVENOUS	930	0.129
INTRAVENOUS	1700	0.156
INTRAVENOUS	2450	0.175
INTRAVENOUS	3200	0.190

*Predicted at reference values for baseline weight (80kg) and ECOG=0. DEC=decitabine

Source: AXP0205F-Report-Exp-AE Table 63

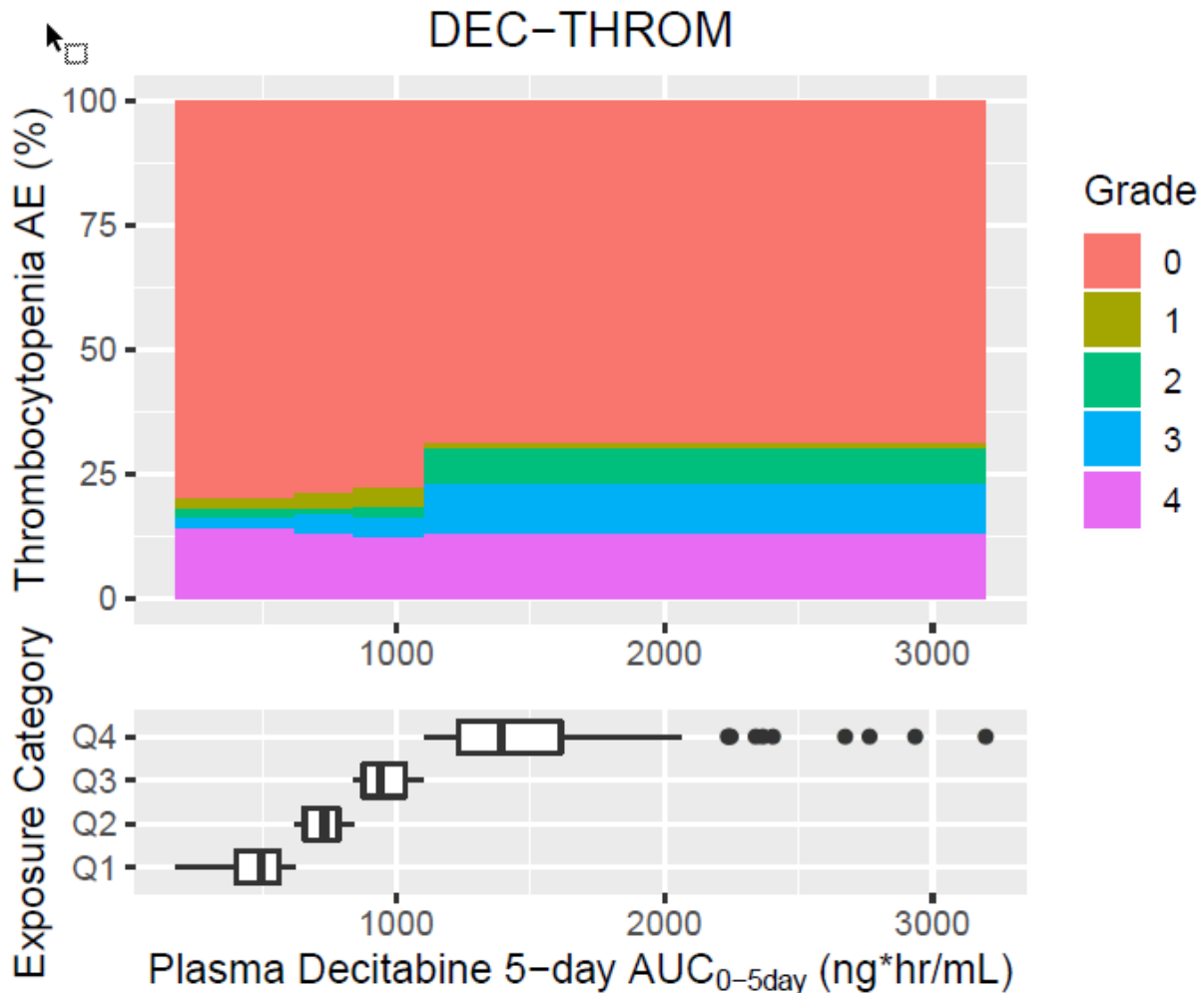
Figure 4. Phase 2 and 3: Incidence of Neutropenia AE vs. Decitabine 5-day AUC Exposure Category, ASTX727 and IV decitabine over the First Two Cycles



Source: AXP0205F-Report-Exp-AE Figure 16

Incidence vs. exposure category is shown in the top panel. The widths of the stacked-bars correspond to the range of 5-day AUC within each exposure category. The distribution of AUC within each exposure category is summarized in the bottom panel with a box-and-whisker plot. Median value is designated by a line in the center of the box. Box indicates the inter-quartile range (IQR). Whiskers represent 1.5*IQR (inter-quartile range) and outliers are marked outside of the whiskers by black circles.

Figure 5. Phase 2 and 3: Incidence of Thrombocytopenia AE vs. Decitabine 5-day AUC Exposure Category, ASTX727 and IV decitabine Over the First Two Cycles



Source: AXP0205F-Report-Exp-AE Figure 17

Incidence vs. exposure category is shown in the top panel. The widths of the stacked-bars correspond to the range of 5-day AUC within each exposure category. The distribution of AUC within each exposure category is summarized in the bottom panel with a box-and-whisker plot. Median value is designated by a line in the center of the box. Box indicates the inter-quartile range (IQR). Whiskers represent 1.5*IQR (inter-quartile range) and outliers are marked outside of the whiskers by black circles.

The Applicant’s Position:

Yes. The PK data from Phase 2 and the pivotal PK data from Phase 3 support that decitabine exposures (mean, individual, and range) from ASTX727 recommended doses are largely equivalent or similar to IV decitabine standard dose of 20 mg/m².

This decitabine plasma exposure after oral ASTX727 recommended doses resulted in similar

pharmacodynamic effect on LINE-1 demethylation as IV decitabine 20 mg/m².

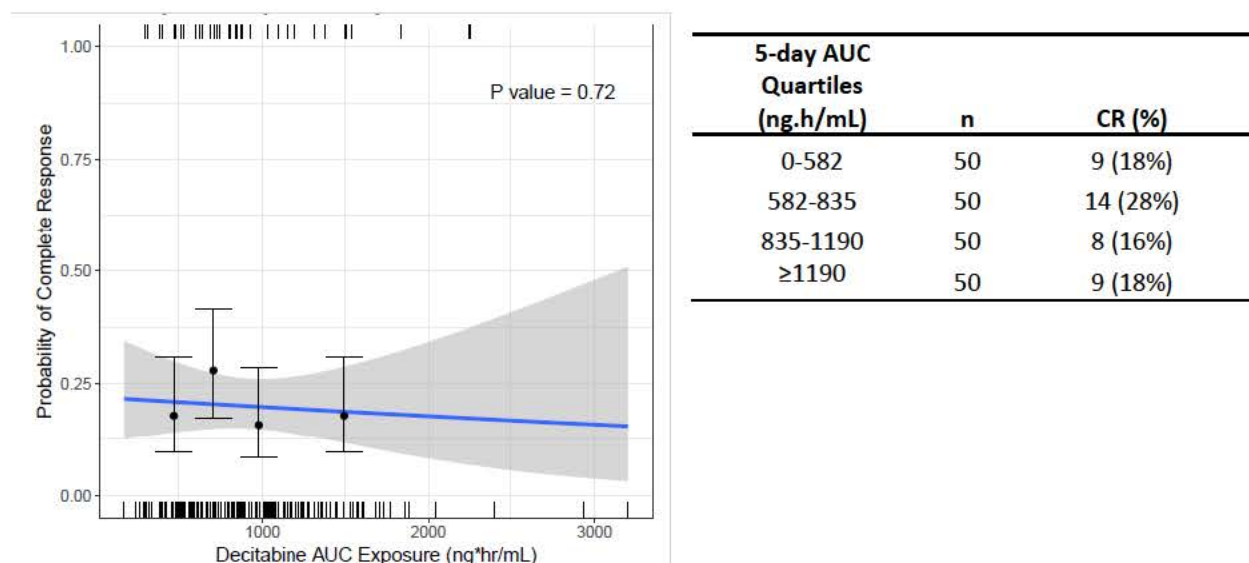
The proposed dosing regimen for ASTX727 is oral administration of 1 tablet (FDC of 100 mg cedazuridine and 35 mg decitabine) each day for the first 5 days of each 28-day cycle. This regimen replicates the decitabine AUC exposures of IV decitabine 20 mg/m² by 1-hr infusion each day for the first 5 days of each 28-day cycle. As such, this ASTX727 dosing regimen is appropriate to the general patient population for which the indication is being sought.

The Regulatory Authorities' Assessment:

The proposed dosing regimen of once daily dosing of ASTX727 tablet (35 mg of decitabine and 100 mg of cedazuridine) for the first 5 days of each 28-day cycle is supported by PK and efficacy results (Refer to Regulatory Authority Assessment under Section 6.3.2.1 and 8.1).

There was a flat relationship between cumulative decitabine exposure and complete response (CR) based on pooled data from Studies ASTX727-01-B and -02 (Figure A)

Figure A: Relationship between 5-day Cumulative Decitabine AUC and Probability of Complete Response (left), and Responders by Exposure Quartiles (right)



Solid blue line represents a loess smooth of original data (tick marks along the x-axes), and the grey region indicates a 95% CI for the smooth. Error bars are 95% CI at quartiles of decitabine exposure.

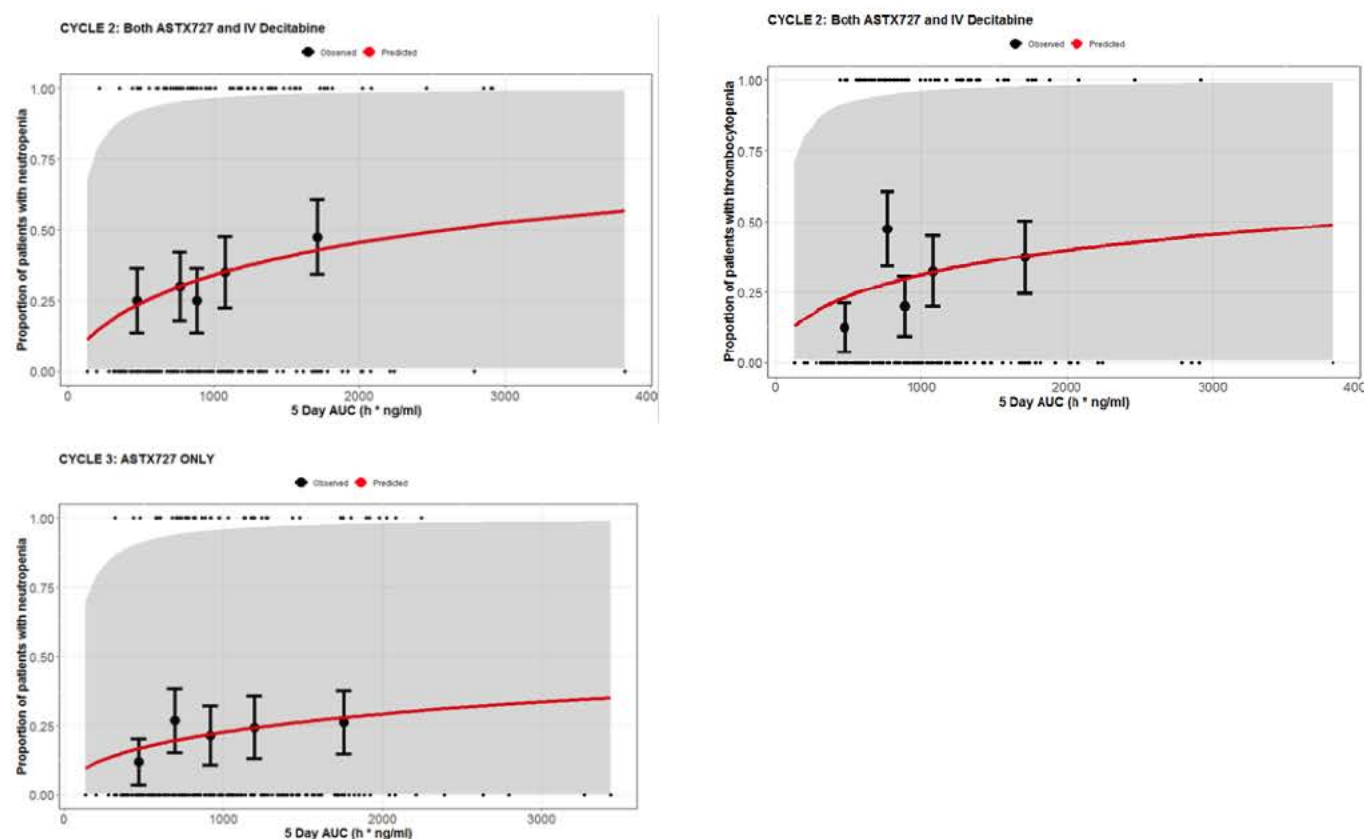
Source: Response to IR, Module 5.3.3.5, SDN39, 4/21/2020

FDA notes that a higher incidence of adverse reactions for ASTX727 compared to IV decitabine were observed in Cycles 1 and 2. Additional details regarding these differences are provided in Section 6.3.2.3 and 8.2. Overall, for all cycles, the common adverse reactions with ASTX727 were cytopenias, specifically neutropenia, followed by infections including pneumonia and sepsis. Majority of these adverse reactions were Grade 3 or higher. Other common adverse

reactions that were Grade 2 or less were gastrointestinal and general disorders.

The exposure-response analyses for safety based on the observed PK data, indicated that 5-day cumulative decitabine AUC (for both ASTX727 and IV decitabine) had a positive relationship for any grade neutropenias and tended to be associated with any grade thrombocytopenias, particularly in Cycle 2 (see Figure B below). Further, higher 5-day cumulative decitabine AUC in Cycles 1 and 2 for ASTX727 appeared to be associated with any grade neutropenias in Cycle 3.

Figure B: Exposure-response for Safety in Studies ASTX727-01-B and ASTX727-02. Relationship between 5-day Cumulative Decitabine exposure and any Grade Neutropenias (top left) and any Grade Thrombocytopenias in Cycle 2 (top right), and between 5-day cumulative Decitabine Exposure in Cycle 1 & 2 versus any Grade Neutropenias in Cycle 3 (bottom)

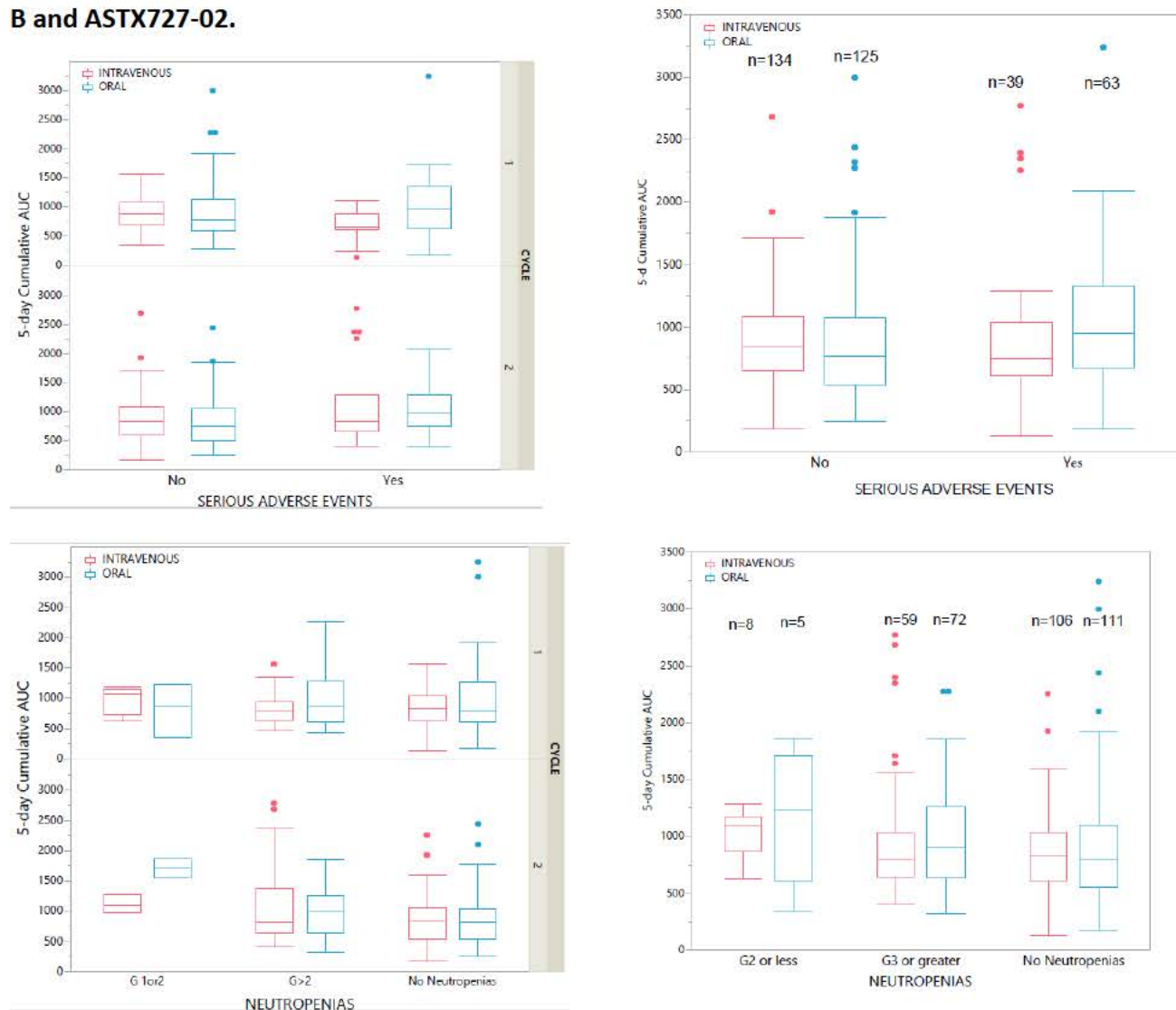


Refer to Appendix 19.4.4

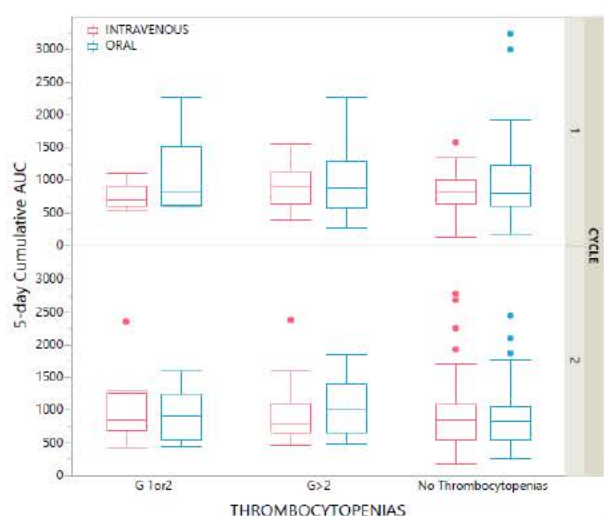
While the likelihood of increased cytopenias with increased cumulative decitabine exposure was observed, majority of these adverse reactions were managed by dose modifications in Studies ASTX727-01-B and ASTX727-02 (refer to “Dose Modification Strategy” subsection below). Further, comparison of the oral and IV formulations shows that the 5-day cumulative decitabine exposure tends to be similar with overlapping variability between ASTX727 and IV decitabine in patients with serious adverse reactions, neutropenia, and thrombocytopenia

(Figure C below), indicating that ASTX727 is not expected to be more toxic than IV decitabine.

Figure C: Comparison of 5-day Cumulative Decitabine Exposure between Oral and IV Decitabine by Cycle (left) and Cycles 1 and 2 combined (right) in Patients with Serious Adverse Events (top), Neutropenias (middle) and Thrombocytopenias (bottom) in Studies ASTX727-01-B and ASTX727-02.

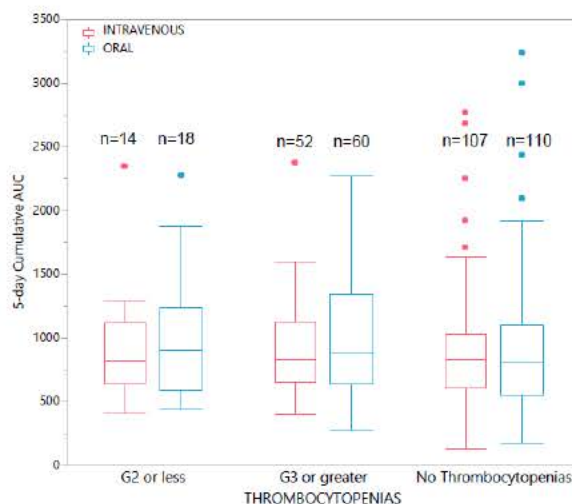


NDA Multi-disciplinary Review and Evaluation
 NDA 212576, Original
 INQOVI (decitabine and cedazuridine)



Adverse events based on AEHLT term in ADAE datasets

Source: Reviewer analysis



Dose Modification Strategy: Dose modifications (dose delays/interruptions and dose reductions) due to hematologic toxicity were common with ASTX727.

The dose delay strategy proposed by the Applicant for hematologic adverse reactions allows for dose delays if cytopenias persist after the first ^(b)₍₄₎ weeks of treatment. Patients may continue dosing if counts recover within ^(b)₍₄₎ weeks after dose delay. The Applicant's proposed dose delay strategy for hematological toxicity is reasonable. However, dose delays can be extended to 4 weeks, instead of ^(b)₍₄₎ weeks, considering that majority of the dose delays were within 28 days with ASTX727 and to be consistent with dose delay criterion for IV decitabine.

In Study ASTX727-02, 68% (91 of 133) patients had dose delays or interruptions. The adverse reactions leading to dose interruptions were mainly cytopenias, particularly neutropenia, followed by infections and infestations. Majority of the dose-delays occurred early in therapy, mostly in Cycles 2 to 4, with a short duration (see Table C). Dose delays greater than 14 days were observed in only 15% of the dose delayed cycles, however, majority were less than 28 days. The dose delays in majority of patients occurred in 1 to 5 cycles (median 2 cycles, range: 0, 15). The complete response (CR) rate in the patient subpopulation with dose delays were higher than in the overall population in Study ASTX727-02.

Table C: Dose Delays and Response in Study ASTX727-02

Event	Dose Delay Population
Patients	91
CR rate (vs. overall)	27% vs. 21%
Median TT first event	74 days (29, 353): 95% CI 80,105

Median Duration	10 days (1, 63): 95% CI 10, 14

Source: Reviewer analysis

The Applicant's proposed dose modification strategy for hematological toxicity includes dose reductions if cytopenias persist for greater than 2 weeks. The Applicant proposes a dose reduction strategy that includes reduction to a 4 day regimen/cycle, and if toxicities persist, further reduction to a 3 day regimen/cycle and finally, to a 3 day, every-other-day regimen per cycle. The proposed dose reduction strategy is reasonable.

In Study ASTX727-02, 50% (66 of 133) of the patients had dose reductions (DR), mainly due to adverse reactions, count recovery, and myelosuppression. Like dose delays, the adverse reactions leading to DR were mainly cytopenias, specifically neutropenia. DR occurred as early as the 3rd cycle (median time to first DR was 116 days, range: 59, 467) and a median duration of 138 days (range: 0, 467 days). The breakdown of the DR in Study ASTX727-02 is listed in Table D and Figure D. Majority of patients had first dose reduction to a 4-day regimen per cycle, with half of them continuing with the 4-day regimen per cycle. Thirty six percent of patients on the 4-day regimen/cycle had a second DR to 3-day regimen/cycle, and 14% of patients had second DR to an every alternating day 3-day regimen. The CR rate in the patient subpopulation with DR was similar to that in the overall population (23% versus 21%) in Study ASTX727-02. Considering the 3-day regimen has higher exposure than the every alternating day 3-day regimen, it would be beneficial to dose reduce first from a 4-day to 3-day regimen, and subsequently to an alternating 3-day regimen, if necessary. Although the decitabine exposure with an alternating day 3-day regimen is only about 40% of that with a 5-day regimen, it may be beneficial to continue decitabine treatment with the 3-day alternating DR regimen for patients who experience adverse reactions with the 3-day regimen.

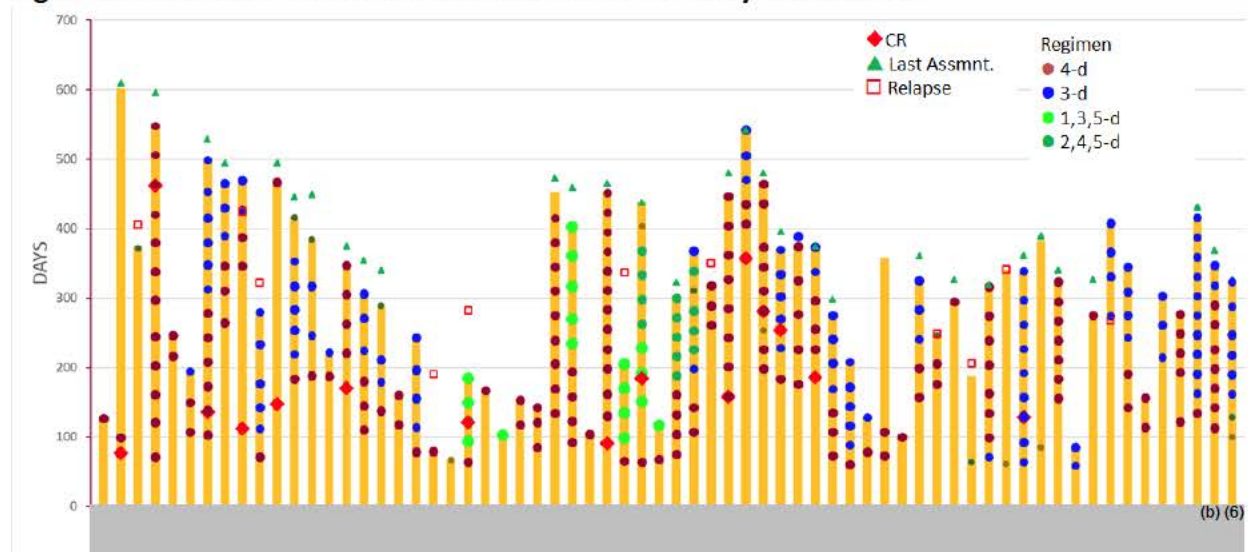
Table D: Dose Reductions in Study ASTX727-02

Dose Reductions (DR)	# Patients	% (of n=133)	% of 5-day AUC
Total	66	50	--
1 st DR to 4-day	56	42	80%
Single 4-d	23	17	
Multiple 4-d	33	25	
≥2 nd DR to			
3-d	24	18	60%
Alternating 3-d	9	7	~40%

4-d= 4-day regimen, 3-d= 3-day regimen, alternating 3-day = Day 1,3,5 or 2,4,5 regimen

Source: Reviewer analysis

Figure D: Dose reductions in Individual Patients in Study ASTX727-02



Source: Reviewer analysis

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

No adjustment to the dosage of ASTX727 is recommended on the basis of age, sex, or weight.

No adjustment to the dosage of ASTX727 is recommended in patients with mild or moderate renal impairment. A recommended dose has not been established for patients with severe renal impairment or patients on dialysis.

(b) (4)
A recommended dose has not been established for patients with severe hepatic impairment.

No clinical studies were conducted to specifically assess the impact of intrinsic factors on PK since the clinical program of ASTX727 included sufficient patient numbers to assess exposure effect based on most intrinsic factors.

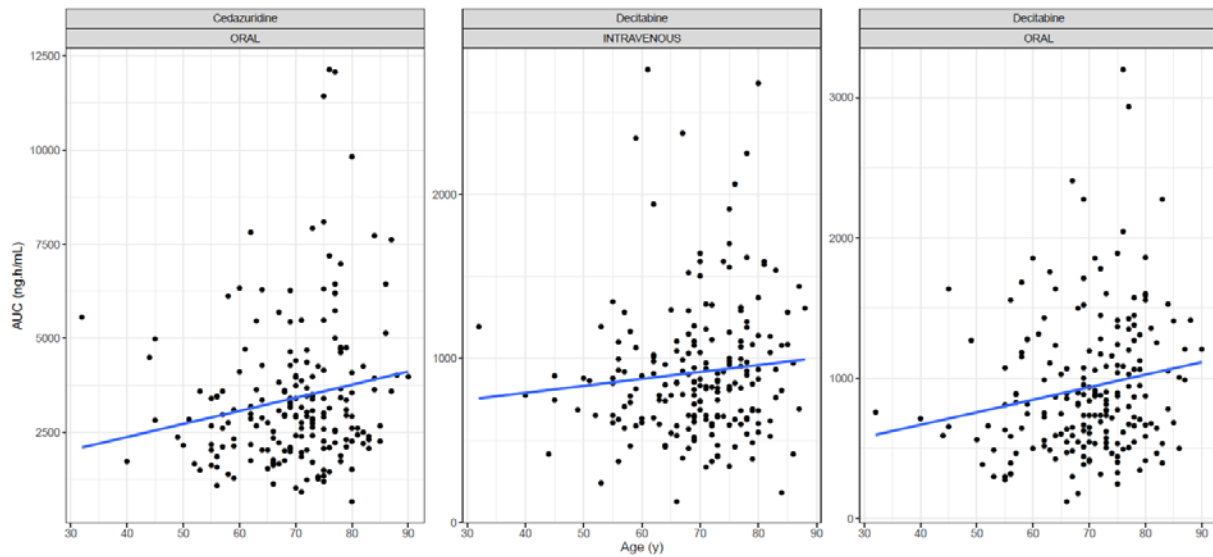
Specific Populations

Age, sex, weight, renal function, and hepatic function were assessed as potential covariates in the PopPK analysis using data from the Phase 2 part of Study ASTX727-01 and from Study ASTX727-02. These studies did not have sufficient racial diversity to inform potential correlations with regard to race or ethnicity.

Age

Age (32 to 90 years; Figure 6) did not have a clinically meaningful effect on the PK of decitabine or cedazuridine after administration of ASTX727. Age was not found to be a significant covariate in the population PK model.

Figure 6. Phase 2/3 Cedazuridine 24-Hour and Decitabine 5-Day Exposures Against Age



AUC=area under the plasma concentration-time curve.

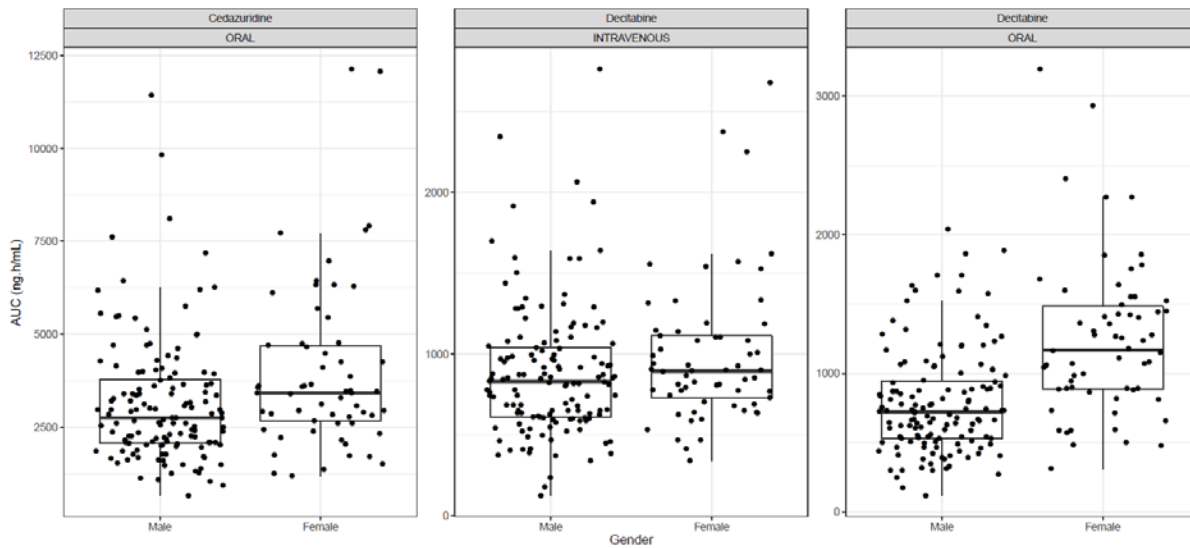
Note: The blue lines represent the linear trend lines and the circles represent the observed data.

Source: ASTX727-Report-PopPK, Figure 20.

Sex

Sex did not have a clinically meaningful effect on the PK of decitabine or cedazuridine after administration of ASTX727 (Figure 7).

Figure 7. Phase 2/3 Cedazuridine 24-Hour and Decitabine 5-Day Exposures Against Sex



AUC=area under the plasma concentration-time curve.

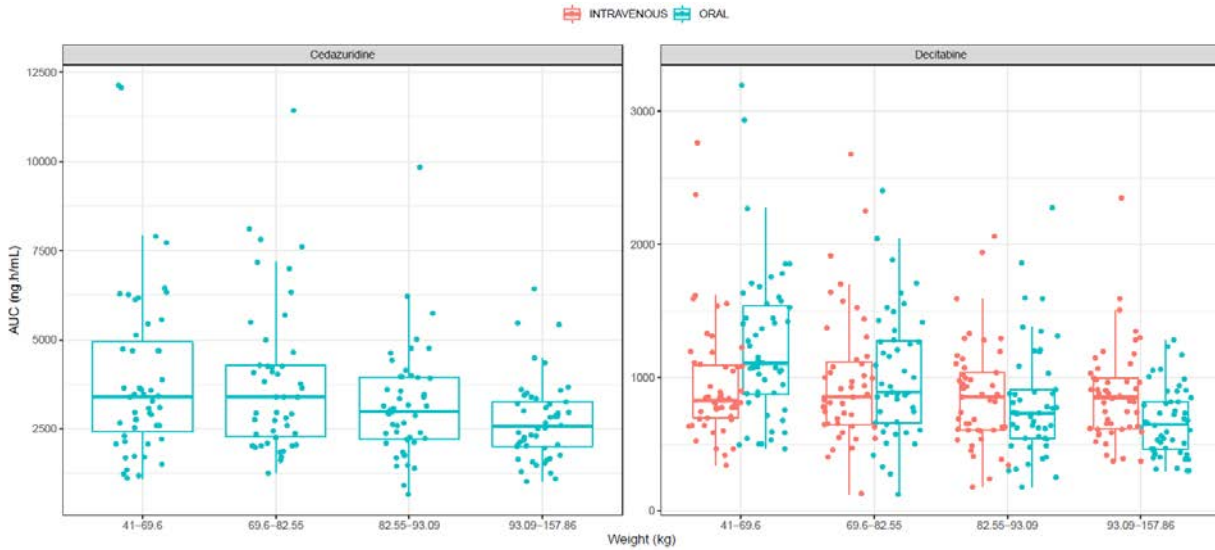
Note: The bottom and top of the boxes represent the 25th and 75th percentiles, respectively; the whiskers represent the 10th and 90th percentiles; the solid line within the box represents the median; the circles represent the observed data.

Source: ASTX727-Report-PopPK, Figure 21.

Body Weight

Body weight (41 to 158 kg) did not have a clinically meaningful effect on the PK of decitabine or cedazuridine after administration of ASTX727 (Figure 8). Although there was a small effect of body weight on decitabine AUC following oral ASTX727, this was not clinically meaningful.

Figure 8. Phase 2/3 Intravenous and Oral Decitabine 5-Day and Oral Cedazuridine 24-Hour Exposures Against Categorical Weight Quantiles



AUC=area under the plasma concentration-time curve; BSA=body surface area.

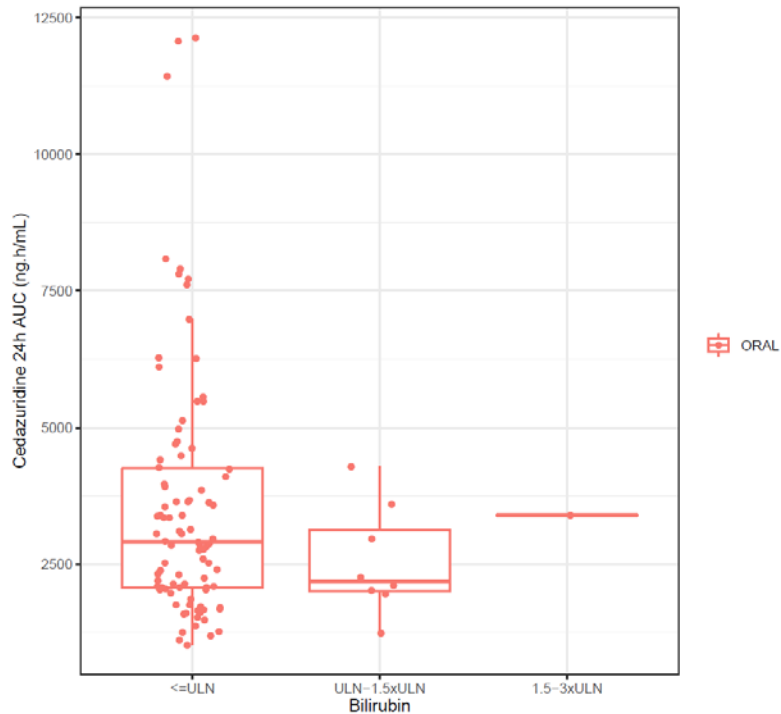
Note: The bottom and top of the boxes represent the 25th and 75th percentiles, respectively; the whiskers represent the 10th and 90th percentiles; the solid line within the box represents the median; the circles represent the observed data.

Source: ASTX727-Report-PopPK, Figure 24.

Hepatic Impairment

Mild to moderate hepatic impairment (total bilirubin >ULN up to $\leq 3 \times$ ULN; Figure 9 and Figure 10) did not have a clinically meaningful effect on the PK of decitabine or cedazuridine after administration of ASTX727.

Figure 9. Phase 2/3 Cedazuridine 24-Hour Exposures Against Categorical Bilirubin Values

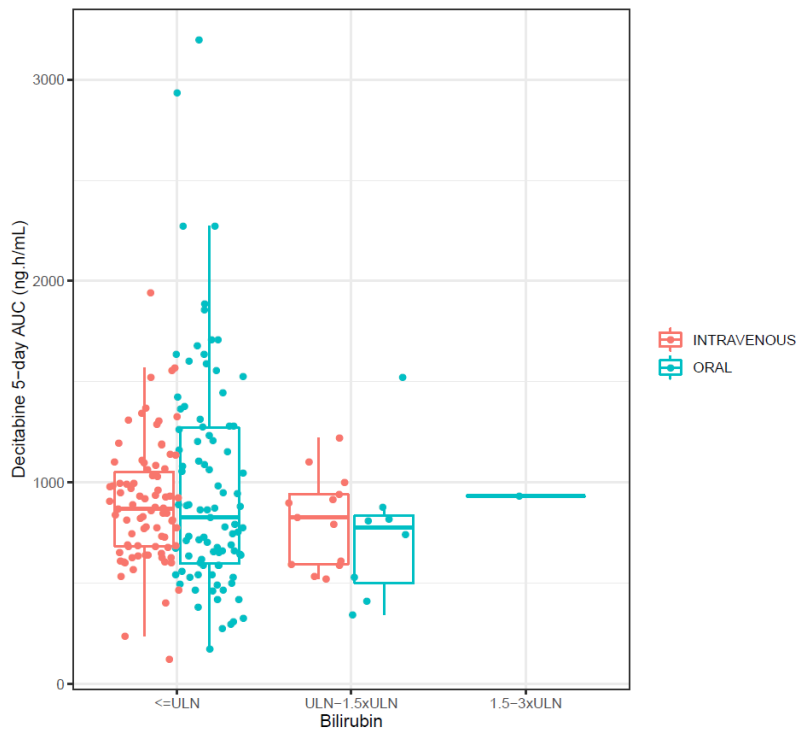


AUC=area under the plasma concentration-time curve; ULN=upper limit of normal.

Note: The bottom and top of the boxes represent the 25th and 75th percentiles, respectively; the whiskers represent the 10th and 90th percentiles; the solid line within the box represents the median; the circles represent the observed data.

Source: ASTX727-Report-PopPK, Figure 18.

Figure 10. Phase 2/3 Decitabine 5-Day Exposures Against Categorical Bilirubin Values



AUC=area under the plasma concentration-time curve; ULN=upper limit of normal.

Note: The bottom and top of the boxes represent the 25th and 75th percentiles, respectively; the whiskers represent the 10th and 90th percentiles; the solid line within the box represents the median; the circles represent the observed data.

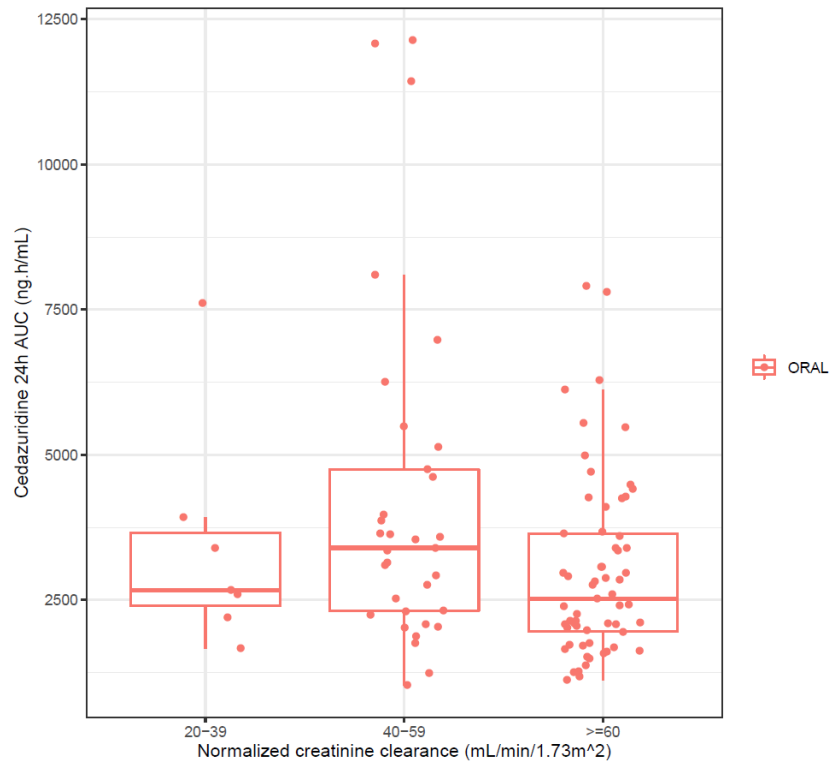
Source: ASTX727-Report-PopPK, Figure 16.

Renal Impairment:

Mild or moderate renal impairment (CRCL ≥ 20 up to 59 mL/min/1.73 m²) Figure 11 and Figure 12 had a relatively modest effect on cedazuridine exposures, but this was not considered to be clinically meaningful and did not result in clinically meaningful effect on decitabine exposure.

The effect of severe renal impairment (CRCL <20 mL/min/1.73 m²) or dialysis on the PK of decitabine or cedazuridine is unknown.

Figure 11. Phase 2/3 Cedazuridine 24-Hour Exposures Against Categorical BSA-Normalized Creatinine Clearance

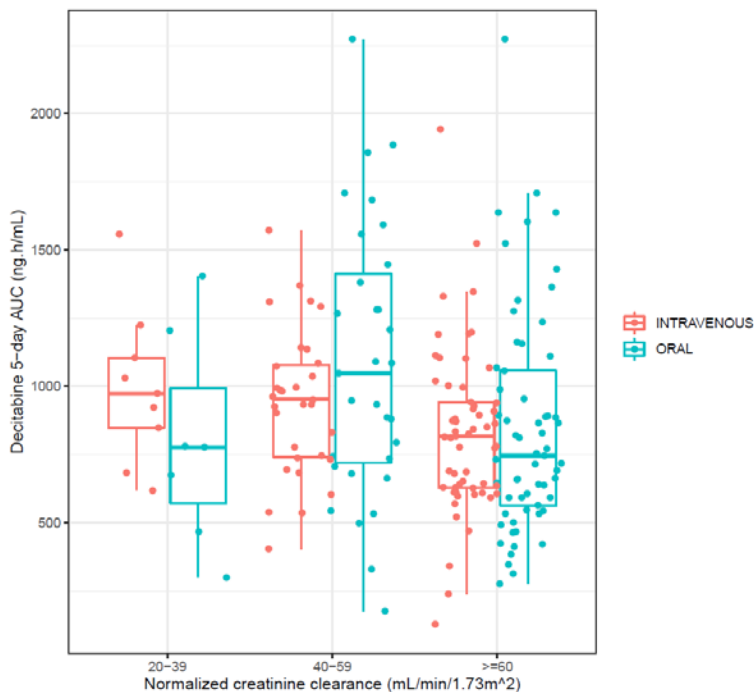


AUC=area under the plasma concentration-time curve; BSA=body surface area.

Note: The bottom and top of the boxes represent the 25th and 75th percentiles, respectively; the whiskers represent the 10th and 90th percentiles; the solid line within the box represents the median; the circles represent the observed data.

Source: ASTX727-Report-PopPK, Figure 13.

Figure 12. Phase 2/3 Decitabine 5-Day Exposures Against Categorical BSA-Normalized Creatinine Clearance



AUC=area under the plasma concentration-time curve; BSA=body surface area.

Note: The bottom and top of the boxes represent the 25th and 75th percentiles, respectively; the whiskers represent the 10th and 90th percentiles; the solid line within the box represents the median; the circles represent the observed data.

Source: ASTX727-Report-PopPK, Figure 11.

The Applicant's Position:

Based on the above data age, sex, or mild to moderate hepatic impairment did not have a clinically meaningful effect on the PK of decitabine or cedazuridine after administration of ASTX727. Mild or moderate renal impairment had an effect on cedazuridine exposures, but this was not considered to be clinically meaningful.

The effect of severe hepatic impairment or of severe renal impairment on the PK of decitabine and cedazuridine is unknown.

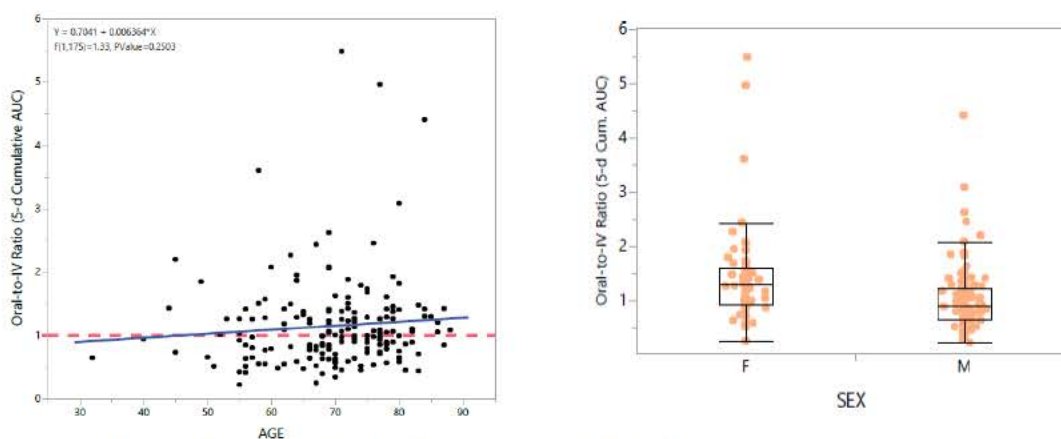
As a result, dose adjustment is not necessary for intrinsic patient factors, but caution should be exercised with severe hepatic or severe renal impairment.

Dose reduction of ASTX727 in response to drug-related myelosuppression, if severe and/or prolonged, could be achieved by reducing the total 5-day decitabine exposures by reducing the number of doses per cycle.

The Regulatory Authorities' Assessment:

Age and Sex: FDA agrees with the Applicant's position with regards to the effect of age and sex. Age did not correlate with the ratio of 5-day cumulative decitabine exposure between oral and IV decitabine formulation in Studies ASTX727-01-B and ASTX727-02 (see Figure E). Decitabine exposure was higher in females compared to males, however, this finding was confounded by body size, and is not clinically meaningful.

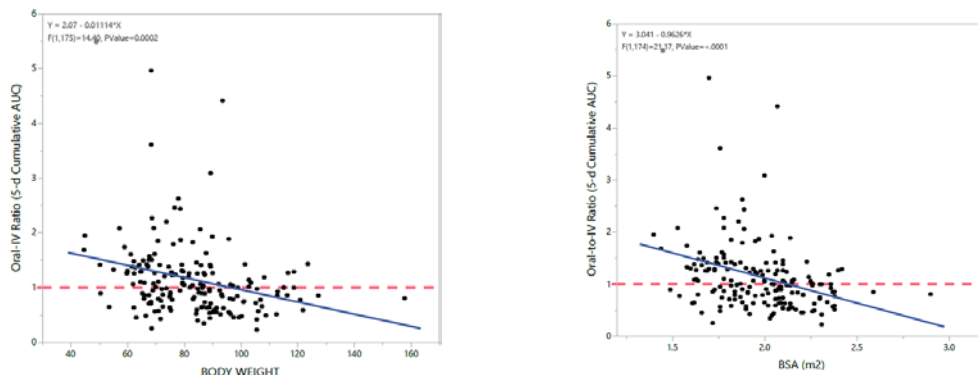
Figure E: Effect of Age (left) and Sex (right) on the Ratio of 5-day Cumulative Decitabine AUC between Oral and IV decitabine formulations in Patients from Studies ASTX727-01-B and ASTX727-02.



Dashed red line refers to a ratio of 1. Blue line represents the fit.
Source: Reviewer analysis

Body Weight and Body Surface Area: FDA agrees with the Applicant's position with regards to the effect of body weight and body surface area (BSA). Body weight and BSA correlated with the 5-day cumulative decitabine exposure ratio as shown in Figure F. An increase in decitabine exposure with a decrease in BSA was observed with ASTX727 compared with IV decitabine. Patients in the lowest BSA group had 25% higher exposures with ASTX727 compared to the patients in the median BSA group. However, a comparison of adverse reactions in Studies ASTX727-01-B and ASTX727-02, shown in Figure G, indicated that proportion of patients with neutropenia, thrombocytopenia, and serious adverse reactions in the lowest BSA quartile was comparable to that in patients in the median BSA quartile (1.78 - 1.99 m²) group.

Figure F: Effect of Body Weight or Body Surface Area (BSA) on the Ratio of 5-day Cumulative Decitabine AUC between Oral and IV Decitabine formulations in Patients from Studies ASTX727-01-B and ASTX727-02.

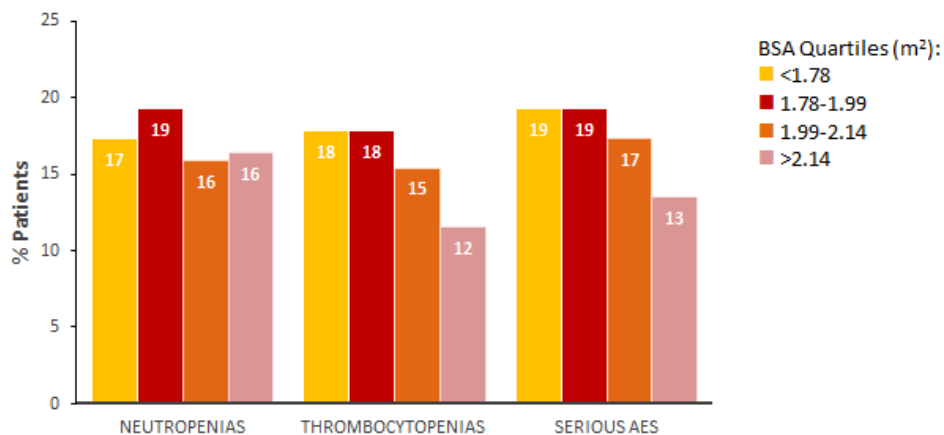


Dashed red line refers to a ratio of 1. Blue line represents the fit.

BSA Quartiles	n	Geometric Mean		
		ratio	CV%	Median
BSA < 1.78 m ²	48	1.25	67.1	1.29
1.78 – 1.97m ²	39	1.08	45.9	1.06
1.97 – 2.14 m ²	50	0.94	63.3	0.96
> 2.14 m ²	39	0.76	34	0.83

Source: Reviewer analysis

Figure G: Proportion of Patients with Neutropenias, Thrombocytopenias, and Serious Adverse Events by BSA Quartiles in Patients from Studies ASTX727-01-B and ASTX727-02.



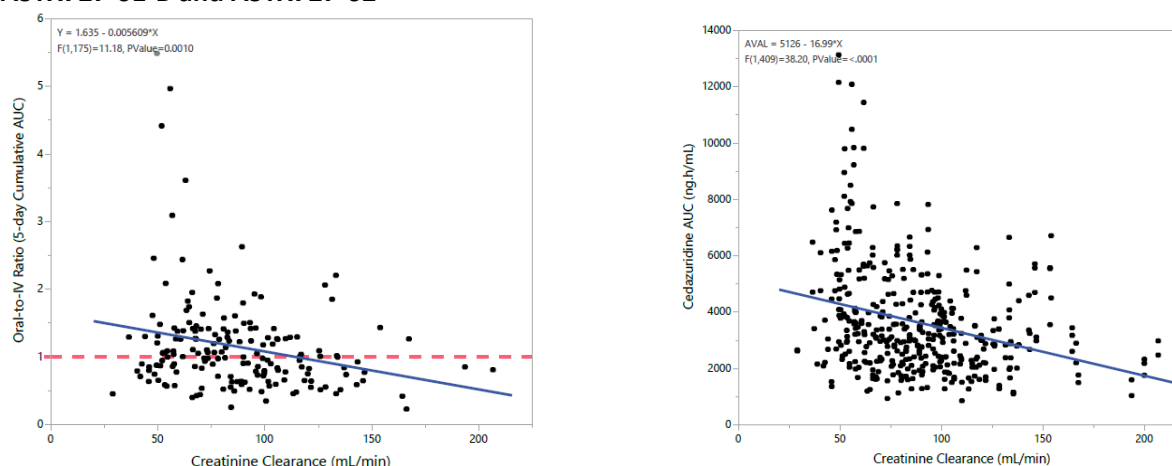
Adverse events based on AEHLT term in ADAE datasets

Source: Reviewer analysis

Effect of Hepatic Impairment: FDA agrees with the Applicant's position that no dose adjustment for patients with mild hepatic impairment (total bilirubin > ULN to 1.5 x ULN or AST > ULN). FDA does not agree that there is sufficient information to address the effect of moderate (total bilirubin >1.5 to 3 x ULN, any AST) and severe (total bilirubin >3 x ULN, any AST) on decitabine and cedazuridine PK, as there were only 3 patients with moderate hepatic impairment and no patients with severe hepatic impairment in Studies ASTX727-01-B and ASTX727-02 (Figure 10). It should be noted that decitabine is mainly eliminated in the liver by CDA. A PMR to determine the dose recommendation for ASTX727 in moderate and severe hepatic impairment will be required.

Effect of Renal Impairment: FDA agrees with the Applicant's position that no dose modification is necessary for patients with mild (creatinine clearance (CLcr) 60 to <90 mL/min) and moderate (CLcr) 30 to <60 mL/min) impairment. As shown in Figure H, increased cedazuridine levels can increase decitabine exposure. Cedazuridine exposure is also inversely correlated with creatinine clearance, with increase in exposure with decreasing renal clearance (Figure H). However, the point estimates for cumulative decitabine exposure between oral and IV decitabine formulations were similar for patients with mild and moderate renal impairment (see Table E below). The mean 5-day decitabine exposures for ASTX727 was less than for IV decitabine for patients with normal renal function, however, the decrease was <20%.

Figure H: Effect of Creatinine Clearance on the Ratio of 5-day Cumulative Decitabine AUC between Oral and IV decitabine formulations (left) and Cedazuridine AUC (right) in Patients from Studies ASTX727-01-B and ASTX727-02



Dashed red line refers to a ratio of 1. Blue line represents the fit.
Source: Reviewer analysis

Table E: Effect of Renal Impairment on the Ratio of Decitabine Exposure between Oral and IV Decitabine Formulations in Patients from Study ASTX727-02

ASTX vs. IV	Geometric Mean Ratio (90% CI)		
	Normal (n=33-35)	Mild (n=49-55)	Moderate (n=31-35)
5-d Cum AUC	0.82 (0.72, 0.93)	0.97 (0.88, 1.09)	1.13 (1.04, 1.23)
Day 5 AUC _{24h}	0.86 (0.76, 0.96)	1.09 (0.98, 1.21)	1.21 (1.08, 1.36)

Source: Reviewer analysis

However, FDA notes the increase in the incidence of serious adverse reactions, dose modifications, and cytopenias for ASTX727 versus IV decitabine in the first 2 cycles in Study ASTX727-02 in patients with moderate renal impairment taking ASTX727 compared to patients with normal renal function (CL_{cr} ≥ 90 ml/min) (Table F). Therefore, patients with moderate renal impairment taking ASTX727 should be closely monitored for adverse reactions.

Table F: Effect of Renal Impairment on Safety in Cycles 1 and 2 of Studies ASTX727-01-B and ASTX727-02

Patients (%)	Normal		Mild		Moderate	
	Cycles 1 or 2		Cycles 1 or 2		Cycles 1 or 2	
	IV	Oral	IV	Oral	IV	Oral
	n=67	n=64	n=80	n=79	n=60	n=64
AEs	96	94	93	97	92	94
Grade ≥ 3 AEs	61	63	60	53	65	77
Serious AEs	24	27	25	35	15	34
Deaths due to AEs	3	0	0	3	2	3
Discontinuation due to AE	0	0	1	0	2	2
Dose reduction/interruption due to AEs	6	6	9	18	8	14
Thrombocytopenia	33	38	39	32	35	48
Anemia	24	25	26	23	27	38
Neutropenia	30	28	31	29	32	34
Febrile Neutropenia	12	17	13	14	7	6
Leukopenia	13	16	14	14	18	22
Fatigue	6	17	24	20	15	30
Grade ≥ 3 AEs						
Thrombocytopenia	31	27	25	25	28	38
Anemia	21	20	23	19	18	28
Neutropenia	25	27	26	28	28	31
Febrile Neutropenia	12	17	11	13	5	6
Leukopenia	9	11	14	11	13	19
Pneumonia	6	5	5	5	3	9

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Sepsis	3	2	0	5	0	5

AE=adverse event, Normal=CLcr≥90 mL/min, Mild= CLcr 60 to <90 mL/min, and Moderate= 30 to <60 mL/min
 Source: Tables 1, 2, 5, 6, 9, and 10, Response to IR, Module 1.11.4, SDN 13, 2/10/2020

There is only one patient with severe renal impairment (CLcr 15 to <30 mL/min) and no patients with ESRD (CLcr <15 mL/min) taking ASTX727. Therefore, a PMR will be submitted to determine the dose recommendation for ASTX727 for patients with severe renal impairment and with ESRD.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Effect of Food

The food effect study, ASTX727-04, found that there was little effect on the PK of cedazuridine when ASTX727 was administered with a high-fat meal (approximately 800-1000 calories, with approximately 150 calories from protein, approximately 250 calories from carbohydrates, and approximately 500-600 calories from fat). Cedazuridine and cedazuridine-epimer exposure parameters were approximately 10% and 20% higher, respectively, with food.

The same food effect study found that there was an effect on the PK of decitabine when ASTX727 was administered with a high-fat meal (Table 16). The extent and rate of decitabine exposures were both reduced. Exposure was reduced by approximately 40% (AUC) to 54% (C_{max}) and the t_{max} was delayed from 1.00 hour to 1.75 hours when administration was with food.

Table 16. Comparison of Decitabine Exposure Between Fed and Fasted States (Study ASTX727-04)

PK Parameter	Fed		Fasted		Percentage Ratio of Geo. LSM (% Fed/Fasted)	90% CI (%)
	N	Geo. LSM	N	Geo. LSM		
AUC ₀₋₈ (ng•h/mL)	16	114.97	16	191.75	60.0	(50.28, 71.50)
AUC ₀₋₂₄ (ng•h/mL)	14	135.54	15	205.85	65.8	(54.92, 78.94)
AUC _{0-inf} (ng•h/mL)	13	132.38	15	202.72	65.3	(52.94, 80.55)
AUC _{0-t} (ng•h/mL)	16	114.38	16	192.61	59.4	(49.41, 71.37)
C _{max} (ng/mL)	16	63.43	16	136.45	46.5	(35.12, 61.53)

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AUC₀₋₈=area under the plasma concentration-time curve from time zero to 8 hours; AUC₀₋₂₄=area under the plasma concentration-time curve from time zero to 24 hours; AUC_{0-inf}=area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC_{0-t}=area under the plasma concentration-time curve from time zero to the last measurable concentration; CI=confidence interval; C_{max}=maximum plasma concentration; Geo. LSM=geometric least squares mean; N=number of subjects; PK=pharmacokinetic.

Source: CSR ASTX727-04 PK Report, Table 6.5-5.

Effect of ASTX727 on Other Drugs

No specific study of the effect of cedazuridine on the PK of other drugs has been conducted.

Cedazuridine is a potent inhibitor of CDA (IC₅₀=281 nmol/L), so it would affect the metabolism and exposure of any coadministered drug that is metabolized via this route.

In vitro, cedazuridine (up to 400 µmol/L) did not induce CYP1A, CYP2B6, CYP2C9, and CYP3A. The fold induction (relative to vehicle) for the CYPs evaluated ranged from 0.8 to 1.5 over the cedazuridine concentration range tested. A

In vitro, cedazuridine did not inhibit any of the CYP isoforms tested 1A, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A; in all cases, the IC₅₀ was >400 µmol/L.

Cedazuridine was not an inhibitor of most of the transporters tested: BCRP, BSEP, P-gp, CNT2, ENT1, ENT2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2 at concentrations up to 300 µmol/L. A weak inhibition of CNT2 and CNT3 by cedazuridine was observed at 300 µmol/L, but this is not considered clinically meaningful (cedazuridine clinical plasma C_{max} is approximately 2 µmol/L).

Drug interaction studies with decitabine have not been conducted. Decitabine is unlikely to cause DDI via CYP enzymes.

Effect of Other Drugs on ASTX727

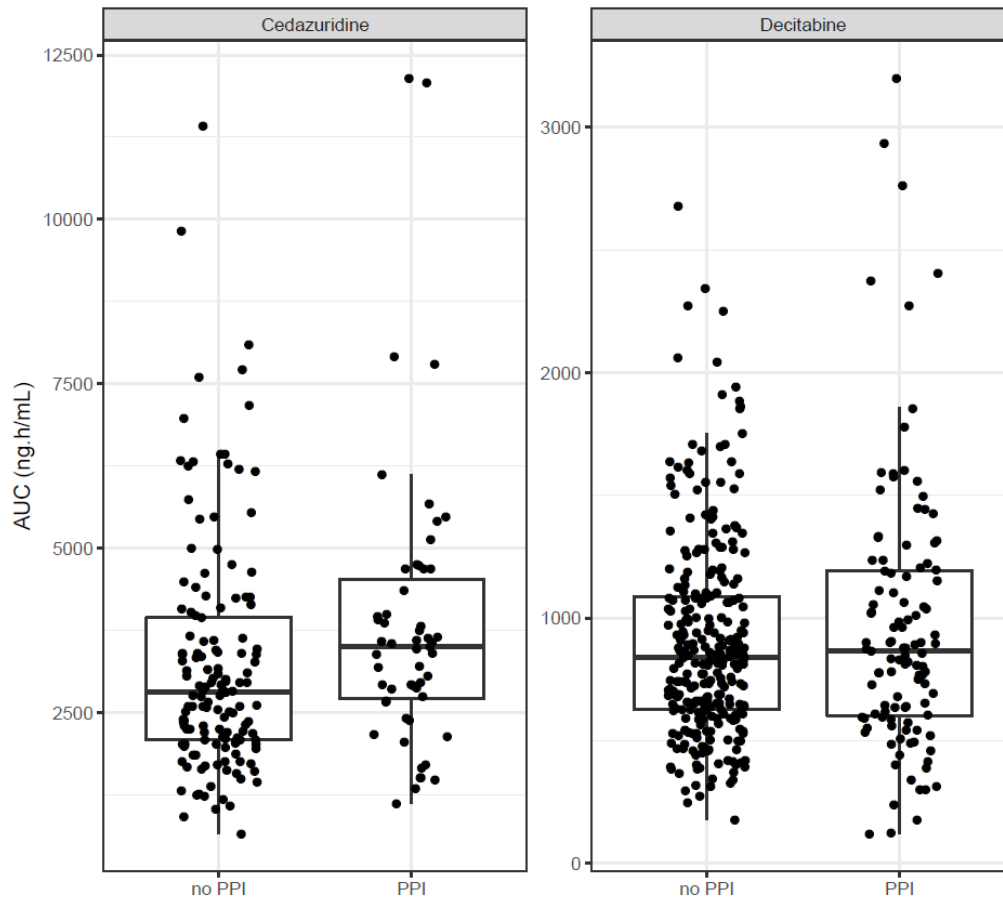
No specific study of the effect of other drugs on the PK of cedazuridine has been conducted.

In vitro, cedazuridine was not metabolized by human liver S9 fractions or liver cytosols and was not a substrate for the majority of transporters. Although cedazuridine was transported by CNT1, CNT3, and ENT2 (3.81-, 4.58-, 2.63-fold, respectively in MDCKII or HEK293 cells expressing the transporters), the potential for drug-drug interactions with comedications is low.

Cedazuridine conversion to its major metabolite (cedazuridine-epimer) occurs prior to its absorption and it was postulated that it may be affected by gastric pH. A PopPK assessment of concomitant proton pump inhibitor medication as a potential covariate found that such comedication did not have a significant impact on decitabine, cedazuridine, and cedazuridine-epimer parameters and subsequent exposures, suggesting that drugs modifying gastric pH are unlikely to affect the PK of cedazuridine or decitabine after ASTX727 administration (Figure 13).

Drug interaction studies with decitabine have not been conducted. Decitabine is not a substrate for CYP enzymes, and the plasma protein binding of decitabine is negligible.

Figure 13. Phase 2/3 Decitabine 5-Day Exposures Against Proton Pump Inhibitor Concomitant Medication



AUC=area under the plasma concentration-time curve; PPI=proton pump inhibitor.

Note: The bottom and top of the boxes represent the 25th and 75th percentiles, respectively; the whiskers represent the 10th and 90th percentiles; the solid line within the box represents the median; the circles represent the observed data.

Source: ASTX727-Report-PopPK, Figure 19.

The Applicant's Position:

Yes. Administration of ASTX727 with food results in lower exposure to decitabine.

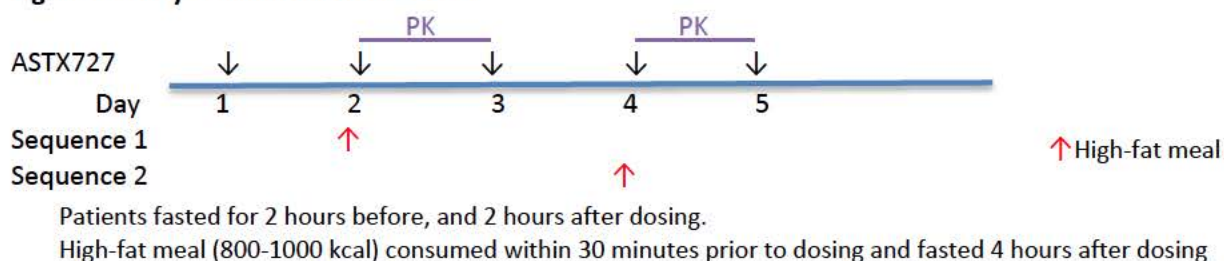
The Applicant recommends that ASTX727 is administered on an empty stomach and patients should avoid eating (b) (4)

There was no effect on decitabine exposure when ASTX727 was co-administered with PPI drugs. No drug-drug interactions are anticipated with comedications that are substrates or inhibitor of major CYP enzymes or major drug transporters. Drugs that are substrate for CDA should be avoided during dosing with ASTX727.

The Regulatory Authorities' Assessment:

Effect of Food: FDA does not agree with Applicant's position on the effect of food on the PK of ASTX727 due to inconsistency in the results in the 2 sequence, cross-over study ASTX727-04 in patients. The study design for ASTX727-04 is shown in Figure I.

Figure I: Study Schema for ASTX727-04



The mean steady state AUC_{24hr} in patients administered ASTX727 initially in the fasted state on Day 2 (Sequence 2) was 2-fold higher than that observed in patients who received ASTX727 in the fasted state on Day 4 (Sequence 1) or in comparison with the mean Day 2 or Day 5 decitabine AUC_{24hr} observed in ASTX727-02 (Table G). In contrast, the decitabine AUC_{24hr} in the fed state was similar in both sequences. This increase in exposure in the fasted state in Sequence 2 confounds the food effect analysis and does not allow for an adequate assessment of the effect of food on decitabine and cedazuridine exposure. Similar results were obtained with AUC_{8hr}.

Table G: Decitabine Exposures and Ratio of Exposure under Fasted and Fed states between Sequences in Study ASTX727-04 (top), and Fasted State in ASTX727-02 (bottom).

ASTX727-04		Fast AUC _{24h}		Fed AUC _{24h}		Fed/Fast Ratio	
Sequence	N	Mean	CV	Mean	CV	Mean	CV
1 (FED to FAST)	7	167	47	155	26	0.93	30
2 (FAST to FED)	7	303	55	136	76	0.45	46

Presented as Geometric mean and geometric CV

ASTX727-02		Fast AUC _{24h}	
Day	N	Mean	CV
Day 2	128	189	55
Day 5	124	178	53

Source: CSR, Table 24

A sensitivity analysis conducted to determine if this inconsistency was due to an imbalance in body weights between sequence, by censoring 2 patients in Sequence 2 with body weights less than 68 kg or greater than 105 kg, did not show that the inconsistent results was due to patient body weight (Table H). As such the effect of food on ASTX727 cannot be reliably determined and additional information will be requested as a PMC.

Table H: Sensitivity Analysis of Decitabine Exposures and Ratio of Exposure under Fasted and Fed States between Sequences in Study ASTX727-04

ASTX727-04		Fast AUC _{24h}		Fed AUC _{24h}		Fed/Fast Ratio	
Sequence	N	Mean	CV	Mean	CV	Mean	CV
1 (FED to FAST)	7	167	47	155	26	0.93	30
2 (FAST to FED)	5	249	49	104	67	0.42	53

- Patient weighing <68 kg or >105 kg were excluded in Sequence 2

Effect of Concomitant drug use: FDA agrees with the Applicant’s position that no dose recommendation for ASTX727 in patients with concomitant drugs and to avoid concomitant drugs that are metabolized by CDA. In vitro studies suggest that cedazuridine is not a substrate or modulators of CYP enzymes or major transporters.

FDA noted that there was an increase in dissolution of ASTX727 with increase in pH. The protocol specifies to avoid gastric acid reducing agents within 4 hours of ASTX727 administration, however, per the Applicant, no specific written instructions were provided to the patients regarding administration of acid reducing agents. Nonetheless, majority of patients on proton pump inhibitors (PPI) were on chronic PPI use in Study ASTX727-02.

Given that cedazuridine conversion to its epimer is believed to occur prior to absorption in the stomach and roughly 30% of patients in the Phase 2 and 3 studies were concomitantly administered PPI, an independent analysis of patients in Study ASTX727-02 who were and were not concomitantly administered PPI that overlapped with administration of ASTX727 was conducted. The analysis (Table I) revealed that the cumulative decitabine exposures were not different between oral and IV decitabine formulations in patients coadministered with PPI and patients not taking PPI: the point estimates were close to 1.

Table I: Effect of Proton Pump Inhibitors use on the Ratio of Decitabine (left) and Cedazuridine (right) Exposures between Oral and IV Decitabine Formulations in Patients from Study ASTX727-02

ASTX vs. IV	Geometric Mean Ratio (90% CI)		PPI vs. No PPI	GMR (90% CI)
	No PPI (n=92-98)	PPI (n=27-31)		
5-d Cum AUC	0.97 (0.91, 1.05)	0.98 (0.84, 1.16)	Day 1 AUC _{24h}	1.23 (0.95, 1.59)
			Day 2 AUC _{24h}	1.13 (0.97, 1.32)

Day 5 AUC_{24h}	1.06 (0.98, 1.15)	1.03 (0.88, 1.20)
Day 1 AUC_{24h}	0.57 (0.52, 0.62)	0.67 (0.56, 0.79)

6.3.2.5 Does this drug(s) prolong the QT or QTc interval?

Data:

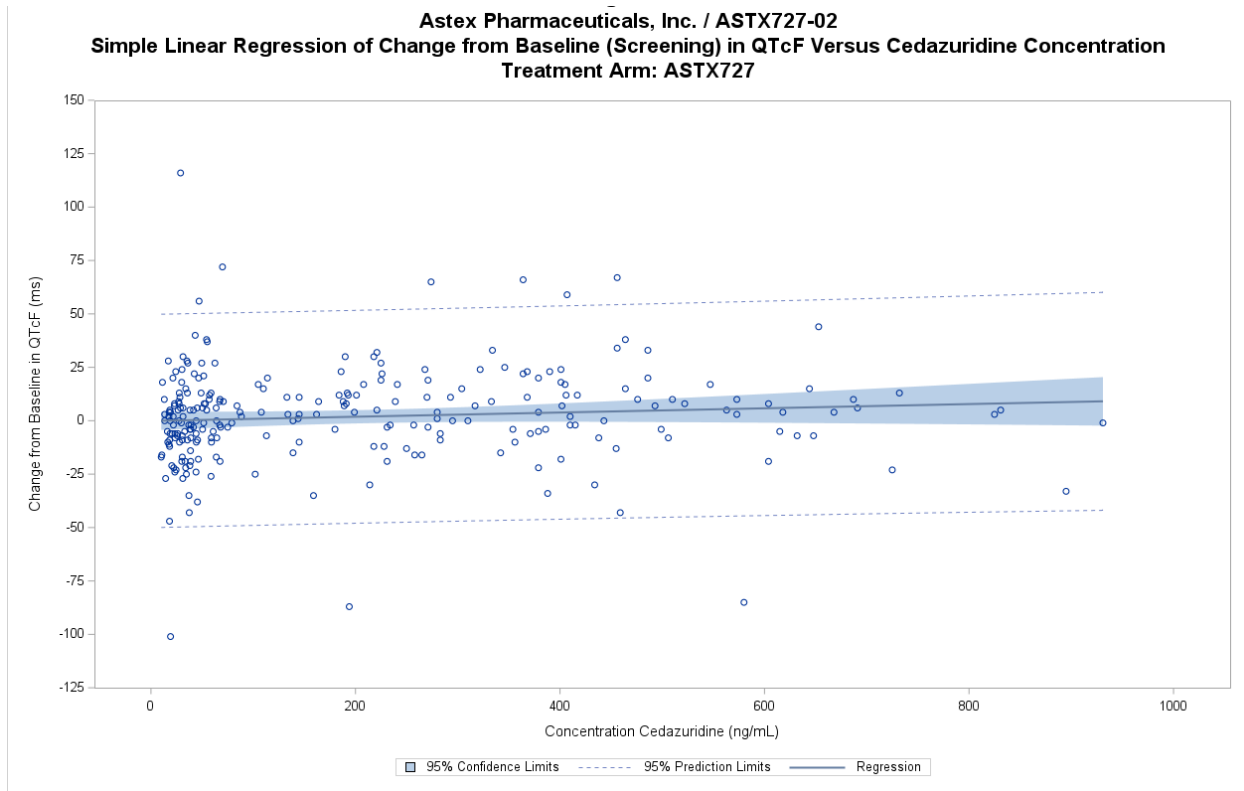
An exposure-response analysis of decitabine, cedazuridine, and cedazuridine-epimer concentrations with the change from baseline in heart rate corrected QT interval (QTc) from Phase 3 Study ASTX727-02 was conducted.

The ECGs were conducted at screening and predose on Day 3 (Cycles 1 and 2) and 3 hours postdose for ASTX727 treatment (time-matched with PK at t_{max} of cedazuridine) and within 10 minutes of the end of infusion for IV decitabine treatment (time-matched with PK at t_{max} of decitabine) on Day 3.

ECG assessments used for determination of QTc interval were time-matched with the PK blood draws.

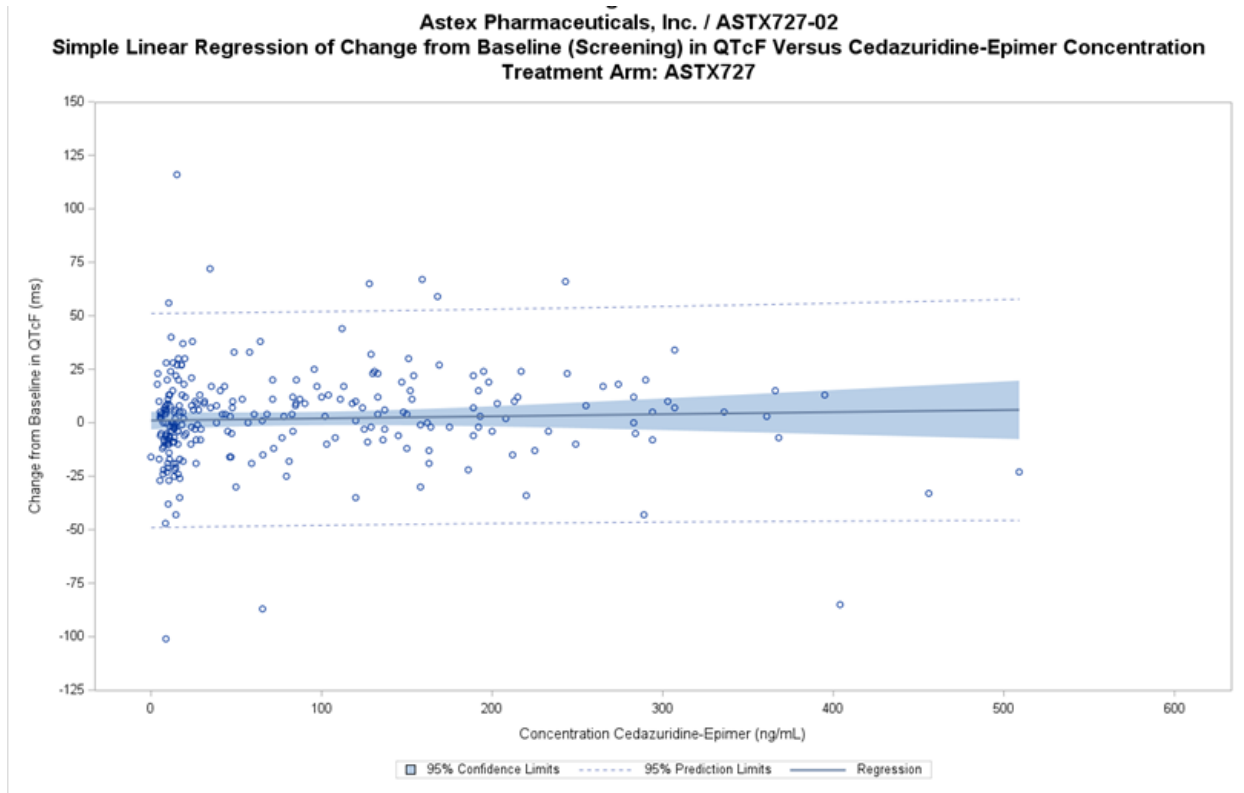
For this analysis, a modified analysis was required because, for each subject, only 2 postdose ECG-plasma concentration were obtained (1 in each period). Therefore, due to the limited number of ECG and plasma concentration time point matches, a formal complete exposure-response analysis was not possible. For this analysis, a general linear modeling approach was used. Results of the linear regression model are presented in Figure 14 (cedazuridine concentration), Figure 15 (cedazuridine-epimer concentration), Figure 16 (decitabine concentration after oral ASTX727), and Figure 17 (decitabine concentration after IV decitabine).

Figure 14. Phase 3: QTcF Change from Baseline- QTcF vs Cedazuridine Plasma Concentration (ng/mL) - Estimates from Simple Linear Regression- ASTX727 Cycle



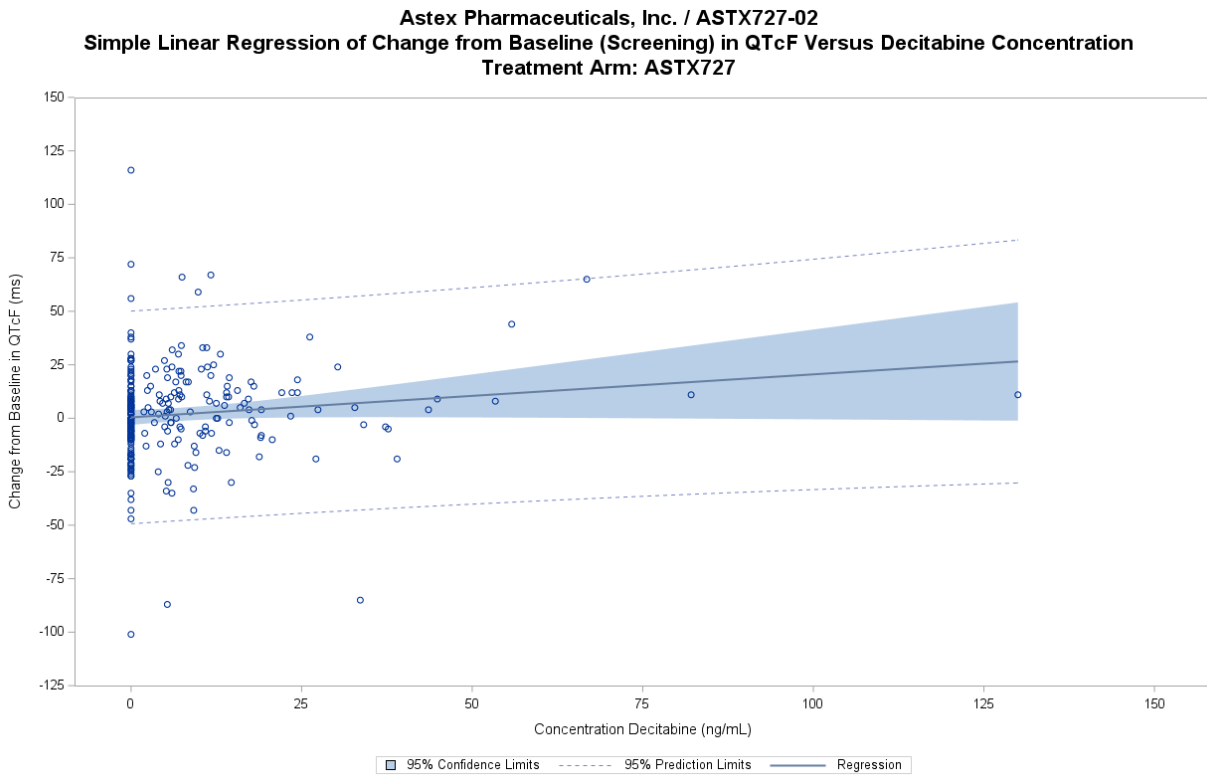
Source: ASTX727-02 CSR Appendix 16.1.13, Figure 2-1

Figure 15. Phase 3: QTcF Change from Baseline- QTcF vs Cedazuridine-Epimer Plasma Concentration (ng/mL) - Estimates from Simple Linear Regression- ASTX727 Cycle



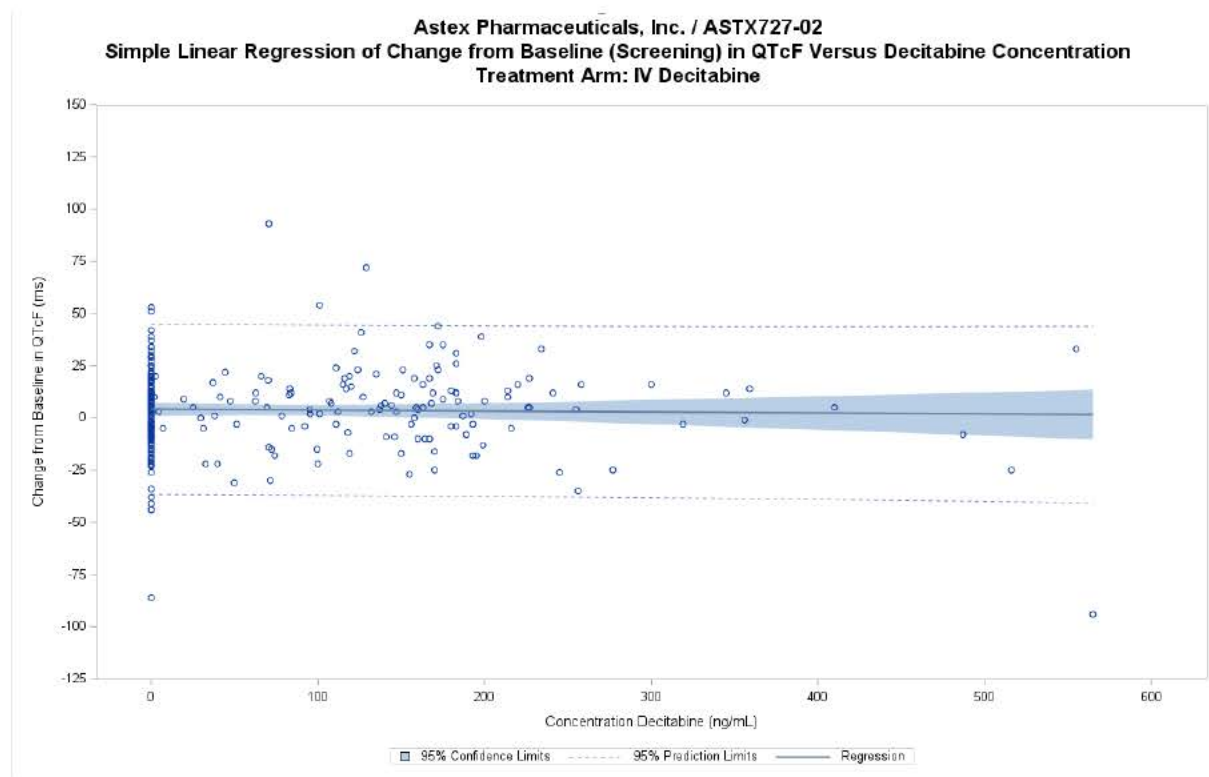
Source: ASTX727-02 CSR Appendix 16.1.13, Figure 2-2

Figure 16. Phase 3: QTcF Change from Baseline- QTcF vs Decitabine Plasma Concentration (ng/mL) - Estimates from Simple Linear Regression- ASTX727 Cycle



Source: ASTX727-02 CSR Appendix 16.1.13, Figure 2-3

Figure 17. QTcF Change from Baseline- QTcF vs Decitabine Plasma Concentration (ng/mL) - Estimates from Simple Linear Regression– IV Decitabine Cycle



Source: ASTX727-02 CSR Appendix 16.1.13, Figure 2-4

Within the limitation of the study, at the therapeutic exposures with the recommended dosing regimen, no large mean changes in the QTc interval (i.e., >10 msec) were observed. The exposure-QTc analysis suggested no concentration-dependent QTc interval prolongation for either decitabine or cedazuridine.

The Applicant's Position:

An assessment of ASTX727 on prolongation of the QT interval has been conducted in Phase 3.

(b) (4)

The Regulatory Authorities' Assessment:

FDA does not agree with Applicant's position

(b) (4)

The FDA notes that the ECG collection times from Study ASTX727-02 do not allow for adequate characterization the QTc interval. Additionally, the PK/ECG data from ASTX727 do not support the proposed concentration-QTc analysis because the Applicant did not collect an appropriate pre-treatment/baseline ECG measurement, the exposure range was too narrow to support the assessment, and the sparse sampling schedule

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does not allow an evaluation of any delayed effects (e.g., PK/PD hysteresis). The QT-IRT concluded that the PK and ECG data from ASTX727-02 are not adequate to characterize the effect of cedazuridine from ASTX727 on the QTc interval (QT-IRT Review, DARRTS ID 4572035). Therefore, a PMR study will be requested to evaluate the QT prolongation potential of cedazuridine.

X

X

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Justin Earp, PhD
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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 17. Listing of Clinical Trials Relevant to this Submission

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
ASTX727-02 Phase 3	03306264	Randomized, open-label, 2-period, 2-sequence crossover	ASTX727 FDC tablet (100 mg cedazuridine and 35 mg decitabine) Cycles 1 and 2 (2-way crossover): ASTX727 FDC tablet Daily×5, 1 cycle IV decitabine 20 mg/m ² Daily×5, 1 cycle Cycle ≥3: ASTX727 FDC tablet Daily×5 in each 28-day cycle until disease progression, unacceptable toxicity, or withdrawal by the subject	Primary: Total 5-day AUC exposures of decitabine for ASTX727 vs IV decitabine Secondary: Safety Maximum %LINE-1 demethylation Other PK parameters Clinical response RBC or platelet transfusion independence Leukemia-free survival Overall survival	Continuous Median 4 cycles (max 11) Median follow-up 155 days (5 months)	138 (133 treated)	Adults (≥18 yrs) with MDS including IPSS Int-1, Int-2, or high risk, or CMML	37 centers US and Canada
ASTX727-01 Phase 2 ^a	02103478	Randomized, open-label, 2-sequence crossover	100 mg cedazuridine, 35 mg decitabine Dose confirmation: Cycles 1 and 2 (2-way crossover):	Primary: Mean decitabine AUC and mean maximum %LINE-1 demethylation for ASTX727 vs IV decitabine	Continuous Median 7 cycles (max 29)	86 (80 treated)	Adults (≥18 yrs) with MDS including	15 centers US and Canada

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Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
(CSR ASTX727-01-B)			Cedazuridine/ decitabine Daily×5 (administered concomitantly as separate capsules), 1 cycle IV decitabine 20 mg/m ² Daily×5, 1 cycle Cycle ≥3: cedazuridine/ decitabine Daily×5 in each 28-day cycle, until disease progression or unacceptable toxicity	Response rate <u>Secondary:</u> Incidence and severity of AEs and clinically significant abnormal laboratory values Duration of response, hematological improvement, rate of transfusion independence time to AML, overall survival Other PK parameters	Median follow-up 729 days (24 months)		IPSS Int-1, Int-2 or high risk, or CMML	

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
ASTX727-01 Phase 2 (continued)			Fixed-dose combination: Cycles 1 and 2 (2-way crossover): ASTX727 FDC tablet Daily×5, 1 cycle IV decitabine 20 mg/m ² Daily×5, 1 cycle Cycle ≥3: ASTX727 FDC tablet Daily×5 in each 28-day cycle, until disease progression, unacceptable toxicity, or withdrawal by subject					
Other Studies Pertinent to Review of Efficacy or Safety								
ASTX727-01 Phase 1 ^a	02103478	First-in-human,	Cycle 1 Day -3: single dose decitabine (capsule) PO	Mean decitabine AUC oral/IV	Continuous	44	Adults (≥18 yrs)	12 centers US

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Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
(CSR ASTX727-01-A)		open-label, dose escalation	Cycle 1 Day 1: 20 mg/m ² IV decitabine Cycle 1 Days 2-5, and Days 1-5 of subsequent cycles: concomitant administration of cedazuridine/ and decitabine capsules (mg): Cohort 1: 40/20 Cohort 2: 60/20 Cohort 3: 100/20 Cohort 4: 100/40 Cohort 5: 100/30 Cycle 2 Day -3: single dose oral cedazuridine	Incidence and severity of dose-limiting toxicities Other PK parameters Incidence and severity of AEs and clinically significant laboratory values Mean maximum %LINE-1 demethylation Overall response rate, duration of response, hematological improvement, rate of transfusion independence, time to AML, overall survival	Median 5 cycles (max 35) Median follow-up 710 days (24 months)	(44 treated)	with MDS including IPSS Int-1, Int-2 or high risk; or CMML	
ASTX727-04 Phase 1b	03813186	Open-label, randomized (with response to timing of high calorie, high fat breakfast), 2-sequence	ASTX727 FDC tablet (100 mg cedazuridine and 35 mg decitabine), Daily×5 in each 28-day cycle (Randomization to high calorie, high fat breakfast administered predose on either Day 2 or Day 4 of Cycle 1)	AUC and other PK parameters in fed vs fasted state Response Incidence and severity of adverse events	Continuous Median 2 cycles (max 6)	18 (17 treated)	Adults (≥18 yrs) with MDS including IPSS Int-1, Int-2 and high risk; CMML, or AML who are not candidates for intensive chemotherapy	4 centers US
E7727-01 Phase 1	NA	Open-label, 2-treatment period, fixed-	Period 1: Single dose of cedazuridine 100 mg capsule PO followed 3 hours	Mass balance and ADME	Two single doses separated	8 (8 treated)	Healthy volunteers ≥65 years	1 center Netherlands

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Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
		sequence, mass balance and bioavailability	later by microtracer dose (100 µg) of ¹⁴ C-cedazuridine IV Period 2: Single dose of ¹⁴ C-cedazuridine 100 mg capsule PO		by a washout			

ADME: absorption, distribution, metabolism, excretion; AML: acute myeloid leukemia; CMML: chronic myelomonocytic leukemia; CSR: clinical study report; FDC: fixed-dose combination; IPSS: International Prognostic Scoring System; Int-1: IPSS Intermediate-1 risk group; Int-2: IPSS Intermediate-1 risk group; IV: intravenous; MDS: myelodysplastic syndrome; PK: pharmacokinetic(s); PO: by mouth.

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

Source: ASTX727-02 CSR, ASTX727-01-B CSR, ASTX727-01-A CSR, ASTX727-04 CSR, E7727-01 CSR

The Applicant's Position:

Astex believes the studies included in the submission provide adequate data to support the clinical pharmacology, AUC equivalence, efficacy, and safety of ASTX727 in patients with MDS or CMML. Since the application is primarily based on a PK bridging approach the long-term effectiveness and safety of ASTX727 are provided from single-arm treatment with ASTX727 after the first 2 randomized cycles. In addition to the systemic decitabine AUC exposure equivalence and similarity of the biological DNA demethylation effect between ASTX727 and IV decitabine in the first 2 randomized cycles, we have also used prior decitabine approval ([Dacogen USPI 2019](#)) and the published single-arm study of IV decitabine (5-day regimen) from [Steensma et al 2009](#) as a reference of the expected effectiveness and safety of IV decitabine compared to data from ASTX727 treatment in the clinical program.

The Regulatory Authorities' Assessment:

We agree with the summary of Studies presented in Table 17 above. It is notable that Study ASTX727-02 enrolled patients with all FAB classes as well, which included patients with low-risk IPSS score.

On Study ASTX727-01-A, the Phase 1, single arm, dose escalation trial, prior azacitidine was allowed with no limitation on the number of prior cycles. On the Phase 2 and Phase 3 studies (ASTX727-01-B and ASTX727-02) patients could have only received 1 prior cycle of azacitidine or decitabine.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Applicant's Position:

Extensive nonclinical and clinical information as well as postmarketing information are available for IV decitabine; therefore, the ASTX727 development program was designed to generate comprehensive pharmacokinetic (PK) data to bridge ASTX727 to safety and efficacy evidence for decitabine. This PK bridging approach is in accordance with FDA guidance for industry, "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products," dated May 1998. The design of the clinical protocol for Phase 3 study ASTX727-02 was developed based on the end of Phase 2 agreement between Astex and the FDA.

In addition to the PK bridging to efficacy and safety, the randomized crossover design of the Phase 2 and Phase 3 studies in the first 2 treatment cycles allowed intra-patient comparison of ASTX727 (100 mg cedazuridine and 35 mg decitabine) and IV decitabine (20 mg/m²), both given once daily for 5 consecutive days (Daily×5), to also assess the PD effect on global DNA methylation (LINE-1 DNA) and safety, over the first 2 cycles. As designed, these studies included continuation of treatment with ASTX727 from Cycle 3 onwards, as long as the subject continued to benefit, in order to generate single-arm, long-term safety and efficacy data for ASTX727 in the treated disease population. The Phase 1 part of study ASTX727-01 (ASTX727-01-A CSR) was also conducted in MDS and CMML patients and had the longest follow up (minimum 18 months). All subjects were treated with ASTX727 in all cycles (except Cycle 1 Day 1 when IV decitabine at 20 mg/m² was administered) but with different oral doses of cedazuridine (40, 60, and 100 mg) and decitabine (20, 30, and 40 mg). The main other difference between Phase 1 and the Phase 2 and 3 studies is that prior azacitidine was allowed in Phase 1 without limitation of number of prior azacitidine cycles. In Phase 2 and 3, prior decitabine or azacitidine treatment were limited to only one prior cycle.

Eligible subjects in all 3 studies were males or females ≥18 years of age with de novo or previously treated (any number of cycles of prior azacitidine in Phase 1 but only up to 1 cycle of azacitidine or decitabine in Phase 2 and 3) Int-1, Int-2, or high-risk MDS or CMML. Subjects with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2 were allowed to participate in Phase 1 and 2 but ECOG PS 2 subjects were excluded from Phase 3 to minimize of number of subjects who may not have been able to receive at least the first 2 cycles of treatment, necessary for analysis of the primary endpoint (AUC exposure). In addition, subjects with French-American-British (FAB) classification of refractory anemia with excess blasts in transformation (bone marrow

blasts 20% to 30%) were allowed in Phase 3, as these are included in the FDA approved Dacogen indication, but not in Phase 1 or 2. The duration of treatment and follow-up in the Phase 1 and 2 studies were also longer (median ~24 months) than in the Phase 3 study (median ~5 months). We also note that since the initial studies presented in the Dacogen USPI only used the FAB classification and IPSS score, we did not collect data on the MDS and CMML WHO classification in the studies.

8.1.1. Phase 1 and 2 Studies (ASTX727-01-A and B CSRs)

Trial Design

The Applicant's Description:

Study ASTX727-01 was a Phase 1-2 trial to evaluate ASTX727, for treatment of patients with MDS/CMML. The Phase 1 part of the trial (ASTX727-01-A CSR) was a single-arm, dose-finding, dose-escalation design. The Phase 2 part of the trial (ASTX727-01-B CSR) provided confirmation of the doses selected based on Phase 1 finding.

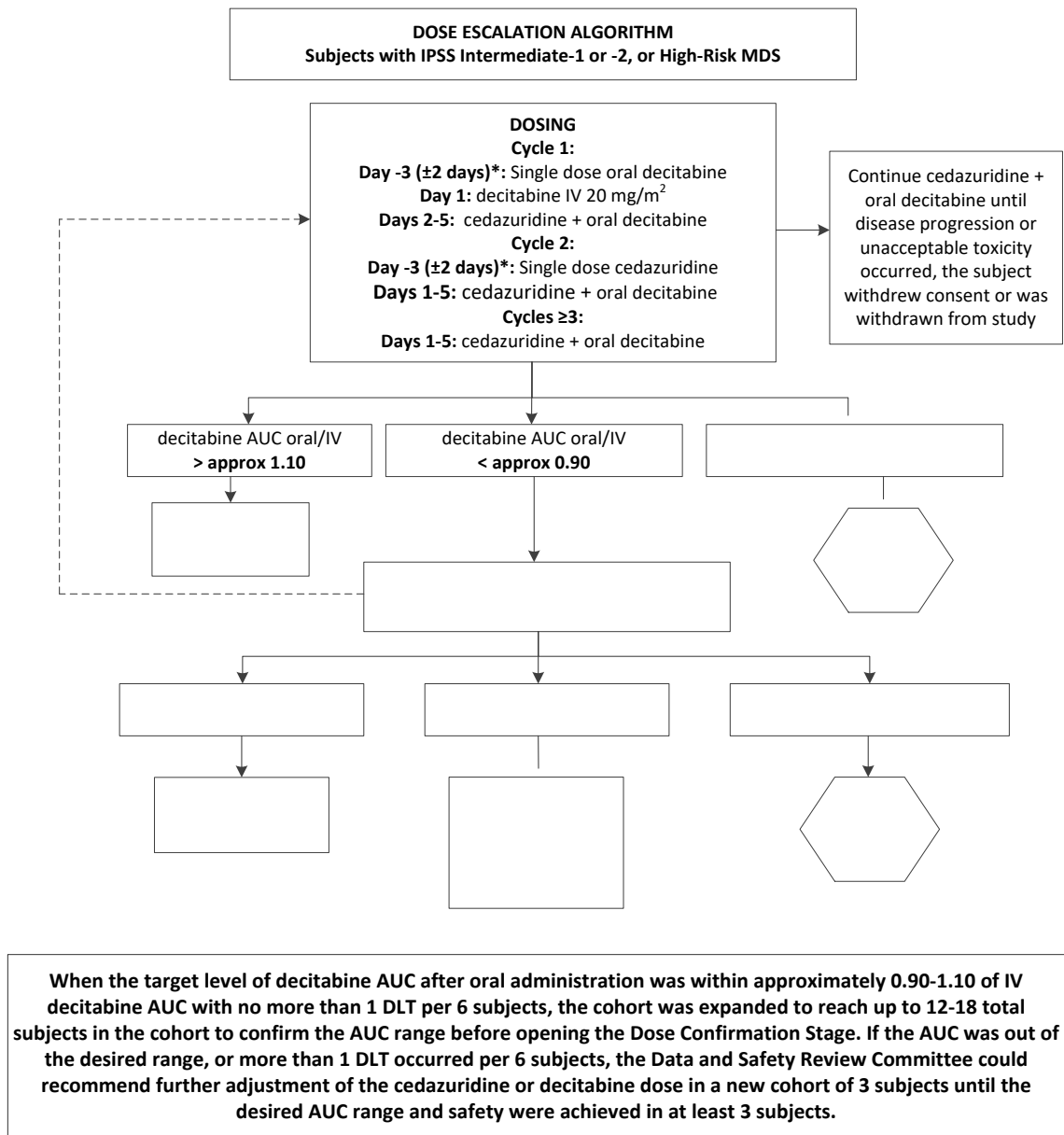
Phase 1:

The Phase 1 portion of Study ASTX727-01 (CSR ASTX727-01-A) was a first-in-human, open-label, non-randomized, single-arm, PK-guided, dose-escalation study to assess the safety, tolerability, and PK profile of oral doses of cedazuridine and decitabine administered concomitantly as separate capsules. The purpose of the study was to identify the doses of oral cedazuridine and oral decitabine that achieved decitabine AUC comparable to that of IV decitabine at the approved dose of 20 mg/m² Daily×5. In this study separate cedazuridine capsules (20-mg capsules) and decitabine capsules (5- and 20-mg capsules) were used. The starting dose was 40 mg cedazuridine and 20 mg decitabine. Doses were escalated using a standard 3+3 design after review of PK and safety data (Figure 18).

The study design included assessments of the PK of oral decitabine (Cycle 1 Day -3 [C1D-3]), IV decitabine (C1D1), oral cedazuridine and decitabine administered concomitantly (C1D2 through C1D5), and oral cedazuridine alone (C2D-3). Oral cedazuridine and decitabine were then administered in 5-day treatment cycles (Days 1 through 5) from Cycle 2 onwards at the same doses used in Cycle 1 (inpatient dose escalation was allowed in subsequent cycles). Cedazuridine and decitabine were administered under fasted conditions (i.e., no food, alcohol, or non-clear liquids for 2 hours before and 2 hours after dosing).

Clinical response was a secondary endpoint in this phase of the study. Efficacy from this study is supportive since it used different doses of cedazuridine and decitabine but also because almost half the subjects (46%) received prior azacitidine or decitabine with no limits in number of prior azacitidine cycles.

Figure 18. ASTX727-01 Phase 1 Study Schema



DLT=dose-limiting toxicity

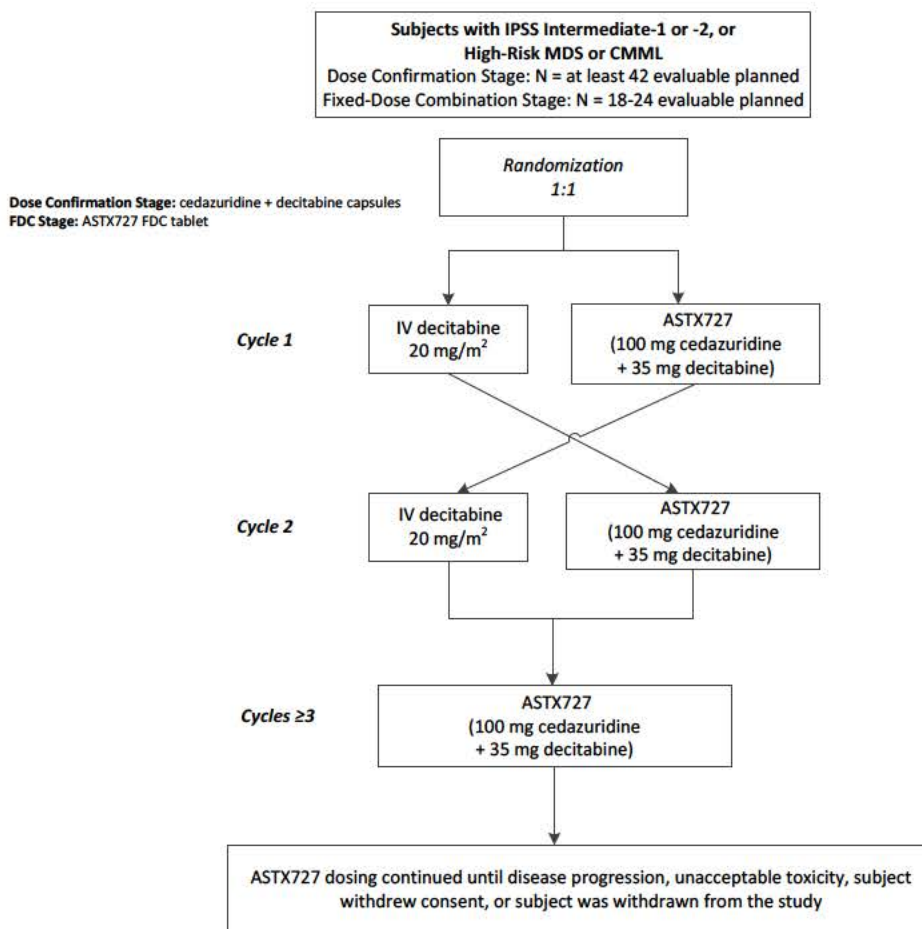
Source: Adapted from ASTX727-01-A CSR Figure 1

Phase 2:

Phase 2 portion of Study ASTX727-01 (CSR ASTX727-01-B) was a Phase 2, open-label, randomized, 2-cycle, 2-sequence crossover study followed by a single-arm continuation of treatment conducted in 2 stages to assess the PK, PD, safety, and efficacy of cedazuridine (100 mg) and decitabine (35 mg) as separate capsules (in the Dose Confirmation Stage) and as the ASTX727 FDC tablet (in the FDC Stage) administered Daily×5. At least 42 subjects were planned to be randomized in the Dose Confirmation Stage, and 18 to 24 subjects were planned to be randomized in the FDC Stage. Treatment continued until disease progression, unacceptable toxicity, the subject withdrew consent, or the subject was withdrawn from the study. The study schema is shown in Figure 19.

A standard 2×2 crossover design during the first 2 cycles of treatment was used for within-subject comparison of decitabine AUCs and LINE-1 demethylation after treatment with ASTX727 and IV decitabine. Masking the treatment assignment was not feasible due to the different routes of administration (oral vs IV).

Figure 19. Phase 2 ASTX727-01 Study Schema



Source: Adapted from ASTX727-01-B CSR Figure 1

Trial Location

Study ASTX727-01 was conducted at 15 centers in North America (11 centers in the United States and 4 centers in Canada).

Choice of Control Group (Phase 2)

The control group in the randomized crossover design was IV decitabine. IV decitabine (20 mg/m² once daily for 5 days) is an approved therapy for MDS/CMML ([Dacogen USPI 2019](#)) and was therefore an appropriate active comparator.

Diagnostic Criteria (Phase 2)

The Phase 2 portion of Study ASTX727-01 enrolled adult patients with MDS with

peripheral blasts or bone marrow blasts <20% or CMML who had received no more than 1 prior cycle of an HMA. Diagnosis was based on local centers pathology assessment of peripheral blood and bone marrow including assessment of the IPSS category (int-1, int-2, or high-risk) to match the FDA-approved indication for IV decitabine ([Dacogen USPI 2019](#)). Data on WHO classification were not collected as part of the study.

Key inclusion criteria:

- Men or women ≥ 18 years with 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 an HMA.
- 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 $\leq 2 \times$ upper limit of normal (ULN); AST/SGOT and ALT/SGPT $\leq 2.5 \times$ ULN.
 - Renal: serum creatinine $\leq 1.5 \times$ 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.
- Able to swallow the number of capsules required for the treatment assignment within a 10-minute period and tolerate 4 hours of fasting.

Key exclusion criteria:

- Previous treatment with at least 2 courses of decitabine or azacitidine.
 - Known or suspected hypersensitivity to decitabine or the components of cedazuridine.
 - Diagnosis of AML with bone marrow or peripheral blast count $\geq 20\%$ or other hematological malignancies.
 - Active uncontrolled gastric or duodenal ulcer.

The diagnosis of MDS and CMML was appropriate matching the IV decitabine FDA approval. The key inclusion and exclusion criteria were appropriate to ensure subjects safety (e.g., organ functions) and allow assessment of efficacy of ASTX727 (exclusion of more than one cycle of prior HMA treatment).

Dose Selection (Phase 2)

Dosing in the Phase 2 portion of Study ASTX727-01 was based on the decitabine AUC findings from the Phase 1 Dose Escalation portion of Study ASTX727-01. In the Phase 1 Dose Escalation (results reported in CSR ASTX727-01-A), decitabine exposure increased when decitabine was administered with cedazuridine, compared with decitabine administered alone, and approached or exceeded the decitabine AUC exposure of IV decitabine (128% oral/IV) at the highest oral decitabine dose of 40 mg. Oral/IV was 81% when the decitabine dose was de-escalated to 30 mg. It was therefore concluded from Phase 1 that an intermediate oral decitabine dose between 30 mg and 40 mg would best replicate the IV exposure and this was confirmed by PK modelling. The assessment led to the selection of the doses of the 2 components of ASTX727 to carry into the Phase 2 part of the trial: 100 mg cedazuridine and 35 mg decitabine.

Study Treatments (Phase 2)

Dose Confirmation Stage:

Test Product (cedazuridine and decitabine capsules)

- Dose: 100 mg cedazuridine (five 20-mg capsules) administered concomitantly with 35 mg decitabine (one 20-mg capsule and three 5-mg capsules) orally once daily on Days 1 through 5 (Daily×5) in 28-day cycles.

Reference Product (IV decitabine, 5-day regimen)

- Dose: 20 mg/m² decitabine by continuous 1-hour IV infusion Daily×5 in 28-day cycles.

FDC Stage:

Test Product (ASTX727 FDC tablet)

- Dose: one ASTX727 FDC tablet (100 mg cedazuridine and 35 mg decitabine) administered orally Daily×5 in 28-day cycles.

Reference Product (IV decitabine, 5-day regimen)

- Dose: 20 mg/m² decitabine by continuous 1-hour IV infusion Daily×5 in 28-day cycles.

Study drugs (test and reference products) were administered at the study center under the supervision of study personnel during Cycle 1 and Cycle 2 of the Dose Confirmation and FDC Stages. In Cycles ≥3 of both stages, the test products (capsules or tablets) were administered on an outpatient basis. The study drugs (test and reference) were to be taken in the morning at the same time of day (±1 hour) on each dosing day, in at least the first 2 cycles of treatment.

Assignment to Treatment (Phase 2)

Individual subject treatment assignments in each study stage were determined through a computer generated randomization scheme and accessed through the electronic data capture system used for study data management. Subjects were randomized in a 1:1 ratio and stratified by IPSS risk level (IPSS Int-1 vs IPSS Int-2 and high-risk [subjects with CMML were randomized into the IPSS Intermediate-2/high risk stratum]) to one of the following treatment sequences:

- Sequence A: cedazuridine + oral decitabine capsules (Dose Confirmation Stage) or the ASTX727 FDC tablet (FDC Stage) in Cycle 1 and then IV decitabine Cycle 2, or
- Sequence B: IV decitabine Cycle 1 and then cedazuridine + oral decitabine capsules (Dose Confirmation Stage) or the ASTX727 FDC tablet (FDC Stage) in Cycle 2.

All subjects received ASTX727 from Cycle 3 until treatment discontinuation. The randomization code and treatment assignment for each subject are provided in the submission (ASTX727-01-B CSR, Appendix 16.1.7).

Blinding (Phase 2)

This was an open-label study.

The primary PK and PD endpoints (total cycle AUC, LINE-1 methylation), were not susceptible to bias due to the objective nature of the measurements of PK and the LINE-1 assay. Efficacy response rate assessment is subject to bias; however, response assessments were done in Phase 2 by Astex medical personnel following the International Working Group (IWG) 2006 criteria by medical review of objective hematology data provided by the center (peripheral blood, bone marrow, and transfusion data). Efficacy survival data are not subject to bias.

Dose Modification/Dose Discontinuation (Phase 2)

Dose modification was not allowed during the first 2 cycles in order not to bias the PK and PD assessments. Subjects should receive the full intended dose of cedazuridine (100 mg) and decitabine (35 mg) as either separate capsules (Dose Confirmation Stage) or as the ASTX727 FDC tablet (FDC Stage) and IV decitabine dose (20 mg/m²) in the first 2 cycles. Cycle 2 can be delayed until blood count recovery from drug related hematological toxicity, to allow full dose in Cycle 2.

Guidelines for dose delay or dose reduction in response to toxicity are detailed in the ASTX727-01 Protocol (Section 7.3). In summary, ASTX727 dose reduction in Phase 2 was recommended by reducing the number of dosing days from 5 to 4 then 3. There was no

guidelines for dose modification of IV decitabine as it was administered for only one cycle.

Administrative Structure (Phase 2)

The Applicant was responsible for all aspects of the study, including oversight of the contract research organization responsible for study management and monitoring. An additional organization coordinated monitoring activities and support for Canadian study centers.

A Data and Safety Review Committee (DSRC) met periodically, mainly during the Phase 1 part of the study, to discuss and agree on the dose escalation for each subsequent cohort after assessment of safety, PK, and PD data from the previous cohort.

Response was assessed independently by 2 Astex medical monitors as described in Appendix 1 of the SAP for ASTX727-01-B using local center peripheral blood, bone marrow, and transfusion data and applying the IWG 2006 response criteria.

Procedures and Schedule (Phase 2)

The schedule of events is provided below in Table 18.

NDA Multi-disciplinary Review and Evaluation
 NDA 212576, Original
 INQOVI (decitabine and cedazuridine)

Table 18. ASTX727-01 Phase 2: Schedule of Events

Cycle (28 Days)		1					2					≥3					Tx Term	30-Day FU	Surv.
Cycle Day		1	2-5	8	15	22	1	2-5	8	15	22	1	2-5	8	15	22			
Study Treatment Administration		x	x				x	x				x	x						
PROCEDURES	Screening																		
Informed consent	x																		
Medical history	x																		
Investigator’s confirmation of eligibility	x																		
Physical exam or (symptom-directed PE)	x	x	(x)	(x)	(x)	(x)	x	(x)	(x)	(x)	(x)	x					x	(x)	
Height	x																		
Weight/BSA calculation	x	x					x										x		
Vital signs	x	x	(x)				x	(x)				x					x		
ECOG status	x	x					x					x					x	x	
12-lead ECG	x	x					x					x					x		
ECHO or MUGA	x																		
Concomitant medications/AEs	x	x	(x)	x	x	x	x	(x)	x	x	x	x					x	x	
Transfusion requirements	x	x	(x)	x	x	x	x	(x)	x	x	x	x					x		
Hematology	x	x		x	x	x	x		x	x	x	x					x		
Chemistry	x	x					x					x					x		
Urinalysis	x	x															x		
Serum or urine pregnancy test	x																x		
IPSS Risk Category	x																		
LINE-1 DNA methylation; Baseline gene mutation	x	x		x	x	x	x		x	x	x	x							
PK – Dose Confirmation Stage		x	x				x	x											
PK – FDC Stage		x	x				x	x											
Response assessment		x										x						x	

NDA Multi-disciplinary Review and Evaluation
 NDA 212576, Original
 INQOVI (decitabine and cedazuridine)

Cycle (28 Days)	1					2					≥3					Tx Term	30-Day FU	Surv.	
	Cycle Day	1	2-5	8	15	22	1	2-5	8	15	22	1	2-5	8	15				22
Bone marrow aspirate/biopsy	×											×						×	
Conversion to AML																			×

TX=treatment; FU=follow up; Surv.=survival; (×) = investigator discretion. Bone marrow aspirate and/or biopsy was collected at baseline, the beginning of Cycle 3, and every other cycle as long as the subject was responding.

Conversion to AML and survival were assessed every 3 months after treatment discontinuation.

Source: Adapted from ASTX727-01-B CSR Table 4

Dietary Restrictions/Instructions (Phase 2)

Subjects were permitted to have only clear liquids for 2 hours before and 2 hours after administration of the oral test product (cedazuridine and decitabine capsules or the ASTX727 FDC tablet). No dietary restrictions were in place when subjects received IV decitabine.

Concurrent Medications (Phase 2)

Supportive treatment such as antiemetics, blood and platelet transfusions, antibiotics including antifungal treatment were permitted at the investigator discretion according to the institution's standard of practice.

Hematopoietic growth factors were permitted in the event of a life-threatening septic event, at the discretion of the treating physician. Erythropoietin and/or Neupogen could be used after Cycle 1 and 2 in Phase 2.

Prohibited concomitant therapies were radiation therapy, chemotherapy, immunotherapy, or any experimental therapy. Other nucleosides or drugs that are metabolized by cytidine deaminase were also prohibited when cedazuridine was being administered.

Medications that may affect gastric pH were allowed, but were recommended not to be taken within ± 4 hours of administration of oral ASTX727.

Treatment Compliance (Phase 2)

During the first 2 cycles, all treatments (oral and IV) were administered by study personnel at each study center. In Cycles ≥ 3 , test products (capsules or tablets) were self administered on an outpatient basis. Drug accountability was determined by counting the number of capsules or tablets dispensed and returned by the subject to the study center.

Rescue Medications (Phase 2)

No rescue medications per se were planned in the trial apart from the permitted concomitant medications and supportive treatments described above.

Subject Completion, Discontinuation, or Withdrawal (Phase 2)

Subjects may discontinue study treatment for reasons such as disease progression or unacceptable toxicity, but they should continue on study follow up to assess AML transformation and survival. Subjects were considered to have completed the study

when they were withdrawn from the study for any of the following reasons:

- Death.
- Withdrawal of consent.
- Lost to follow up.

Subjects lost to follow up were included in the statistical analysis to the point of last evaluation. For analyses of survival time and time to progression to AML, subjects were censored on the last date of contact if lost to follow up prior to reaching a time-to-event endpoint.

Enrollment continued until the required number of evaluable subjects was reached.

For subjects who discontinued treatment, follow-up procedures and assessments were conducted at the 30-day follow-up visit and thereafter at approximately 3-month intervals to assess conversion to AML and to assess overall survival. See Table 18 for more details.

Regulatory Authorities' Assessment:

We agree with the Applicant's description of the trial design of the Phase 1 and 2 Studies (ASTX727-01-A and -B).

Study Endpoints (Phase 2)

The Applicant's Description:

The objective of the study was to establish and then confirm the doses of the two components to be used in the final product (ASTX727 FDC tablet). To that effect Phase 2 described multiple primary endpoints (decitabine AUC for PK; and LINE-1 for treatment PD effect on DNA methylation both using randomized comparison of IV and oral in the first 2 cycles of treatment) and response rate from study treatment assessed as a single arm. The multiple primary endpoints were needed to ensure that the selected oral ASTX727 doses achieved similar decitabine exposure, similar DNA demethylation compared to IV decitabine, and that the response rate following multiple cycles of oral ASTX727 was consistent with expected response rate from IV decitabine. This assurance was deemed necessary before finalizing the dose for the Phase 3 study, which was discussed with FDA at the EOP2 meeting.

Primary Endpoints (Phase 2)

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

- Response rate in all subjects (based on IWG 2006 MDS response criteria).

Secondary Endpoints (Phase 2)

- Incidence and severity grades of adverse events and clinically significant abnormal laboratory values.
- Duration of response, hematological improvement, rate of transfusion independence, time to AML, and overall survival.
- Other PK parameters of oral decitabine, cedazuridine, and cedazuridine-epimer (if needed).

Exploratory Endpoint (Phase 2)

- Gene mutations and correlation with response.

The endpoints in Phase 2 were standard endpoints and appropriate based on the main objective of confirming the final doses of ASTX727 to proceed to Phase 3. While PK, PD, and response rates were all primary in the Phase 2 part of the ASTX727-01 study, they have different emphasis for this NDA. The efficacy data in Phase 2 (80 patients randomized and received any amount of treatment) are considered the primary efficacy results in this application due to the long follow-up necessary to achieve mature efficacy assessment, which was achieved in this study (minimum follow-up of 12 months; median follow up of 24 months, and median number of 7 cycles with a range of 1 to 29 cycles). In contrast, the PK and PD endpoints in Phase 2 are considered supportive in the application since the sample size in Phase 2 was not designed with sufficient power to achieve AUC equivalence definition (oral/IV ratio with 90% CI between 80% and 125%). Phase 1 efficacy data are supportive since it is also a mature study with minimum follow-up of 18 months (median follow-up ~ 24 months, median cycle 5 (range 1-35)). Response rate in both Phase 1 and 2 was based on the most recent and standard criteria for MDS response assessment (IWG 2006 criteria). Local center objective laboratory and clinical data from peripheral blood (PB), bone marrow (BM), and transfusions at baseline and subsequently were carefully reviewed by Astex medical personnel to assign response category and did not just rely on investigator judgment.

Efficacy Assessments (Phase 2)

Hematology with peripheral blood counts was assessed at baseline and on Day 1, 8, 15 and 22 during Cycles 1 and 2 and at least on Day 1 in Cycle ≥ 3 . Bone marrow was assessed at baseline and within 7 days before the start of Cycles 3, 5, and 7; then according to institution practice as long as the subject was responding.

Evaluation of response was based on IWG 2006 MDS Response Criteria ([Cheson et al 2006](#)) and was conducted by 2 Astex medical monitors (independently of each other) by review of peripheral blood and bone marrow data from each cycle and assisted by programmed data listings as described in Appendix 1 of the SAP for ASTX727-01-B.

The frequency of assessment (multiple PK samples during treatment days); LINE-1 assessment at baseline and weekly in cycles 1 and 2; the frequency of PB, and bone marrow assessments at baseline and subsequently were sufficient to capture response category, duration of response, and time to AML transformation. Subjects were followed monthly (every 4 weeks) during treatment and every 3 months after treatment discontinuation to adequately capture survival data. Transfusion requirements were assessed weekly in the first 2 cycles then on Day 1 of each subsequent cycle.

The Regulatory Authorities' Assessment:

We agree with the Applicant's description of the study endpoints of the Phase 2 Study (ASTX727-01-B).

Statistical Analysis Plan and Amendments (Phase 2)

The Applicant's Description:

The planned analyses for this Phase 2 study are described in two different documents, the Pharmacometric Analysis Plan (27 August 2018) and the Statistical Analysis Plan (08 August 2018). The Pharmacometric Analysis Plan (PAP) addressed the PK analyses of plasma decitabine, cedazuridine and cedazuridine-epimer following single and multiple once daily oral doses of decitabine and cedazuridine for dose-confirmation and fixed-dose combination stages. The planned analyses of AUC exposures of decitabine after treatment with ASTX727 (administered as individual capsules of cedazuridine and decitabine in the dose-confirmation stage and as a fixed dose tablet in the FDC stage) versus IV decitabine, as well as planned analyses of secondary PK parameters, were described in the PAP. The Statistical Analysis Plan (SAP) described the planned analyses of all other clinical and PD endpoints.

Sample Size

In the Dose Confirmation Stage of the study, an intra-subject CV of 0.50 (estimated from a previous study described in the Dacogen Prescribing Information) was chosen to calculate the sample size to include in the 2 one-sided equivalence tests of the mean decitabine AUCs of ASTX727 (estimated from 5-days of dosing) compared with IV decitabine. A sample size of 42 subjects provides 86% power at the statistical significance level of 0.10, when the true ratio of geometric means is 1.0 and the equivalence limits for the mean ratio are 0.75 and 1.33. This same sample size of 42 in the same 2x2 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.

For the FDC 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 provided 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.

The 18-24 subjects who completed Cycles 1 and 2 with sufficient LINE-1 data in the same 2x2 crossover design provided 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 SD is 0.15 and the significance level is 0.10.

Analysis Populations

Two Pharmacokinetic Analysis Populations were used for analysis of PK data and were defined as follows:

The **Primary PK Analysis Set** was used for analyses of the primary study endpoint. This analysis set included all randomized subjects who receive 2 cycles of treatment and who had sufficient plasma concentration data to allow AUC_{0-t} determination for each cycle.

The **Complete PK Analysis Set** included subjects who received at least one dose of study drug (cedazuridine + oral decitabine, or ASTX727, or IV decitabine) with sufficient plasma sample data to assess PK parameters (including unpaired AUC comparison) and with no protocol deviations affecting assessment of the primary study endpoint.

The following Analysis Sets were used for analysis of all non-PK primary and secondary endpoints:

The **All Subject Analysis Set** includes data from all randomized subjects including those who did not receive any study treatment. This dataset was used to summarize disposition.

The **Efficacy Analysis Set** includes data from all randomized subjects who received any amount of study treatment.

The **Safety Analysis Set** includes data from all randomized subjects who received any amount of study treatment. In the safety analysis, no data exclusion was allowed because of protocol deviations.

The **PD LINE-1 Analysis Set** includes data from subjects if they received at least one cycle (Days 1 through 5) of study treatment and had LINE-1 methylation data at baseline (Day 1) and on either Day 8 or Day 15. Based on prior experience with decitabine treatment, maximum effect on LINE-1 % methylation is mostly achieved on Day 8 or Day 15 following in the 5-day dosing schedule.

Methods for Handling Missing Data (Phase 2)

Handling of Missing Plasma Concentrations

For the PK parameter calculations, imputation of missing data may be done for:

- In instances where there is a missing plasma concentration at the end time of the predefined partial AUC (i.e., AUC_{0-24} , AUC_{0-8}), the following data extrapolation / interpolation was applied:
 - If the predefined end time falls within the range of the available data but does not coincide with an observed data point, then the plasma concentration corresponding to the end time of the predefined partial AUC will be calculated (imputed) by performing a linear or logarithmic interpolation, as applicable.
 - If the sample was collected before the end time of the predefined partial AUC (e.g., 23.5 h for AUC_{0-24}) and corresponds to the last sample collected for the predefined partial AUC, then the plasma concentration corresponding to the end time of the predefined partial AUC will be calculated by extrapolation using λ_z (i.e., concentration at 24 h for AUC_{0-24}).
 - If λ_z is not estimable, the observed partial AUC up to the time of the last sample preceding the end time of the pre-defined partial AUC will be used only if the actual end time of the predefined partial AUC is within 20% time window of the nominal end time (i.e. >6.4h for AUC_{0-8} and >19.2h for AUC_{0-24}).
 - Otherwise, the predefined partial AUC will not be calculated.
- Missing pre-dose values:
 - The pre-dose concentration will be set to 0 for the first dose.
 - After multiples doses, the pre-dose concentration will be set to C_{min} following the previous dose for cedazuridine and zero for decitabine.

Unless otherwise noted, data summaries will be performed only on observed data.

Incomplete Dosing Information

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

Missing Sampling Dates and/or Times

For concentration-time profiles from subjects with missing sample dates and/or times, the nominal sampling day and/or time (as appropriate) will be assumed for the calculation of PK parameters.

Unexpected Data

A visual inspection of concentration-time profiles will be performed to determine dataset integrity and potential outliers. Descriptive statistics of PK parameters may be calculated with and without subjects who could be potential outliers. Subjects with potential outlier data will be reviewed by (b) (4) and the Sponsor for inclusion or exclusion from the descriptive statistics on a case-by-case basis.

Non-zero predose concentration values will be identified in the study report and included in the computation of PK parameters. Concentration profiles and PK parameters for subjects with non-zero predose concentrations greater than 5% of C_{max} will be reviewed by (b) (4) and the Sponsor for inclusion or exclusion from the descriptive statistics on a case-by-case basis.

Any plasma concentrations that cannot be uniquely and unequivocally attributed to a particular subject, period and/or time point based on case report form (CRF) records or other observed data records in the study will be treated as incomplete data. Such data will be compiled, commented, and listed separately in the appendix of the report. Incomplete and/or non-compliant data, if any, will be excluded from analysis datasets; no analyses, summaries or graphs will be produced using these data.

Vomiting

For subjects receiving, oral decitabine or combination treatment of decitabine and cedazuridine who may experience emesis on the day or during the serial sampling, if vomiting occurs at or before 2 times median t_{max} of cedazuridine or decitabine (whichever median t_{max} occurs later), then subject data for decitabine, cedazuridine and its circulating metabolites (E7727-epimer) will be excluded from PK statistical analysis for the treatment in which this occurs.

The Regulatory Authorities' Assessment:

We agree with the Applicant's description of the SAP of the Phase 2 Study (ASTX727-01-B).

Protocol Amendments (Phase 2)

The Applicant's Description:

Three of the four ASTX727-01 protocol amendments affected the Phase 2 portion of the study (Amendments 2 through 4). The key changes are shown in Table 19.

Table 19. ASTX727-01 Phase 2 Protocol Amendments

Protocol Amendment	Effective Date	Key Changes in Amendment
2	23 Sept 2015	Added PK assessments on Days 2, 3, and 4 during the ASTX727 cycle in the Dose Confirmation Stage to better estimate PK over 5 dosing days.
3	26 July 2016	Added “FDC stage” to confirm ASTX727 FDC tablet formulation yields PK and PD data similar to data for IV decitabine in addition to the “Dose Confirmation” stage of the study protocol, which assessed cedazuridine and decitabine given as separate capsules and to gather additional efficacy and safety data with the FDC tablet.
4	06 Apr 2017	Require transition of long-term ongoing subjects in the Dose Confirmation Stage from cedazuridine and oral decitabine capsules to the ASTX727 FDC tablet (due to expiry of the capsules).

The Regulatory Authorities’ Assessment:

We agree with the Applicant’s description of protocol amendments.

8.1.2. Study Results (Phase 2)

Compliance with Good Clinical Practices (Phase 2)

Data:

This study was conducted in accordance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable local regulatory requirements. Written informed consent was obtained from subjects prior to Screening assessments. The ASTX727-01-B CSR includes a GCP compliance statement.

The Applicant’s Position:

ASTX727-01 was conducted in accordance with the Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR Part 50), Institutional Review Boards (21 CFR Part 56), the Responsibilities of Sponsors and Investigators (21 CFR Parts 312.50 to 312.70), Financial Disclosure by Clinical Investigators (12 CFR Part 54), and in accordance with ICH GCP guidelines.

The Regulatory Authorities’ Assessment:

We confirm the Applicant’s position.

Financial Disclosure (Phase 2)

Data:

Astex has adequately disclosed financial interests/arrangements with clinical

investigators participating in Study ASTX727-01, as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

With the exception of Dr. (b) (6) and Dr. (b) (6) (as identified in Form FDA 3455 within the NDA), Astex certifies that we have not entered into any financial arrangement with any other clinical investigators participating in Study ASTX727-01, as listed in the FDA Form 3454 attachment.

- Dr. (b) (6) participated as a clinical investigator in Study ASTX727-01 and had a financial arrangement with Astex that was required to be disclosed. Dr. (b) (6) received “significant payments of other sorts” from Astex as he was also contracted to be (b) (6).
The financial arrangement with Dr. (b) (6) does not raise any data integrity concerns, as the primary PK Analysis Assessment for Study ASTX727-02 was conducted by a third party and data were not accessible to Dr. (b) (6). In regards to the Response Assessment, Dr. (b) (6) did not conduct response assessment for Phase 2, (b) (6) thus reducing the potential for bias.
- Dr. (b) (6) participated as a clinical investigator in Study ASTX727-01 and had a financial arrangement with Astex that was required to be disclosed. Dr. (b) (6) received “significant payments of other sorts” from Astex (b) (6).
As a result, payments were made to (b) (6), which included payments for Dr. (b) (6).
The financial arrangement with Dr. (b) (6) does not raise any data integrity concerns, as the PK Analysis Assessment conducted by a third party and data were not accessible to Dr. (b) (6). In regards to the Response Assessments, the response data were assessed by internal Astex medical reviewers, not by Dr. (b) (6).

The Applicant’s Position:

With the two exceptions noted above, Astex certifies that: 1) the company has not entered into any financial arrangement whereby the value of compensation to the investigator could be affected by the outcome of the study; 2) no listed investigator

disclosed a proprietary interest in the product or a significant equity holding in Astex; and 3) no listed investigator was the recipient of significant payments of other sorts. As listed above, the financial arrangements made with both Dr. (b) (6) and Dr. (b) (6) do not raise any concerns with data integrity.

The Regulatory Authorities' Assessment:
We confirm the Applicant's position.

Patient Disposition (Phase 2)

Data:

A total of 86 subjects were randomized in the Phase 2 portion of the study from 11 centers in the US and 4 in Canada. The Efficacy Analysis Set and the Safety Analysis Set were composed of the 80 randomized subjects who received any amount of study treatment, no treated subjects were excluded. Six subjects were randomized but did not receive any treatment (1 died before receiving treatment, 1 because of pathologist change of diagnosis from MDS to myelofibrosis, 1 withdrew because of disease progression, 1 withdrew consent before treatment, and 2 withdrew due to elevated liver function tests). It is to be noted that appendix 16.2.3 of the submitted Phase 1 and 2 CSRs (ASTX727-01-A and ASTX727-01-B) was mislabeled "subjects excluded from efficacy analysis" when in fact they are listing of subjects who failed screening and were not enrolled/randomized to the study.

As of the Phase 2 CSR data cutoff date (05 June 2018), 13 subjects were alive and ongoing treatment. The median duration of follow up was 729 days (~24 months) with a minimum of 12 months (range, 365 to 876 days). The median duration of treatment was 7 treatment cycles (range, 1 to 29 cycles).

As the FDC stage began after enrollment in the Dose Confirmation Stage had finished, the median follow up time in the Dose Confirmation Stage (809.5 days) was longer than in the FDC Stage (460 days).

Table 20. Disposition Phase 2 Overall (All Subject Analysis Set)

	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	41 (82.0%)	26 (86.7%)	67 (83.8%)
Adverse Event	3 (6.0%)	3 (10.0%)	6 (7.5%)
Death	6 (12.0%)	6 (20.0%)	12 (15.0%)
Progressive Disease	14 (28.0%)	7 (23.3%)	21 (26.3%)
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 ^c	7 (14.0%)	4 (13.3%)	11 (13.8%)
Subjects on Treatment at Data Cutoff	9 (18.0%)	4 (13.3%)	13 (16.3%)
Study Withdrawal ^b	33 (66.0%)	17 (56.7%)	50 (62.5%)
Adverse Event	1 (2.0%)	0	1 (1.3%)
Death	24 (48.0%)	16 (53.3%)	40 (50.0%)
Progressive Disease	3 (6.0%)	0	3 (3.8%)
Withdrawal by Subject	1 (2.0%)	1 (3.3%)	2 (2.5%)
Lost to Follow-Up	0	0	0
Other ^d	4 (8.0%)	0	4 (5.0%)

^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 (i.e., either ASTX727 or IV decitabine). Efficacy/Safety data sets.

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

^c Included Investigator decision (4 subjects).

^d All subjects proceeded to stem cell transplant.

Source: ASTX727-01-B CSR Table 14.1.1.2, Table 14.1.1.3

The Applicant’s Position:

None of the subjects who received treatment were excluded from planned efficacy or safety analyses. Since efficacy in Phase 2 was assessed as a single arm, it is appropriate to conduct the efficacy assessment based on subjects who actually received treatment.

The Regulatory Authorities’ Assessment:

FDA performed an analysis of disposition on the Phase 2 Study ASTX727-01-B using data from the 120-day safety update received on 4/6/2020. The 120-day safety update used a cutoff date of 11/1/2019. For the purposes of determining reasons for treatment discontinuation, FDA considers death under the primary reason for discontinuation (i.e., either primary disease or adverse event). Thus, the reason “adverse event” included 9 deaths due to an adverse event, in addition to the disposition events coded as adverse event. The reason “primary disease” included 2 deaths due to primary disease, in addition to the disposition events coded as progressive disease.

Of the 17 treatment discontinuations for “Other” in the overall treated population, 5 were “rollover,” 4 appeared to be due to the primary disease, 4 were physician decision, 2 were moved to palliative/hospice care, one was considered not a good candidate for the trial, and one was the subject’s decision.

Reasons for Treatment Discontinuation on Study ASTX727-01-B

	ASTX727* (N=80) n (%)
Therapy ongoing	1 (1%)
Discontinued therapy	
Primary disease	28 (35%)
Adverse event	17 (21%)
HSCT	12 (15%)
Withdrawal by subject	5 (6%)
Other	17 (21%)

Source: FDA analysis

*Includes both the dose confirmation and FDC stages

Protocol Violations/Deviations (Phase 2)

Data:

Categories of important protocol deviations were identified by the study team during protocol deviation review throughout the study.

Important Protocol Deviations: A subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

For this study, important protocol deviations were further defined as those that potentially affected evaluation of the study endpoints, particularly the PK primary endpoint in each study stage. Deviations such as out-of-window assessment/procedures were not considered important; in addition, PK sampling out-of-window was not considered significant, as the actual (not the scheduled) PK sampling time was used to compensate and was considered sufficient for assessment of the primary study endpoint.

Six deviations were considered to be important and are described by deviation category as follows:

- Safety: 2 occurrences of study center failure to report an SAE to the sponsor with 24 hours and to the local IRB.
- Study procedures: PK sampling was not collected per protocol for 1 subject.
- Informed consent: the screening informed consent process was not in the study source documentation at 1 study center.
- Randomization/enrollment: 1 subject was treated prior to being randomized to a treatment sequence (Subject (b) (6) described below).

Astex subject matter experts and the medical monitor reviewed the listings for confirmation of the assignment of importance and for deviation trends across study centers.

No subjects were randomized who did not meet study entry criteria. Subject (b) (6) was not randomized prior to treatment; this subject was subsequently manually assigned a treatment sequence corresponding to the actual treatment received; this was documented in the EDC and submitted to the study center's IRB.

The Applicant's Position:

These deviations did not affect the study conclusions.

The Regulatory Authorities' Assessment:

We agree with the Applicant's assessment. None of the deviations were likely to bias the study in favor of the study drug. Therefore, all patients, including those with important protocol deviations, were included in our analysis of efficacy endpoints.

Table of Demographic Characteristics (Phase 2)

Data:

Demographic characteristics are presented for the efficacy and safety datasets (all 80 treated subjects). Of the 80 treated subjects, 64 were treated in the US and 16 were treated in Canada. The geographic location of each site and the number of subjects screened, randomized, and treated are provided in Appendix 16.1.4 of the ASTX727-01-B CSR. Efficacy analyses by geographic region were not conducted.

Table 21. ASTX727-01 Phase 2 Subject Baseline Demographics (Efficacy Analysis Set)

Baseline Characteristics	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			
Male	32 (78.0%)	29 (74.4%)	61 (76.3%)
Female	9 (22.0%)	10 (25.6%)	19 (23.8%)
Race			
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			
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%)
Body Surface Area (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

Source: ASTX727-01-B CSR Table 14.2.1.2

The Applicant's Position:

Overall, the demographic characteristics of subjects in this study is representative of MDS and CMML patients in the general population. Most subjects were elderly (median age >70 years), males, and predominantly white. The study included a broad range of BSA (1.3 to 2.4 m²).

No differences in demographic characteristics between subjects in Sequence A and Sequence B were apparent in Phase 2. Efficacy endpoints were not compared between treatment sequences. Also, demographic characteristics are not shown here by Phase 2 study stage (Dose Confirmation Stage using separate capsule and FDC Stage using FDC tablets) since efficacy endpoints are not shown here between the 2 stages. Since all subjects received the same doses of ASTX727 and all of them received no more than 1 cycle of IV decitabine there was no clinical reason to present efficacy by sequence or by

stage.

The Regulatory Authorities' Assessment:
 We agree with the Applicant's assessment.

Other Baseline Characteristics (Phase 2)

Data:

Baseline disease characteristics are summarized below. WHO classification of MDS/CMML was not collected for this study.

Table 22. ASTX727-01 Phase 2 Baseline Disease Characteristics (Efficacy Analysis Set)

	Sequence A (N=41)	Sequence B (N=39)	Total (N=80)
Study Disease, n (%)			
MDS	33 (80.5%)	30 (76.9%)	63 (78.7%)
CMML	8 (19.5%)	9 (23.1%)	17 (21.3%)
Time since diagnosis (days)*			
Mean	305.6	292.7	299.3
SD	562.40	616.24	585.53
Median	55.0	41.0	52.5
Min, Max	6, 2729	6, 3077	6, 3077
ECOG Performance Score			
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%)
Prior HMA Therapy	3	4	7
Prior Azacitidine	3	1	4
Prior Decitabine	0	3	3
IPSS for MDS, 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%)
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

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 INQOVI (decitabine and cedazuridine)

	Sequence A (N=41)	Sequence B (N=39)	Total (N=80)
Platelets (10⁹/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 or Platelet Transfusion Dependence^{a, *}			
Yes	22 (53.7%)	19 (48.7%)	41 (51.3%)
No	19 (46.3%)	20 (51.3%)	39 (48.7%)
RBC Transfusion Dependence^b			
Yes	20 (48.8%)	18 (46.2%)	38 (47.5%)
No	21 (51.2%)	21 (53.8%)	42 (52.5%)
Platelet Transfusion Dependence^b			
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	22 (57.9%)	19 (48.7%)	41 (53.2%)

Source: ASTX727-01-B CSR Table 14.2.1.2

* Indicates source of data is from a supplemental table

^a RBC Transfusion Dependence at baseline or Platelet Transfusion Dependence at baseline

^b Transfusion dependent = documentation of 2 units or more of transfusion within 56 days of the first day of study treatment

The Applicant's Position:

The baseline disease characteristics of subjects in this study are representative of the patient population intended to receive the marketed product. Most IPSS risk categories were represented and patients with CMML were also included. No clinically meaningful differences in baseline characteristics between the study stages or the 2 treatment sequences were apparent.

The Regulatory Authorities' Assessment:

The mean time since diagnosis was 299.3 days and median time since diagnosis was 52.5 days. Of note, this is shorter than the mean and median time since diagnosis noted in the IV decitabine label (mean 86 weeks and median 29 weeks on the decitabine arm of the randomized trial and mean 444 days and median 154 days on the single-arm trial).

Only 7 (9%) received up to 1 cycle of prior HMA therapy prior to enrolling on the trial.

FDA obtained further information from the Applicant regarding prior therapies in a response to information request received on 3/10/2020. Results of FDA's subsequent analysis of prior therapies are displayed in the Table below.

Prior Anticancer Therapy in Phase 2 (ASTX727-01-B)

	Total (N=80) n (%)
Subjects with any prior anti-cancer therapy	15 (19%)
Lenalidomide	5 (6%)
Erythropoietin or erythropoietin stimulating agents	4 (5%)
Azacitidine	3 (4%)
Decitabine	3 (4%)
Bendamustine and rituximab ¹	1 (1%)
Busulfan	1 (1%)
Ciclosporin	1 (1%)
Danazol	1 (1%)
Fludarabine	1 (1%)
Hypomethylating agent (not specified)	1 (1%)
Imatinib mesylate	1 (1%)
Ruxolitinib	1 (1%)

Source: FDA analysis

¹ Subject (b) (6) received prior bendamustine and rituximab for CLL

Of note, the USPI for IV decitabine states that 30% of patients on the decitabine arm of the randomized trial and 27% of patients on the single arm trial received previous MDS therapy. The percentage here (19%) is lower, consistent with the shorter time from diagnosis to beginning treatment. Of note, per the Applicant, no subjects were reported as having prior HSCT in the Phase 2 database, but subject (b) (6) who received prior fludarabine and busulfan received peripheral blood stem cell transplant according to e-mail communication with the site. The median duration of treatment of prior anticancer therapy (excluding azacitidine and decitabine which were given for only one cycle) was 47.5 days (range 1 to 1827 days). Subject (b) (6) received lenalidomide for 1827 days.

Of note, the 17 (21%) of patients without IPSS results documented had CMML. Cytogenetic risk categories for the 80 patients were better in 27 (34%), intermediate in 22 (28%), poor in 15 (19%), and missing/unknown in 16 (20%).

FDA found that 40 (50%) of patients had bone marrow blasts > 5% at baseline, which is slightly different from 41 (53%) reported by the Sponsor.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use (Phase 2)

Data:

During the 2-way crossover, 73 of the 80 subjects treated (91.3%) received the first 2 cycles of treatment.

The median number of cycles received overall in Phase 2 was 7 (range, 1 to 29) and 50 subjects (62.5%) received 6 or more cycles. Overall in Phase 2, 51.3% of subjects had delayed cycles and 40% of subjects had dose-reduced cycles (Table 23).

Table 23. ASTX727-01 Phase 2 Treatment Exposure (Safety Analysis Set)

Treatment Exposure	Dose Confirmation Stage (N=50)	Fixed-Dose Combination Stage (N=30)	Phase 2 Overall (N=80)
Summary of Cycles Received ^a			
Mean	9.6	7.4	8.8
SD	8.1	4.5	7.0
Median	6.5	7.0	7.0
Min, Max	1, 29	1, 16	1, 29
Number of Treatment Cycles	481	221	702
Number of Delayed Cycles ^b	72 (15.0%)	43 (19.5%)	115 (16.4%)
Number of Dose Reduced Cycles ^c	75 (15.6%)	26 (11.8%)	101 (14.4%)
Number of Subjects with Delayed Cycles	28 (56.0%)	13 (43.3%)	41 (51.3%)
Number of Subjects with Dose-Reduced Cycles	23 (46.0%)	9 (30.0%)	32 (40.0%)

^a Completed or partially completed cycles.

^b Delayed treatment cycle was defined by the investigator.

^c Dose-Reduced Cycle is based on any missing treatment days in Cycles 1 and 2 during the PK assessments, dose adjusted or reduced treatment days by the investigator in subsequent cycles, or any drug returned by the subject at the end of each cycle.

Sources: ASTX727-01-B CSR Table 14.1.2.1.1, Table 14.1.2.1.2, Table 14.1.2.1.3

Therapeutic classes of concomitant medications most commonly used were antibacterials (93.8%), analgesics (76.3%), and antimycotics for systemic use (67.5%). Rescue medications were not used in this study.

The Applicant's Position:

Treatment compliance was well controlled/managed at the study centers during the first 2 cycles as all treatments (oral and IV) were administered by study center personnel. Compliance with treatment was adequate based on the median number of 7 cycles (range 1, 29), which is consistent with prior IV decitabine 5-day regimen study: median of 5 cycles (range 1, 17) (Steensma et al 2009).

Dose reduced cycles and treatment cycle delays were permitted for management of cytopenias. Overall, 60% of subjects did not have a dose reduced cycle during the Phase 2 study. For the primary PK endpoint, only subjects who received both treatments (oral and IV) and had adequate PK samples to be able to calculate 5-day AUC for both treatments were included in the primary paired PK analysis. No formal statistical comparisons between treatments (oral and IV) were performed for efficacy endpoints since subjects only received one cycle of IV decitabine by study design.

Concomitant medications used during the study were mainly used as supportive treatment or treatment for other comorbidities so they did not affect the efficacy results.

The Regulatory Authorities' Assessment:

FDA performed a separate analysis of exposure based on months on therapy (instead of number of treatment cycles) (see Table below). Note that this data was obtained using the original cutoff date of 6/5/2018 included in the original NDA submission. Updated efficacy data was not submitted for the Phase 2 trial with the 120-day safety update.

Exposure in Phase 2 (ASTX727-01-B)

	Total (N=80)
Median (range)	6.6 (<0.1-27.9)
0-3	24 (30%)
>3-6	9 (11%)
>6-9	16 (20%)
>9-12	11 (14%)
>12	20 (25%)

Source: FDA analysis

Most patients were treated for more than 6 months and up to a total of almost 28 months. A quarter of patients remained on therapy for more than a year.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) (Phase 2)

Data:

The primary endpoints in the Phase 2 study included PK, PD, and efficacy endpoints. The results of the primary PK endpoint (5-day decitabine AUC) are presented above in Section 6.3.1 (Table 12 and Table 13). The results from the primary PD endpoint (LINE-1 methylation) are also presented above in Section 6.3.2 (Table 9).

The results of the primary efficacy endpoint (response rate) are presented below (Table 24). Overall, 21.3% of treated subjects in this study achieved a CR and 22.5% achieved

mCR. Duration of response in Phase 2 is discussed below in Durability of Response.

Table 24. ASTX727-01 Phase 2: Analysis of Best Response (Efficacy Analysis Set)

Type of Response ^a	Phase 2 Overall (N=80)	
	n (%)	95%CI
Complete Response [CR]	17 (21.3%)	(12.9, 31.8)
Partial Response [PR]	0	
Marrow Complete Response [mCR]	18 (22.5%)	(13.9, 33.2)
Hematologic Improvement [HI]	13 (16.3%)	(8.9, 26.2)
HI-E	8 (10.0%)	(4.4, 18.8)
HI-N	2 (2.5%)	(0.3, 8.7)
HI-P	11 (13.8%)	(7.1, 23.3)
Overall Response [CR+PR+mCR+HI]	48 (60.0%)	(48.4, 70.8)
mCR with HI	6 (7.5%)	(2.8, 15.6)
No Response	32 (40.0%)	(29.2, 51.6)

^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.

Source: ASTX727-01-B CSR Table 14.3.1.1.1

Additional Analyses on the Primary Endpoint

Exploratory subgroup analyses for efficacy endpoints based on demographic (age, sex, and race), disease-specific characteristics (disease status and IPSS risk), and country are presented below. In the tables below, 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.

Table 25. ASTX727-01 Phase 2: Best Response by Age and Sex

Type of Response	Phase 2 (All Treated Subjects), n (%)			
	Age		Sex	
	<65 (N=17)	≥65 (N=63)	Male (N=61)	Female (N=19)
Complete Response (CR)	4 (23.5%)	13 (20.6%)	14 (23.0%)	3 (15.8%)
Partial Response (PR)	0	0	0	0
Marrow CR (mCR)	1 (5.9%)	17 (27.0%)	14 (23.0%)	4 (21.1%)
mCR with HI	0	6 (9.5%)	5 (8.2%)	1 (5.3%)
Hematologic Improvement (HI)	4 (23.5%)	9 (14.3%)	10 (16.4%)	3 (15.8%)
HI-E	2 (11.8%)	6 (9.5%)	6 (9.8%)	2 (10.5%)
HI-N	0	2 (3.2%)	1 (1.6%)	1 (5.3%)
HI-P	4 (23.5%)	7 (11.1%)	8 (13.1%)	3 (15.8%)
Overall Response (CR+PR+mCR+HI)	9 (52.9%)	39 (61.9%)	38 (62.3%)	10 (52.6%)
No Response ^a	8 (47.1%)	24 (38.1%)	23 (37.7%)	9 (47.4%)

^a Includes the categories of Stable Disease, Progressive Disease, and Not Evaluable

Source: Supplemental tables

Table 26. ASTX727-01 Phase 2: Best Response by Country and Race

Type of Response	Phase 2 (All Treated Subjects), n (%)			
	Country		Race [*]	
	US (N=64)	Canada (N=16)	White (N=74)	Non-White (N=6)
Complete Response (CR)	14 (21.9%)	3 (18.8%)	16 (21.6%)	1 (16.7%)
Partial Response (PR)	0	0	0	0
Marrow CR (mCR)	13 (20.3%)	5 (31.3%)	18 (24.3%)	0
mCR with HI	3 (4.7%)	3 (18.8%)	6 (8.1%)	0
Hematologic Improvement (HI)	12 (18.8%)	1 (6.3%)	11 (14.9%)	2 (33.3%)
HI-E	8 (12.5%)	0	8 (10.8%)	0
HI-N	2 (3.1%)	0	2 (2.7%)	0
HI-P	10 (15.6%)	1 (6.3%)	9 (12.2%)	2 (33.3%)
Overall Response (CR+PR+mCR+HI)	39 (60.9%)	9 (56.3%)	45 (60.8%)	3 (50%)
No Response ^a	25 (39.1%)	7 (43.8%)	29 (39.2%)	3 (50%)

^a Includes the categories of Stable Disease, Progressive Disease, and Not Evaluable

Source: Attachment 1-Phase 2 Supplemental Efficacy Table 1 and Table 2

* Indicates source of data is from a supplemental table

Table 27. ASTX727-01 Phase 2: Best Response by Disease Status and IPSS Risk

Type of Response	Phase 2 (All Treated Subjects), n (%)			
	Disease Status		MDS IPSS Risk*	
	MDS Subjects (N=63)	CMML Subjects (N=17)	Int-1 (N=35)	Int-2 and high- risk (N=28)
Complete Response (CR)	12 (19.0%)	5 (29.4%)	7 (20.0%)	5 (17.9%)
Partial Response (PR)	0	0	0	0
Marrow CR (mCR)	12 (19.0%)	6 (35.3%)	4 (11.4%)	8 (28.6%)
mCR with HI	4 (6.3%)	2 (11.8%)	1 (2.9%)	3 (10.7%)
Hematologic Improvement (HI)	11 (17.5%)	2 (11.8%)	8 (22.9%)	3 (10.7%)
HI-E	7 (11.1%)	1 (5.9%)	5 (14.3%)	2 (7.1%)
HI-N	2 (3.2%)	0	2 (5.7%)	0
HI-P	9 (14.3%)	2 (11.8%)	6 (17.1%)	3 (10.7%)
Overall Response (CR+PR+mCR+HI)	35 (55.6%)	13 (76.5%)	19 (54.3%)	16 (57.1%)
No Response ^a	28 (44.4%)	4 (23.5%)	16 (45.7%)	12 (42.9%)

^a Includes the categories of Stable Disease, Progressive Disease and Not Evaluable

Source: Attachment 1-Phase 2 Supplemental Efficacy Table 1 and Table 2

* Indicates source of data is from a supplemental table

The Applicant's Position:

PK: The primary PK objectives of this study were achieved and demonstrated that the dose of 100 mg cedazuridine combined with 35 mg decitabine produced decitabine exposures (5-day AUC) that were highly comparable with 20 mg/m² IV decitabine, regardless of the formulation administered (Table 12 and Table 13). Therefore, the efficacy results presented here include the overall Phase 2 population (N=80). The 80% CI of the oral/IV AUC were within the limits defined in the study analysis plan for each of the Dose Confirmation stage and the FDC stage.

PD: Oral administration of ASTX727 achieved LINE-1 DNA demethylation similar to IV decitabine at 20 mg/m² (Table 9, Figure 3)

Efficacy: The efficacy endpoint of response rate in this study was not compared between treatment sequences (Sequence A and B). There was no clinical reason to conduct such a comparison since all patients in the trial only received ASTX727 except for one cycle of IV decitabine, and all patients received the same doses of cedazuridine and decitabine in ASTX727.

The CR and overall response rates of 21% and 60%, respectively, overall in Phase 2 (Table 24), were consistent with historical results observed with IV decitabine using the same IWG 2006 criteria (CR of 17% and overall response of 51% in [Steensma et al 2009](#)). Additional analysis of response by age, sex, country, race, disease type (MDS and

CMML), and IPSS score showed that ASTX727 was clinically active in all patient subgroups within the limitation of patient numbers in certain subgroups.

The Regulatory Authorities' Assessment:

See Section 6 of the Assessment Aid for FDA's assessment of PK and PD results from the Phase 2 trial.

The acceptable response rate for MDS appropriate for regulatory decision making is overall response rate (ORR), defined as CR+PR responses. ORR served as the basis for approval of IV decitabine. There were no PR responses on the Phase 2 trial of ASTX727, and therefore, only CR responses will be considered for demonstration of clinical benefit. Lesser responses than CR/PR do not convey clear clinical benefit to patients and will not be included in labeling.

We disagree with the Applicant's assessment of the CR rate. FDA adjudicated CR responses based on evaluation of bone marrow and laboratory results in the submission. We could not confirm CR responses in the following subjects:

- Subject USUBJID ASTX727-01- (b) (6): This patient was noted to have a best response of CR on (b) (6). However, the date of the bone marrow assessment for response was listed as (b) (6), the date of the screening marrow assessment. It is not appropriate to use the screening bone marrow for an assessment of response. Furthermore, the ANC on (b) (6) was < 1 Gi/L. At the time of the next marrow assessments (on (b) (6) and (b) (6)), the ANC was still < 1. ANC was normal on (b) (6), but there was no bone marrow evaluation at that time to confirm response. Furthermore, the patient had 0.01 peripheral blasts on their next count check on (b) (6). Then, on (b) (6) (the last assessment on trial), peripheral blasts were back down to 0, but hemoglobin, ANC, and platelets were below the CR thresholds again. Given 1) the last bone marrow assessment several months prior and 2) the lack of a "robust" CR response (Cheson requires responses to last at least 4 weeks), we are unable to confirm CR response in this patient and consider them to be a non-responder.
- Subject USUBJID ASTX727-01 (b) (6): This patient was noted to have a best response of CR on (b) (6). However, the date of the bone marrow assessment was 3 months earlier on (b) (6), at which time there was erythroid and myeloid dysplasia on the marrow and peripheral count recovery was not achieved. Furthermore, the patient only achieved peripheral count recovery on one date ((b) (6)). All subsequent count checks were below the required thresholds for CR response, up until the next marrow assessment on (b) (6), which showed 9% blasts. The marrow on (b) (6) showed 2% blasts, but with persistent dysplasia

and lack of peripheral blood count recovery. In addition to the bone marrow assessment months before the count recovery, the peripheral blood response did not last at least 4 weeks (per Cheson guidelines). Therefore, we are unable to confirm CR response in this patient and consider them to be a non-responder.

- Subject USUBJID ASTX727-01 (b) (6) This patient was noted to have a best response of CR on (b) (6). However, the date of the bone marrow assessment was a year earlier on (b) (6), at which time the patient did not have peripheral count recovery. The patient did not have any subsequent bone marrow assessments on the trial. The patient only had peripheral count recovery on (b) (6), with no further count checks meeting all CR criteria. No CR response was confirmed due to the yearlong interval between the last marrow assessment and peripheral blood CR criteria and lack of maintenance of peripheral count recovery per Cheson guidelines. Therefore, we consider this patient to be a non-responder.

Taking out the 3 patients above, we calculate the ORR (CR+PR) rate = CR rate to be 14/80 (18%; 95% CI 10-28%) for the overall population. This remains similar to the ORR in the USPI for IV decitabine, which was 17% for the randomized trial and 16% for the single arm trial (CR rates of 9% and 15%, respectively).

The Applicant confirmed FDA's analysis of the CR results and provided updated efficacy data including the FDA-adjudicated CR responses with the 120-day safety update.

Of note, the protocol used IWG 2006 MDS Response Criteria, which differs from that used in the IV decitabine prescribing information (IWG 2000 MDS Response Criteria) (Cheson, Bennett et al. 2000). The major differences are that the IWG 2000 criteria required an ANC of 1.5 Gi/L or more with no dysplasia for CR responses, whereas the 2006 criteria only required an ANC of 1 Gi/L or more with allowance of persistent dysplasia. Therefore, the CR responses reported in the decitabine USPI of 9-15% would likely be higher using the updated response criteria.

The following subgroup analyses were performed in patients with FDA-adjudicated CR

responses:

- CR rate < 65 years 3/17 (18%) and >= 65 years 11/63 (17%)
- CR rate females 2/19 (11%) and males 12/61 (20%)
- CR rate Canada 2/16 (13%) and US 12/64 (19%)
- CR rate White 14/74 (19%) and Non-White 0/6 (0%)
- CR rate MDS 9/63 (14%) and CMML 5/17 (29%)
- CR rate Int-1 IPSS 5/35 (14%) and Int-2 and high-risk 4/28 (14%)
- CR rate Int-2 2/19 (11%) and high-risk 2/9 (22%)

Overall, the responses seen on Phase 2 mirror that observed with IV decitabine. Interpretation of the subgroup analyses is limited by the small sample sizes.

Data Quality and Integrity (Phase 2)

Data:

The Astex Quality Assurance group audited 7 study centers, with a total of 8 investigator audits performed from the 15 centers that randomized subjects (one center was audited twice). No critical audit findings were identified. Appropriate corrective and preventive actions were taken for all audit findings.

The data in this submission are in Electronic Common Document (eCTD) format, in accordance with FDA guidance on electronic submission. The data sets are well documented and include definition files. The data sets, clinical study reports, summary of clinical safety, and summary of clinical efficacy are located in Modules 5 and 2 of the eCTD. \\CDSesub1\evsprod\NDA\annnnn.

The Applicant's Position:

No data quality or data integrity issues were identified. Astex believes the data and datasets required for the Agency to be able to conduct their analysis have been provided in the submission.

The Regulatory Authorities' Assessment:

No issues were identified with the data quality or integrity from the Phase 2 study which could affect the efficacy results, aside from the issues with the response assessments noted above. The submitted datasets are generally consistent, and variables are clearly labeled and/or explained.

We agree with the Applicant's position from a statistical point of view.

Efficacy Results – Secondary and other relevant endpoints (Phase 2)

Secondary efficacy data from Phase 2 are summarized below.

Transfusion Independence (Phase 2)

Transfusion independence post-treatment was defined as no transfusions for ≥56 consecutive days.

Overall, of the 41 patients who were dependent on RBC or platelet transfusions at baseline, 48.8% were RBC and platelet transfusion independent post-baseline.

Of the 38 subjects who were RBC transfusion dependent at baseline, 50% were RBC transfusion independent post-baseline. Of the 12 subjects who were platelet transfusion dependent at baseline, 50% were platelet transfusion independent post-baseline. Details of transfusion independence overall and by response category are summarized in Table 28.

Table 28. ASTX727-01 Phase 2: Transfusion Dependency by Response

Best Overall Response	Baseline Transfusion	Post-Baseline Transfusion		
		Dependent n (%)	Independent n (%)	Not evaluated n (%)
Platelets				
CR (N=17)	Dependent (N=2)	0	2 (100)	0
	Independent (N=15)	0	15 (100)	0
mCR (N=18)	Dependent (N=3)	0	3 (100)	0
	Independent (N=15)	1 (6.7)	14 (93.3)	0
HI (N=13)	Dependent (N=1)	0	1 (100)	0
	Independent (N=12)	1 (8.3)	11 (91.7)	0
NR (N=32)	Dependent (N=6)	6 (100)	0	0
	Independent (N=26)	13 (50)	13 (50)	0
Overall (N=80)	Dependent (N=12)	6 (50)	6 (50)	0
	Independent (N=68)	15 (22.1)	53 (77.9)	0
Red blood cells				
CR (N=17)	Dependent (N=6)	1 (16.7)	5 (83.3)	0
	Independent (N=11)	0	11 (100)	0
mCR (N=18)	Dependent (N=11)	4 (36.4)	7 (63.6)	0
	Independent (N=7)	2 (28.6)	5 (71.4)	0
HI (N=13)	Dependent (N=6)	2 (33.3)	4 (66.7)	0
	Independent (N=7)	0	7 (100)	0
NR (N=32)	Dependent (N=15)	12 (80)	3 (20)	0
	Independent (N=17)	11 (64.7)	6 (35.3)	0

Overall (N=80)	Dependent (N=38)	19 (50)	19 (50)	0
	Independent (N=42)	13 (30.9)	29 (69.1)	0
Any platelet or red blood cell transfusion^a				
CR (N=17)	Dependent (N= 6)	1 (16.7)	5 (83.3)	0
	Independent (N= 11)	0	11 (100)	0
mCR (N=18)	Dependent (N=12)	4 (33.3)	8 (66.7)	0
	Independent (N=6)	2 (33.3)	4 (66.7)	0
HI (N=13)	Dependent (N=6)	2 (33.3)	4 (66.7)	0
	Independent (N=7)	1 (14.3)	6 (85.7)	0
NR (N=32)	Dependent (N=17)	14 (82.4)	3 (17.6)	0
	Independent (N=15)	11 (73.3)	4 (26.7)	0
Overall (N=80)	Dependent (N=41)	21 (51.2)	20 (48.8)	0
	Independent (N=39)	14 (35.9)	25 (64.1)	0

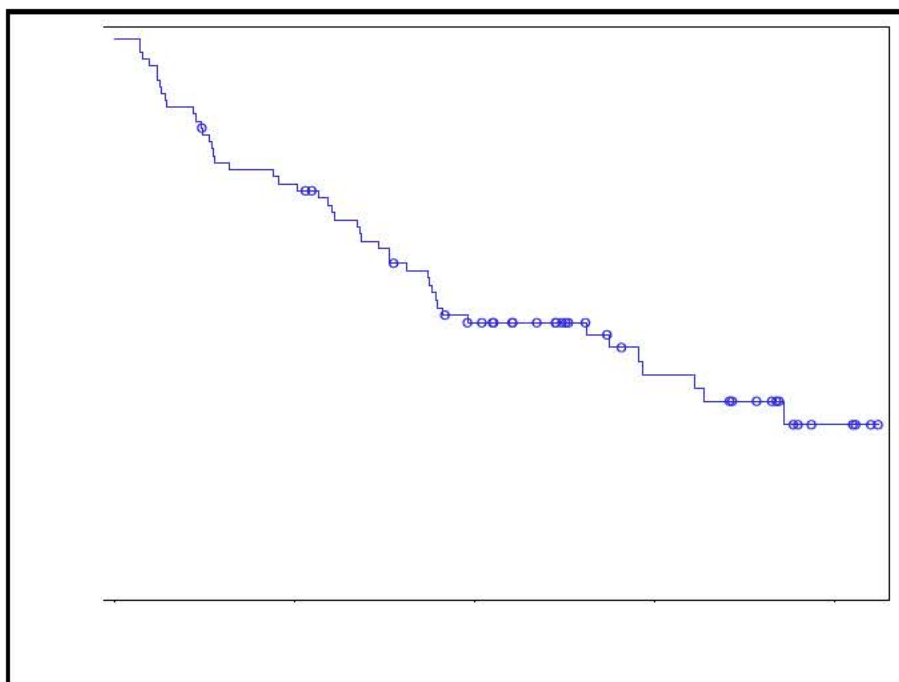
^a A patient was considered transfusion independent if the subject was both RBC and platelet transfusion free post-treatment for ≥ 56 consecutive days.

Almost all patients with CR (83% to 100%) were also RBC and platelet transfusion independent post-treatment regardless of their status at baseline. About two thirds or more of patients with mCR or HI (66.7% to 85.7%) were also RBC and platelet transfusion independent post-treatment regardless of their baseline status.

Time to AML or Death (Phase 2)

Of the 80 treated subjects, 58.8% reached the event (AML or death), and data were censored for the remaining 41.3% of subjects. Median time to AML or death was 364 days. Figure 20 shows a plot of the Kaplan-Meier analysis.

Figure 20. ASTX727-01 Phase 2: Kaplan-Meier Estimate for Time to AML or Death

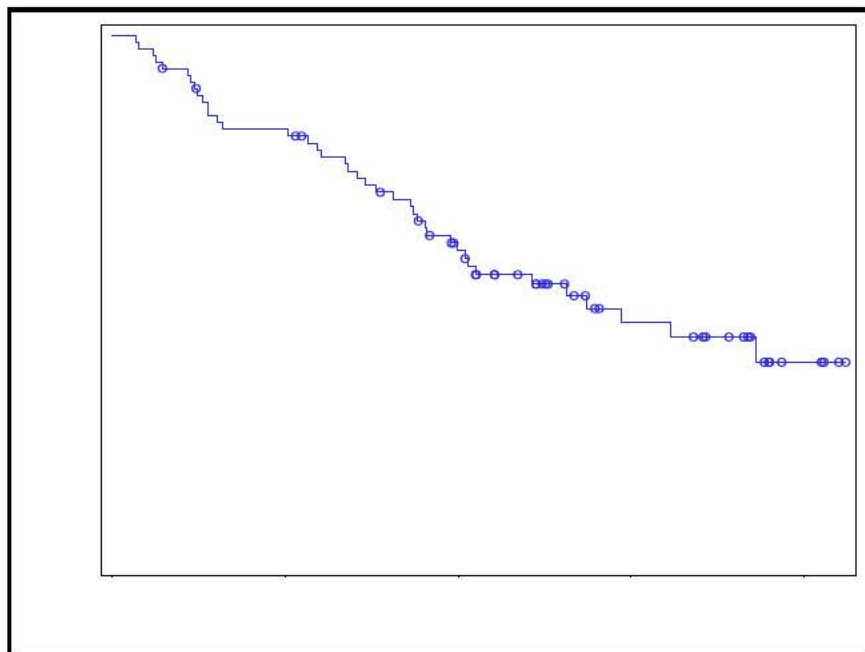


Source: Attachment 1-Phase 2 Supplemental Efficacy Figure 2

Overall Survival (Phase 2)

Of the 80 treated subjects, 50% were alive as of the data cutoff date (05 June 2018), and 50% had died. Median survival time was 549 days (18.3 months). Figure 21 shows a plot of the Kaplan-Meier analysis.

Figure 21. ASTX727-01 Phase 2: Kaplan-Meier Estimate for Overall Survival



Source: SCE Attachment 1-Phase 2 Supplemental Efficacy Figure 1

The Applicant's Position:

[Redacted content]

(b) (4)

The Regulatory Authorities' Assessment:

We agree with the Applicant's assessment of conversion from transfusion dependence to transfusion independence and maintenance of transfusion independence for at least 56 days post-baseline for the overall population. However, we disagree with the Applicant's assessment of RBC and platelet transfusion independence by response. We repeated the analyses of transfusion independence based on FDA-adjudicated CR responses (see Table below).

Of note, results from time to event variables in a single arm study are not interpretable.

ASTX727-01 Phase 2: Transfusion Dependency by FDA-Adjudicated Response

Best Overall Response	Baseline Transfusion	Post-Baseline Transfusion		
		Dependent n (%)	Independent n (%)	Not evaluated n (%)
Platelets				
CR (N=14)	Dependent (N=2)	0	2(100)	0
	Independent (N=12)	0	12(100)	0
NR (N=66)	Dependent (N=10)	6 (60)	4 (40)	0
	Independent (N=56)	15 (27)	41 (73)	0
Overall (N=80)	Dependent (N=12)	6 (50)	6 (50)	0
	Independent (N=68)	15 (22)	53 (78)	0
Red blood cells				
CR (N=14)	Dependent (N=4)	1 (25)	3 (75)	0
	Independent (N=10)	0	10 (100)	0
NR (N=66)	Dependent (N=34)	18 (53)	16 (47)	0
	Independent (N=32)	13 (41)	19 (59)	0
Overall (N=80)	Dependent (N=38)	19 (50)	19 (50)	0
	Independent (N=42)	13 (31)	29 (69)	0
Any platelet or red blood cell transfusion*				
CR (N=14)	Dependent (N=4)	1 (25)	3 (75)	0
	Independent (N= 10)	0	10 (100)	0
NR (N=66)	Dependent (N=37)	20 (54)	17 (46)	0
	Independent (N=29)	14 (48)	15 (52)	0
Overall (N=80)	Dependent (N=41)	21 (51)	20 (49)	0
	Independent (N=39)	14 (36)	25 (64)	0

Source: FDA analysis

* A patient was considered transfusion independent if the subject was both RBC and platelet transfusion free post-treatment for ≥56 consecutive days.

Dose/Dose Response (Phase 1-2)

Data:

A fixed dose was used in the Phase 2 study; assessment of response by dose was not evaluated in that study. Study ASTX727-01 also had a dose-escalation stage that included 44 subjects with MDS or CMML who were treated with various doses of cedazuridine/decitabine (in mg): 40/20, 60/20, 100/20, 100/40, and 100/30 (ASTX727-01-A CSR). The number of patients were relatively small to assess dose/response as the study was not designed with that objective. However, responses were observed in each cohort. It is worth noting that in the Phase 1 study, a larger proportion of patients had

prior HMA treatment mostly azacitidine without limitation of number of cycles (46%) compared to only 9% of patients with prior one cycle HMA in Phase 2. The Phase 1 study had the longest follow-up (minimum 18 months, median 24 months) and responses were observed in all doses (Table 29).

Table 29. ASTX727-01 Phase 1: Summary of Key Efficacy Results

Category	Cedazuridine/Decitabine Dose					Dose Escalation
	40/20 (N=7)	60/20 (N=6)	100/20 (N=6)	100/40 (N=6)	100/30 (N=19)	Total (N=44)
Best Response:						
ORR	4 (57.1%)	3 (50.0%)	2 (33.3%)	1 (16.7%)	3 (15.8%)	13 (29.5%)
CR+PR+mCR	1 (14.3%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	2 (10.5%)	7 (15.9%)
CR	1 (14.3%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	0	5 (11.4%)
mCR	0	0	0	0	2 (10.5%)	2 (4.5%)
HI as Best Response	3 (42.9%)	1 (16.7%)	1 (16.7%)	0	1 (5.3%)	6 (13.6%)
Any HI	4 (57.1%)	3 (50.0%)	2 (33.3%)	0	3 (15.8%)	12 (27.3%)
HI-E	1 (14.3%)	2 (33.3%)	2 (33.3%)	0	3 (15.8%)	8 (18.2%)
HI-N	0	1 (16.7%)	0	0	0	1 (2.3%)
HI-P	3 (42.9%)	1 (16.7%)	1 (16.7%)	0	3 (15.8%)	8 (18.2%)
No Response	3 (42.9%)	3 (50.0%)	4 (66.7%)	5 (83.3%)	16 (84.2%)	31 (70.5%)
Median (range) duration of response, days						
CR	546.00 (546.0, 546.0)	364.00 (56.0, 672.0)	470.00 (470.0, 470.0)	29.00 (29.0, 29.0)	NA	470.00 (29.0, 672.0)
mCR	--	--	--	--	390.50 (332.0, 449.0)	390.50 (332.0, 449.0)

ORR = Overall Response Rate (CR+PR+mCR+HI)

Source: ASTX727-01-A CSR Tables 14.3.1.1, Table 14.3.1.2,

The Applicant's Position:

The ASTX727 clinical program was designed to support PK bridging of ASTX727 at the selected doses of 100 mg cedazuridine and 35 mg decitabine with IV decitabine dose of 20 mg/m² in a 5-day regimen. However, data from Phase 1 supports clinical activity at a broad range of doses (cedazuridine 40 to 100 mg) and decitabine (20 to 40 mg) within the limitation of the small number of patients at each dose level and the large percentage of patients with prior HMA treatment in the Phase 1 study.

The Regulatory Authorities' Assessment:

We agree with the Applicant's overall assessment. FDA did not independently adjudicate responses on the Phase 1 trial given the exploratory nature of the efficacy findings on this trial.

Durability of Response (Phase 2)

Data:

Duration of response was analyzed based on the subjects who achieved a CR or mCR

using both K-M method and simple descriptive statistics. In the K-M method, subjects' data were censored on the last date of disease assessment in the absence of progressive disease.

The median duration of response from the K-M method was 399 days for subjects with a best response of CR (IQR 195, 413) and was 397 days (IQR 170, 560) for subjects with a best response of mCR.

Using descriptive statistics, the median (min, max) duration of response was 286 days (range 32, 553) for subjects with a best response of CR and was 143 days (range 49, 662) for subjects with a best response of mCR.

Table 30. ASTX727-01 Phase 2: Duration of Response

	Phase 2 ASTX727-01-B (N=80)
Complete Response	
Number of Subjects, n (%)	
Censored	5 (29.4%)
Event	12 (70.6%)
K-M Estimate (Days, (95% CI))	
25 th percentile	195.0 (112.0, 309.0)
Median	399.0 (195.0, 413.0)
75 th percentile	413.0 (309.0, 553.0)
Simple Descriptive Statistics (CR patients only N=17)	
Median	286
Range (min, max)	32, 553
Marrow Complete Response	
Number of Subjects, n (%)	
Censored	11 (61.1%)
Event	7 (38.9%)
K-M Estimate (Days, (95% CI))	
25 th percentile	170.0 (56.0, 397.0)
Median	397.0 (139.0, NE)
75 th percentile	560.0 (397.0, NE)
Simple Descriptive Statistics (mCR patients only N=18)	
Median	143
Range (min, max)	49,662

CI=confidence interval; NE=not estimable; K-M=Kaplan-Meier.

Sources: ASTX727-01-B CSR Table 14.3.2.1, Table 14.3.2.2

* Indicates source of data is from a supplemental table

The Applicant's Position:

As expected with IV decitabine and HMA treatment in general, responses are often

durable. Median duration of CR was 9.5 or 13 months depending on the method used to calculate duration of response. This duration is consistent with previously reported median duration of response of 10 months with IV decitabine 5-day regimen (Steensma et al 2009).

The Regulatory Authorities' Assessment:

In addition to the three CR responses that FDA could not verify above, FDA determined several discrepancies in the ADEFF.xpt dataset with regards to the date of best response, which will affect calculations of duration of response and time to response. These discrepancies were noted in the following patients:

- Subject USUBJID ASTX727-01- (b) (6): This subject was noted to have a best response of CR on (b) (6). However, the date of the bone marrow assessment for response was listed as (b) (6), the date of the screening marrow assessment. It is not appropriate to use the screening bone marrow for an assessment of response. We note that this patient had 3% blasts on their Cycle 3 Day 1 marrow on (b) (6) (the next marrow). Therefore, the date of achievement of CR should be (b) (6).
- Subject USUBJID ASTX727-01- (b) (6): This patient was noted to have a best response of CR on (b) (6). However, the date of the bone marrow assessment for response was listed as (b) (6), the date of the screening marrow assessment. It is not appropriate to use the screening bone marrow for an assessment of response. We note that this patient had 2% blasts on their next marrow on (b) (6). The patient met all CR criteria at that time. Therefore, the date of achievement of CR should be (b) (6).
- Subject USUBJID ASTX727-01- (b) (6): This patient was noted to have a best response of CR on (b) (6). However, the date of the bone marrow assessment for response was listed as (b) (6), the date of the screening marrow assessment. It is not appropriate to use the screening bone marrow for an assessment of response. Furthermore, the patient had 8% bone marrow blasts at that time. We note that this patient had 1% blasts on their next marrow on (b) (6), but hemoglobin was 10.6 at the time. Count recovery did not occur until (b) (6). Therefore, the date of achievement of CR should be (b) (6).
- Subject USUBJID ASTX727-01- (b) (6): This patient is noted to have a best response of CR on (b) (6). However, the date of the bone marrow assessment for response was listed as (b) (6), which was the screening bone marrow. It is not appropriate to use a screening bone marrow for assessment of response. We note that this patient had 2% blasts on their next marrow on (b) (6). The patient met CR criteria at that time. Therefore, the date of achievement of CR should be (b) (6).

(b) (6)

The Applicant submitted an updated ADEFF.xpt file with the 120 day safety update, which included FDA's adjudicated dates of response in the four patients noted above. Using the updated efficacy data, we determined a median duration of CR of 265 days (range 35 – 553 days). This is equivalent to 8.7 months (range 1.1 – 18.2 months).

Persistence of Effect (Phase 2)

Data:

Median duration of response for Phase 2 subjects with best response of CR was >1 year (399 days) and was 397 days for subjects with best response of mCR. Twelve subjects (15%) proceeded to transplant (bone marrow/stem cell transplant). Median overall survival time (as of the data cutoff date) was 549 days (18.3 months).

The Applicant's Position:

As with most anticancer therapies, loss of therapeutic effect eventually occurs as resistance to the drug's mechanism of action eventually develops; however, responses to ASTX727 were durable, as noted above.

The Regulatory Authorities' Assessment:

As noted above, we determined that median duration of response for phase 2 subjects with best response of CR was 8.7 months (range 1.1 – 18.2 months).

We confirm that 12 (15%) of patients proceeded to transplant and that median OS was 549 days.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints (Phase 2)

Data:

There were no study endpoints evaluating patient-reported outcomes in this study.

The Applicant's Position:

Not applicable

The Regulatory Authorities' Assessment:

We agree with the Applicant's position.

Additional Analyses Conducted on the Individual Trial (Phase 2)

Data:

The median (range) time to response for CR was 147 days (29-571) and was 64 days

(49-218) for mCR; mCR was therefore achieved earlier but reaching a complete response requires multiple cycles (approximately 4 to 6 cycles consistent with median time to CR of 147 days).

Exploratory analysis for the presence of mutations in 7 relevant genes (CBL, IDH2, ASXL1, DNMT3A, TP53, RUNX1, and SF3B1) in the baseline bone marrow of 33 subjects was performed, and the presence of mutations or suspicious variants were correlated with response. Of the 14 subjects who had the RUNX1 mutation, 6 (42.9%) had a best response of CR. None of the mutations for the remaining 6 genes was correlated with response.

A K-M analysis of OS by gene mutation status for the 3 genes (RUNX1, ASXL1, and TP53) with the highest number of subjects with identified mutations was performed. No definitive conclusions can be made due to the small sample size, although median survival time appeared to be lower for the mutant vs. wild type for the 3 genes shown (particularly for the TP53 mutation).

The Applicant's Position:

Achieving a best response of CR usually requires 4 to 6 cycles (median time to CR 147 days). The exploratory analysis of response and survival by gene mutation is inconclusive due the small number of patients with available mutation data in the study. It does seem to confirm the known poor survival prognosis of TP53 mutation.

The Regulatory Authorities' Assessment:

Using the updated response files submitted with the 120-day safety update (correcting the dates of CR response per FDA adjudication), the median time to CR was unchanged at 147 days (range 51 - 303 days). This is equivalent to 4.8 months (range 1.7 - 10.0 months).

We performed an analysis of FDA-adjudicated CR responses in the 33 patients with available genomic data at baseline:

- RUNX1 (n=14): CR 5 (36%)
- ASXL1 (n=13): CR 2 (15%)
- TP53 (n=5): CR 0 (0%)
- SF3B1 (n=2): CR 0 (0%)
- DNMT3A (n=1): CR 0 (0%)
- IDH2 (n=1): CR 0 (0%)

These analyses are considered exploratory only. The small sample size of the subgroups explored limits the statistical power of such inferences.

8.1.3. Phase 3 Study ASTX727-02

Trial Design

The Applicant's Description:

Phase 3 Study ASTX727-02 (CSR ASTX727-02) design was identical to Phase 2, and was an open-label, randomized, 2-cycle, 2-sequence crossover study followed by a single-arm continuation of treatment to assess the PK, PD, safety, and efficacy of the ASTX727 FDC tablet (100 mg cedazuridine and 35 mg decitabine) Daily×5 and IV decitabine 20 mg/m² Daily×5. At least 118 subjects were planned to be randomized. Treatment continued until disease progression, unacceptable toxicity, treatment discontinuation for other reasons, or withdrawal of consent. The study schema is the same as Phase 2 (Figure 19), all patients received ASTX727 as FDC tablet.

Trial Location (Phase 3)

Phase 3 Study ASTX727-02 was conducted at 37 centers in North America (30 centers in the United States and 7 centers in Canada).

Choice of Control Group (Phase 3)

The purpose of this study was to establish the total 5-day cycle decitabine AUC equivalence of ASTX727 and IV decitabine in adult patients with MDS or CMML.

Intravenous decitabine (20 mg/m² once daily for 5 days) is an approved therapy for MDS/CMML ([Dacogen USPI 2019](#)) and was therefore the appropriate active comparator.

Diagnostic Criteria (Phase 3)

Phase 3 Study ASTX727-02 enrolled adult patients with MDS or CMML who had no more than 1 prior cycle of an HMA. Eligibility criteria were similar to Phase 2 with few exceptions. Eligible MDS patients were eligible by either FAB or IPSS criteria to match the Dacogen US label. ECOG PS 2 and other poor general condition criteria (recent hospitalization for infection, proliferative disease, or life expectancy <12 weeks) were excluded in Phase 3 in an effort to minimize the number of patients who may not be able to receive 2 complete cycles of treatment with sufficient PK assessment to be evaluable for the primary endpoint of AUC equivalence.

Key inclusion criteria:

- Men or women ≥ 18 years who are candidates to receive IV decitabine, i.e., subjects with MDS previously treated or untreated with de novo or secondary MDS, including all French-American-British 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.
- Eastern Cooperative Oncology Group performance status of 0 to 1.
- Adequate organ function defined as follows:
 - Hepatic: Total or direct bilirubin $\leq 2 \times$ ULN; AST/SGOT and ALT/SGPT $\leq 2.5 \times$ ULN.
 - Renal: serum creatinine $\leq 1.5 \times$ ULN or calculated creatinine clearance or glomerular filtration rate >50 mL/min/1.73 m² for subjects with creatinine levels above institutional normal.
- Life expectancy of at least 3 months.

Key exclusion criteria:

- Prior treatment with more than 1 cycle of azacitidine or decitabine.
- Hospitalization for more than 2 days for documented febrile neutropenia, pneumonia, sepsis, or systemic infection in the 30 days before screening.
- 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 AEs from previous treatment.
- Cytotoxic chemotherapy or prior azacitidine or decitabine within 4 weeks of first dose of study treatment.
- Concurrent MDS therapies, including lenalidomide, erythropoietin, cyclosporine/tacrolimus, granulocyte-colony stimulating factor, 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.)
- Rapidly progressive or highly proliferative disease (total white blood cell count of $>15 \times 10^9$ /L) or other criteria that render the subject at high risk of requiring intensive cytotoxic chemotherapy within the next 3 months.

Other than the relatively small differences between Phase 2 and 3 eligibility, the diagnostic criteria and eligibility criteria were appropriate for assessment of the treatment effect.

Dose Selection (Phase 3)

Dose selection for Phase 3 was the same dose tested in Phase 2 and discussed above in Section 8.1.1.

Study Treatments (Phase 3)

- Test Product: ASTX727 FDC tablet (100 mg cedazuridine and 35 mg decitabine).
 - Dose: one ASTX727 tablet administered orally once daily on Days 1 through 5 (Daily×5) in 28-day cycles.
- Reference Product (IV decitabine 5-day regimen).
 - Dose: 20 mg/m² continuous 1-hour IV infusion Daily×5 in Cycle 1 or 2.

Study drugs (ASTX727 FDC tablets and IV decitabine) were administered by study center personnel in Cycles 1 and 2. The actual doses ASTX727 and IV decitabine administered were recorded in the CRF.

In Cycles ≥3, ASTX727 was administered at the study center on Day 1 of each cycle, and subjects were given the remaining 4 ASTX727 tablets in a 5-count bottle for home dosing; subjects were also given IRB approved home dosing logs (diaries) to record home dosing of ASTX727.

Assignment to Treatment (Phase 3)

Individual subject treatment assignments were determined through a computer-generated randomization schedule and accessed through an interactive web response system. No stratification was performed. Subjects were randomized in a 1:1 ratio to one of the following treatment sequences:

- Sequence A: ASTX727 tablet in Cycle 1 and then IV decitabine in Cycle 2, or
- Sequence B: IV decitabine in Cycle 1 and then ASTX727 tablet in Cycle 2.

The randomization and treatment assignment for each subject are provided in the submission (ASTX727-02 CSR, Appendix 16.1.7).

Blinding (Phase 3)

This is an open-label study.

Dose Modification / Dose Discontinuation (Phase 3)

Guidelines for adjusting or withholding study treatment are detailed in the protocol for

ASTX727-02 (Section 7.6). In summary, 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 from drug-related myelosuppression.

Administrative Structure (Phase 3)

The Applicant was responsible for all aspects of the study, including oversight of the contract research organizations overseeing study management activities in the US and Canada.

An Independent Review Committee composed of 3 disease experts (who did not participate as investigators in the study) was established for independent assessment of clinical response.

Procedures and Schedule (Phase 3)

The schedule of events for the study is shown below in Table 31.

NDA Multi-disciplinary Review and Evaluation
 NDA 212576, Original
 INQOVI (decitabine and cedazuridine)

Table 31. ASTX727-02 Phase 3: Schedule of Events

Cycle (28 Days)		1						2						≥3						Trtmt Disc.	30-Day F/U
Cycle Day	Screening	1	2	3	4	5	8, 15, 22	1	2	3	4	5	8, 15, 22	1	2	3	4	5	15		
Study treatment administration		x	x	x	x	x		x	x	x	x	x		x	x	x	x	x			
Procedures	Screening																				
Informed consent; IPSS risk category, eligibility confirmation	x																				
Medical history	x																				
Randomization	x																				
Physical exam/(symptom-directed PE)	x	(x)						(x)						(x)					x	(x)	
Height	x																				
Weight / BSA calculation	x	x						x						x							
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x						x	
ECOG status	x							x						x						x	x
12-lead ECG	x			x						x											
ECHO or MUGA	x																				
Concomitant treatments/adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x						x	x
Transfusion requirements	x	x						x						x						x	x
Pharmacokinetic assessments																					
Laboratory Assessments																					
Hematology	x	(x)					x	x					x	x					x	x	
Chemistry	x							x						x						x	
Urinalysis	x							x						x						x	
Serum or urine pregnancy test	x																			x	
%LINE-1 demethylation (blood)		x					x	x					x	x							
Bone marrow aspirate/biopsy	x													x							

NDA Multi-disciplinary Review and Evaluation
NDA 212576, Original
INQOVI (decitabine and cedazuridine)

Trtmt Disc.=treatment discontinuation; F/U=follow up. Bone marrow (BM) assessment was done at baseline and at the beginning of every other cycle in Cycles 3, 5, and 7 then every 3 months in the first year and every 6 months thereafter unless clinically indicated earlier.

Source: Adapted from ASTX727-02 Phase 3 CSR Table 4

Dietary Restrictions/Instructions (Phase 3)

The ASTX727 tablet was to be taken at the same time on each dosing day, with water. Subjects were instructed to fast from food and non-clear liquids for at least 2 hours before and 2 hours after dosing. No dietary restrictions were in place when subjects received IV decitabine.

Concurrent Medications (Phase 3)

Antibiotics were permitted to prevent or manage febrile neutropenia. Hematopoietic growth factors were not to have been routinely used. However, short-term use of G-CSF for febrile neutropenia was permitted.

Drugs that alter gastric pH were allowed but subjects instructed not to take them within ± 4 hours of ASTX727 administration. Other prohibited concomitant therapies were chemotherapy, immunotherapy, or any experimental therapy. Other nucleosides or drugs that are metabolized by CDA were not to have been administered on ASTX727 dosing days.

Treatment Compliance (Phase 3)

Study treatment was administered by study center personnel in Cycles 1 and 2. In Cycles ≥ 3 , ASTX727 was administered at the study center on Day 1 of each cycle, and subjects were given the remaining 4 ASTX727 tablets for home dosing; subjects were also given IRB-approved home dosing diaries to record home dosing of ASTX727. At their next visit, subjects returned the home dosing log and any unused tablets (if a dose reduction occurred) to the study center and study staff entered dosing information into the CRF.

Rescue Medications (Phase 3)

No rescue medications per se were planned in the trial apart from the permitted concomitant medications and supportive treatments described above.

Subject Completion, Discontinuation, or Withdrawal (Phase 3)

Subjects were considered to have completed the study when they were withdrawn from the study for any of the following reasons:

- Death.
- Withdrawal of consent.
- Lost to follow up.

Subjects lost to follow up were included in statistical analyses to the point of the data cut-off date for the CSR.

Regulatory Authorities' Assessment:

We agree with the Applicant's description of the trial design of the Phase 3 Study (ASTX727-02).

Study Endpoints (Phase 3)

The Applicant's Description:

Primary Endpoint (Phase 3)

Comparison between ASTX727 and IV decitabine:

- Total 5-day AUC exposures of decitabine after treatment with ASTX727 versus IV decitabine (based on AUC₀₋₂₄).

Secondary Endpoints

- Safety as assessed by AEs, concomitant medications, physical examination, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs, ECOG performance status, and electrocardiogram.
- Maximum %LINE-1 demethylation.
- Additional secondary PK parameters.
- Clinical response (CR, mCR, PR, and HI) based on International Working Group (IWG) 2006 MDS response criteria.
- Red blood cell (RBC) or platelet transfusion independence (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 $\geq 20\%$, or death from any cause.
- Overall survival, defined as the number of days from the date of randomization to the date of death from any cause.

The primary endpoint for the study was based on agreement with FDA at EOP2 meeting on using a PK bridging approach to primarily establish efficacy. The 5-day total cycle AUC₀₋₂₄ was agreed upon during the pharmacometric analysis plan assessment by FDA. PD assessments of DNA methylation by LINE-1 assay is appropriate for quantitative

comparison of treatment effect on global DNA methylation. Safety assessment from both the randomized first 2 cycles with IV decitabine and long-term from continued ASTX727 treatment is appropriate to assess ASTX727 safety. Finally, efficacy endpoints were secondary in the trial to assess consistency with efficacy previously reported with IV decitabine. At the time of the data cutoff for the CSR, the Phase 3 trial did not have sufficient follow-up (minimum 2 months, median 5 months) to assess response in all treated patients or to assess long-term efficacy such as duration of response, time to AML, or overall survival. These endpoints will be later updated after a minimum follow-up of 12 months.

Efficacy Assessments (Phase 3)

Efficacy assessments were almost identical to assessments previously summarized in Phase 2 (Section 8.1.1 above).

Evaluation of response was based on IWG 2006 MDS Response Criteria ([Cheson et al 2006](#)) like in Phase 2; however, response evaluation in Phase 3 was independently conducted by a panel of 3 external expert medical reviewers who did not participate as investigators in the study based on database listings of hematology results (peripheral blood and bone marrow) and transfusion data.

Additional details regarding assessment of clinical response is provided in the Independent Clinical Response Assessors Charter (ASTX727-02 CSR, Appendix 16.1.13.7).

The Regulatory Authorities' Assessment:

We agree with the Applicant's description of the study endpoints of the Phase 3 Study (ASTX727-02).

Statistical Analysis Plan and Amendments (Phase 3)

The Applicant's Description:

The analyses for this Phase 3 study are described in two different documents, the Pharmacometric Analysis Plan (06 December 2018) and the Statistical Analysis Plan (27 February 2019). The Pharmacometric Analysis Plan addressed the PK analyses of plasma decitabine, cedazuridine and cedazuridine-epimer following single and multiple once daily oral doses of decitabine and cedazuridine. The planned analyses of the primary endpoint, total 5-day AUC₀₋₂₄ exposures of decitabine after treatment with ASTX727 versus IV decitabine, were described in the PAP as well as all planned analyses of the secondary PK parameters. The Statistical Analysis Plan (SAP) described the planned analyses of all other secondary endpoints.

Sample Size

The sample size calculation was based on preliminary analysis of 5-day AUC in study ASTX727-01, which showed an estimate of intra-subject CV of 0.5. A conservative CV value of 0.55 was chosen to calculate the sample size to include in the 2 one-sided equivalence tests for the geometric mean ratio of ASTX727 5-day AUC relative to IV decitabine 5-day AUC 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% CI equivalence limits for the ratio of geometric means are 0.8 and 1.25. It was assumed that 10% of subjects may not be evaluable in for the primary PK analysis.

Analysis Populations

Two Pharmacokinetic Analysis Populations were used for analysis of PK data and were defined as follows:

The **Primary Endpoint PK Analysis Population** was used for calculating decitabine 5-day (total cycle) AUC₀₋₂₄ and equivalence statistical analyses. This analysis set included decitabine daily AUC₀₋₂₄ from 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 (i.e., 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 AUC₀₋₂₄ 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 AUC₀₋₂₄. 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.

The **Overall PK Analysis Population** included additional subjects who may not have been included in the Primary Endpoint PK Analysis Set and who:

- Received any amount of study treatment (including subjects who received only 1 cycle of treatment).
- Complied with the protocol sufficiently to ensure PK samples were collected as intended.
- Provided sufficient samples to measure available plasma concentrations for decitabine, cedazuridine, and cedazuridine-epimer.

The Overall PK Analysis Population was used for calculating PK parameters, including decitabine daily AUC₀₋₂₄, which was used to derive the primary PK endpoint of

decitabine cumulative 5-day AUC_{0-24} exposures and other secondary PK parameters for decitabine, cedazuridine, and cedazuridine-epimer.

Two additional analysis populations were used for sensitivity analyses of the PK endpoints:

Evaluable unpaired PK population: the overall sensitivity population, defined as the subjects who contributed PK data, excluding subjects whose samples had integrity issues.

Paired sensitivity population: the subjects in the paired analysis, excluding subjects who received only 1 cycle of treatment.

The following Analysis Sets were used for analysis of all non-PK secondary endpoints:

The **Efficacy Analysis Set** includes data from all subjects who received any amount of study treatment. All data was included, and no subjects excluded because of protocol deviations. Subjects were analyzed according to their randomly assigned treatment sequence.

The **Safety Analysis Set** includes data from all subjects who received any amount of study treatment. In the safety analysis, no data exclusion was allowed because of protocol deviations. Subjects were analyzed according to the treatment sequence received.

The **PD LINE-1 Analysis Set** includes data from subjects if they 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.

Methods for Handling Missing Data (Phase 3)

BLQ Data

All plasma concentrations that were below the lower limit of quantification (LLOQ) or missing were labeled as below the limit of quantification (BLQ) or missing, respectively, in the concentration data listings. Considering the number of PK samples to estimate AUC_{0-24} , BLQ values were set to 0 for statistical summary of concentrations and calculation of PK parameters.

Unless otherwise noted, data summaries were performed on only observed data.

Missing Incomplete Dosing Information

In cases in which 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.

Missing Sampling Dates and/or Times

For concentration-time profiles from subjects with missing sample dates and/or times, the nominal sampling day and/or time (as appropriate) were assumed for the calculation of PK parameters.

Unexpected Data and Potential Scenarios for Exclusion

Every effort was made to include as many of the subjects as possible in the Primary Endpoint PK Analysis Population for the primary analysis. Exclusions of subjects from the primary analysis set were expected to be rare and could have happened under the following circumstances:

- The subject did not complete two full cycles of treatment and PK assessments to include both IV decitabine and ASTX727 cycles.
- The PK profile for the subject manifests as an extreme outlier versus profiles of the remaining population, with an atypical profile possibly a result of contamination during collection of blood samples (i.e., collection from the second lumen of the peripherally inserted central catheter, instead of contralateral arm, following IV infusion).
- Atypical and unexplained PK profile for a subject rendering extrapolation of AUC to 24 hours not possible due to inability to calculate lambda-z.
- Atypical decitabine PK profile influenced by vomiting after ASTX727 dosing.

The Regulatory Authorities' Assessment:

We agree with the Applicant's description of the SAP of the Phase 3 Study (ASTX727-02).

Protocol Amendments (Phase 3)

The Applicant's Description:

The original protocol was amended twice to address minor changes requested by Health Canada; these changes are shown in Table 32.

The study protocol was subsequently amended to include approximately 70 additional subjects with de novo or secondary AML who are not candidates for standard induction chemotherapy [REDACTED] (b) (4). At the end of December 2019, enrollment of subjects with AML has not yet started.

Table 32. ASTX727-02 Phase 3 Protocol Amendments

Protocol Amendment	Effective Date	Key Changes in Amendment
1.1 (not implemented)	18 Jan 2018	- Removed statement in Section 9.6 Missed Evaluations per request from Health Canada: [REDACTED] (b) (4) [REDACTED] ” - Removed statement in Section 14.1.3 Ongoing Communication of Safety information During the Study per request from Health Canada: “ [REDACTED] (b) (4) [REDACTED] ”
1.2	22 May 2018	Per request from Health Canada: - Clarified that the ASTX727 tablet will be given by mouth. - Added text to distinguish between the ASTX727 tablet formulations used in Phase 2 and Phase 3 - Clarified that pregnancy is to be reported up to 90 days after the last dose. - Text added to indicate the Sponsor shall maintain study records for up to 25 years.

Regulatory Authorities’ Assessment:

We agree with the Applicant’s description of protocol amendments.

8.1.4. Study Results (Phase 3)

Compliance with Good Clinical Practices (Phase 3)

Data:

This study was conducted in accordance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable local regulatory requirements. Written informed consent was obtained from subjects prior to Screening assessments. The ASTX727-02 CSR includes a GCP compliance statement.

The Applicant’s Position:

ASTX727-02 was conducted in accordance with the Code of Federal Regulations (CFR)

governing the protection of human subjects (21 CFR Part 50), Institutional Review Boards (21 CFR Part 56), the Responsibilities of Sponsors and Investigators (21 CFR Parts 312.50 to 312.70), Financial Disclosure by Clinical Investigators (12 CFR Part 54), and in accordance with ICH GCP guidelines.

Regulatory Authorities' Assessment:
We confirm the Applicant's position.

Financial Disclosure (Phase 3)

Data:

Astex has adequately disclosed financial interests/arrangements with clinical investigators participating in Study ASTX727-02, as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

With the exception of Dr. (b) (6) (as identified in Form FDA 3455 within the NDA), Astex certifies that we have not entered into any financial arrangement with any other clinical investigators participating in Study ASTX727-02, as listed in the FDA Form 3454 attachment. Financial agreement with Dr. (b) (6) is described under Phase 2 (Section 8.1.1). There were financial agreements with Dr. (b) (6)

The financial arrangements with Drs. (b) (6) and (b) (6) do not raise any integrity of the data as the PK Analysis Assessment was conducted by a third party and data were not accessible to Dr. (b) (6). In regards to the Response Assessments for Study ASTX727-02, the response data were assessed by external independent reviewers, not Dr. (b) (6). Dr. (b) (6) .

The Applicant's Position:

With the exception of Dr. (b) (6) and Dr. (b) (6), Astex certifies that: 1) the company has not entered into any financial arrangement whereby the value of compensation to the investigator could be affected by the outcome of the study; 2) no listed investigator disclosed a proprietary interest in the product or a significant equity in Astex; and 3) no listed investigator was the recipient of significant payments of other sorts.

As listed above, the financial arrangements made with Dr. (b) (6) and Dr. (b) (6) do not raise any issues regarding integrity of the data.

Regulatory Authorities' Assessment:
We confirm the Applicant's position.

Patient Disposition (Phase 3)

Data:

A total of 138 subjects were randomized in the Phase 3 study from 30 study centers in the US and 7 in Canada. The Efficacy Analysis Set and the Safety Analysis Set were composed of the 133 treated subjects. All randomized and treated subjects were included in the efficacy and safety analyses datasets. Five subjects were randomized but not treated (3 subjects withdrew prior to treatment, 1 withdrew due to elevation of bilirubin and creatinine before treatment, and 1 subject was lost to follow up after randomization).

As of the CSR data cutoff date (19 March 2019), 94 subjects were alive and ongoing treatment. The median duration of follow-up was 155 days (~5 months; range 57 to 397 days). The median duration of treatment was 4 cycles (range, 1 to 11 cycles).

Table 33. Subject Disposition in ASTX727-02 (Randomized Subject Analysis Set)

Subject Disposition	Total (N=138) n (%)
Not treated	5 (3.6)
Received treatment	133 (96.4)
ASTX727 Only	1 (0.7)
IV Only	3 (2.2)
ASTX727 and IV	129 (93.5)
Discontinued treatment ^a	39 (29.3)
Adverse Event	3 (2.3)
Death	6 (4.5)
Progressive Disease	6 (4.5)
Alternative MDS/CMML Therapy ^b	2 (1.5)
Subject Decision to Permanently Stop Treatment	2 (1.5)
Bone Marrow/Stem Cell Transplant	16 (12.0)
Lost to follow up	0
Other ^c	4 (3.0)
Withdrawn from study	17 (12.3)
Death ^d	11 (8.0)
Consent Withdrawal	5 (3.6)
Lost to follow up	1 (0.7)
Continuing in study	121 (87.7)
On study treatment	94 (68.1)
Survival follow up (off study treatment)	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.

Source: ASTX727-02 CSR Table 14.1.4, Appendix 16.2.1.1

The Applicant's Position:

None of the treated subjects were excluded from planned preliminary efficacy or safety analyses.

Regulatory Authorities' Assessment:

FDA performed an updated analysis of subject disposition based on updated efficacy data from Study ASTX727-02 received with the 120 day safety update. The 120-day update used a cutoff date of 11/1/2019. For the purposes of determining reasons for treatment discontinuation, FDA considers death under the primary reason for discontinuation (i.e., either primary disease or adverse event). The reason "adverse event" included 8 deaths due to an adverse event, in addition to the disposition events

coded as adverse event. There were no deaths in the category for “primary disease.”

Of the 12 treatment discontinuations for “Other,” 7 appeared to be due to the primary disease, 3 were physician decision, one was due to prolonged myelosuppression, and one was due to withdrawal of consent.

Reasons for Treatment Discontinuation on Study ASTX727-02

	ASTX727 (N=133) n (%)
Therapy ongoing	60 (45%)
Discontinued therapy	
HSCT	27 (20%)
Primary disease	17 (13%)
Adverse event	12 (9%)
Alternative therapy	3 (2%)
Withdrawal by subject	2 (2%)
Other	12 (9%)

Source: FDA analysis

Protocol Violations/Deviations (Phase 3)

Data:

Important deviations as determined by the Astex medical monitor and PK expert were those that affected a subject’s rights, safety or welfare, and/or the integrity of the study data. A total of 15 subjects had at least 1 important protocol deviation. Categories of important deviations, numbers of subjects in each category, and brief descriptions are as follows:

- Eligibility criteria: 2 (1 subject had a 27-day washout from prior azacitidine treatment instead of 28-day and 1 subject was hospitalized more than 2 days within 30 days of screening)
- Study drug administration: 1 (94 mL of IV decitabine infusion was given rather than the full 108 mL)
- Study procedures: 9 (various PK and LINE-1 sample collection time points missed)
- Safety: 3 (SAEs not reported to Astex with 24 hours)

The Applicant’s Position:

These protocol deviations did not affect the study outcome or conclusions.

The Regulatory Authorities’ Assessment:

We agree with the Applicant’s assessment. None of the deviations were likely to bias the study in favor of the study drug. Therefore, all patients, including those with important protocol deviations, were included in our analysis of efficacy endpoints.

Table of Demographic Characteristics (Phase 3)

Data:

Of the 133 treated subjects, 110 were treated in the US, and 23 were treated in Canada. No efficacy analyses by geographic region were conducted.

Table 34. ASTX727-02 Phase 3 Subject Baseline Demographics (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)
	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
Body Surface Area (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

Source: ASTX727-02 CSR Table 14.2.1.2

The Applicant's Position:

Overall, the demographic characteristics of subjects in this study are representative of MDS and CMML patients in the general population. Most subjects were elderly with median age >70 years, majority male, and mainly white with broad range of BSA.

No differences in demographic characteristics between subjects in Sequence A and Sequence B were apparent. Efficacy endpoints were not compared between treatment sequences.

The Regulatory Authorities' Assessment:

We agree with the Applicant's assessment.

Other Baseline Characteristics (Phase 3)

Data:

Baseline disease characteristics are summarized below. WHO classification of MDS/CMML was not collected for this study.

Table 35. ASTX727-02 Phase 3 Subject 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 for MDS, n (%)	MDS Low Risk ^a	4 (6.1)	7 (10.4)	11 (8.3)
	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 High Risk	14 (21.2)	7 (10.4)	21 (15.8)
	N/A ^b	5 (7.6)	11 (16.4)	16 (12.0)
IPSS 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)
Hemoglobin (g/L)	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)	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)

NDA Multi-disciplinary Review and Evaluation
NDA 212576, Original
INQOVI (decitabine and cedazuridine)

Baseline Characteristics		Sequence A (N=66)	Sequence B (N=67)	Total (N=133)
	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)	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 or Platelet Transfusion Dependence, ^{c,*} n (%)	Yes	28 (42.2)	27 (40.3)	55 (41.4)
	No	38 (57.6)	40 (59.7)	78 (58.7)
RBC Transfusion Dependence, ^d n (%)	Yes	26 (39.4)	26 (38.8)	52 (39.1)
	No	40 (60.6)	41 (61.2)	81 (60.9)
Platelet Transfusion Dependence, ^d n (%)	Yes	6 (9.1)	4 (6.0)	10 (7.5)
	No	60 (90.9)	63 (94.0)	123 (92.5)
Bone Marrow Blasts (%)	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)
ECOG PS, n (%)	0	25 (37.9)	30 (44.8)	55 (41.4)
	1	41 (62.1)	37 (55.2)	78 (58.6)

^a Subjects with Low-Risk MDS were eligible according to the FAB classification criteria in the Dacogen USPI.

^b N/A= not applicable (CMML subjects)

^c RBC Transfusion Dependence at baseline or Platelet Transfusion Dependence at baseline

^d Transfusion dependent = 2 units or more of transfusion within 56 days of the first dose of study treatment.

Source: ASTX727-02 CSR Table 14.2.1.2

* Indicates source of data is from a supplemental table

The Applicant's Position:

Baseline disease characteristics of subjects in this study are representative of the patient population intended to receive the marketed product. All IPSS risk categories were represented and patients with CMML were also included.

Baseline disease characteristics were generally balanced between the treatment sequences, but there were some imbalances that may confer worse prognosis for patients randomized to Sequence A vs Sequence B. Sequence A (ASTX727 in Cycle 1) compared with Sequence B (IV decitabine in Cycle 1) had a notably lower representation of CMML subjects (7.6% vs 16.4%), a higher representation of IPSS High-Risk MDS subjects (21.2% vs 10.4%), more subjects with low baseline neutrophils (42.4% vs 31.3% <1000/ μ L), and fewer subjects with high baseline neutrophils (37.9% vs 49.3% >1500/ μ L).

The Regulatory Authorities' Assessment:

In the Phase 3 trial, the mean time since diagnosis was 548.9 days (78.4 weeks) and median time since diagnosis was 83 days (11.9 weeks). This is more comparable to the mean and median duration of therapy noted in the IV decitabine label (mean 86 weeks and median 29 weeks on the randomized trial and mean 444 days and median 154 days on the single-arm trial).

Only 10 (8%) received up to 1 cycle of prior HMA therapy prior to enrolling on the trial. FDA obtained further information from the Applicant regarding prior therapies in a response to information request received on 3/10/2020. Results of FDA's subsequent analysis of prior therapies are displayed in the Table below. Our analysis differed from the Sponsor's only in that we identified an additional patient who received G-CSF (n=3; Subjects (b) (6)). The Sponsor had only reported 2 (2%) subjects with prior G-CSF.

Prior Anticancer Therapy in Phase 3 (ASTX727-02)

	Total (N=80) n (%)
Subjects with any prior anti-cancer therapy	30 (23%)
Erythropoietin or erythropoietin stimulating agents	9 (7%)
Azacitidine	6 (5%)
Lenalidomide	5 (4%)
Decitabine	4 (3%)
Hydroxyurea	4 (3%)
Granulocyte colony stimulating factor	3 (4%)
Eltrombopag	2 (2%)
Investigational antineoplastic drugs ²	2 (2%)
Cyclosporin	1 (1%)
Danazol	1 (1%)
Dexamethasone	1 (1%)
IVIg	1 (1%)
Prednisone	1 (1%)
Ruxolitinib	1 (1%)

Source: FDA analysis

¹ Subject (b) (6) received luspatercept

Again, the USPI for IV decitabine states that 30% of patients on the decitabine arm of the randomized trial and 27% of patients on the single arm trial received previous MDS therapy. The percentage here (23%) is slightly lower. No subjects were reported as

having prior HSCT in the Phase 3 database. The median duration of treatment of prior anticancer therapy (excluding azacitidine and decitabine which were given for only one cycle) was 124.5 days (range 1 to 1158 days). Subject (b) (6) received lenalidomide for 1158 days.

Of note, the 16 (12%) of patients without IPSS results documented had CMML. IPSS cytogenetic risk classification was missing/not evaluable in 12 (9%). Median baseline ANC was 1.21 in Sequence A, 1.50 in Sequence B, and 1.36 in all subjects. Of note, the Applicant excluded missing values when calculating the number of patients with bone marrow blasts > 5% at baseline. FDA found that 26 (39%) of patients in Sequence A, 27 (40%) of patients in Sequence B, and 53 (40%) of patients overall had bone marrow blasts > 5% at baseline.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use (Phase 3)

Data:

During the 2-way crossover, 129 subjects (97%) received both cycles of treatment (oral and IV).

The median number of cycles received was 4 (range, 1 to 11) and 39 subjects (29.3%) received 6 or more cycles. Eighty-two subjects (61.7%) had dose delayed cycles, and 27.1% had dose reduced cycles. However, the study is ongoing and the median follow up at the time of data cutoff was only 5 months.

Table 36. ASTX727-02 Phase 3 Treatment Exposure (Safety Analysis Set)

Treatment Exposure	Total (N=133)
Frequency of Cycles Received ^a (Subject Level), n (%)	
≥1	133 (100.0)
≥2	129 (97.0)
≥3	119 (89.5)
≥4	96 (72.2)
≥5	64 (48.1)
≥6	39 (29.3)
Summary of Cycles Received ^a (Subject Level)	
Mean	4.8
SD	2.23
Median	4.0
Min, Max	1, 11
Total Number of Cycles	645
No. Dose Delayed Cycles ^b , n (%)	212 (32.9)
No. Dose Reduced Cycles ^c , n (%)	83 (15.8)
No. Subjects with Delayed Cycles, n (%)	82 (61.7)
No. Subjects with Dose-Reduced Cycles, n (%)	36 (27.1)

^a Completed or partially completed cycles.

^b Delayed treatment cycle was defined by the investigator.

^c Dose-Reduced Cycles are based on any missing treatment in Cycles 1 and 2, dose adjustment by investigator or any drug return by patient for Cycles >2.

Source: ASTX727-02 CSR Table 14.1.6

The most commonly used concomitant medication classes were Antibacterials for Systemic Use (78.2%); Analgesics (74.4%), and Antivirals for Systemic Use (68.4%). Rescue medications were not used in this study.

The Applicant's Position:

Treatment compliance was well controlled/managed at the study centers during the first 2 cycles as all treatments (ASTX727 and IV decitabine) were administered by study center personnel.

Dose reduced cycles and treatment cycle delays were permitted for management of cytopenias. Overall, most (72.9%) subjects did not have a dose reduced cycle during the Phase 3 study as of the CSR data cutoff. For the primary PK endpoint, only subjects who received both treatments (ASTX727 FDC tablets and IV decitabine) and had adequate PK samples to be able to calculate 5-day AUC for both treatments were included in the primary paired PK analysis. No formal statistical comparisons between treatments (oral and IV) were performed for efficacy endpoints.

Concomitant medications used during the study were mainly for supportive treatment or treatment for comorbidities, so they did not affect the efficacy results.

The Regulatory Authorities' Assessment:

FDA performed a separate analysis of exposure based on months on therapy using the updated efficacy data from the 120-day update (see Table below).

Exposure in Phase 3 (ASTX727-02) – 120 Day Update

	Total (N=133)
Median (range)	8.1 (0.1-19.7)
0-3	23 (17%)
>3-6	31 (23%)
>6-9	15 (11%)
>9-12	35 (26%)
>12	29 (22%)

Source: FDA analysis

At the time of the initial submission, only 21% of patients were treated for more than 6 months, but at the time of the efficacy update, this increased to 59%. Furthermore, the maximum duration of therapy was initially just over 12 months and is now up to 19.7 months. A total of 22% now have remained on therapy for more than a year. This should provide a more accurate representation of efficacy than what was provided with the initial submission.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) (Phase 3)

Data:

The primary study endpoint for this study was a PK endpoint (total cycle 5-day decitabine AUC). The results of the comparison of 5-day decitabine AUC (oral vs IV), including sensitivity analyses, are presented above in Section 6.3.1 (Table 6). In this Phase 3 study, efficacy endpoints were secondary (Table 37).

The Applicant's Position:

The primary objective of this study was achieved and demonstrated that the decitabine exposures (5-day AUC) achieved from ASTX727 FDC tablets was equivalent to IV decitabine. The preliminary efficacy results in this study are supportive of the efficacy results achieved in the Phase 2 study and are presented below.

The Regulatory Authorities' Assessment:

See Section 6 of the Assessment Aid for FDA's assessment of PK results from the Phase 3 trial.

Data Quality and Integrity (Phase 3)

Data:

The Astex Quality Assurance group audited 5 centers from the 37 centers that randomized subjects. No critical audit findings were identified at 4 of the centers audited. Appropriate corrective and preventive actions were taken for all audit findings. Data integrity concerns were identified at one center (Site 217) as part of a for-cause audit. These findings were reported to the OSI on 21 November 2019.

The data in this submission are in eCTD format, in accordance with FDA guidance on electronic submission. The data sets are well documented and include definition files. The data sets, clinical study reports, summary of clinical safety, and summary of clinical efficacy are located in Modules 5 and 2 of the eCTD. \\CDSESUB1\evsprod\NDA\annnn.

The Applicant's Position:

The PK data collected at Site 217 was not useable and the PK data collected from the 2 subjects randomized at this site were not included in the primary PK analysis.

The Regulatory Authorities' Assessment:

No issues were identified with the data quality or integrity from the pivotal study which could affect the efficacy results, aside from the issues with the response assessments noted above. The submitted datasets are generally consistent, and variables are clearly labeled and/or explained.

Efficacy Results – Secondary and other relevant endpoints (Phase 3)

Data:

Efficacy was not a primary endpoint in Phase 3. Efficacy results presented in this section are considered preliminary at this time, as almost half the subjects had not completed 6 months of follow-up as of the data cutoff date for the CSR (median duration of follow-up was ~5 months). As of the cutoff date for the primary CSR, only response rates and transfusion independence were evaluated and reported in the Phase 3 CSR.

Long-term efficacy endpoints (duration of response and time to event endpoints) were not assessed or reported in the CSR. Exploratory analysis of these events based on the cutoff date for the CSR are reported in this document and will be updated when all subjects complete a minimum of at least 12 months of follow-up.

Table 37. ASTX727-02 Phase 3: Preliminary Analysis of Best Response

Type of Response	All Subjects (N=133)		Subjects Evaluable for Response (N=101)		Subjects with ≥6 Months' (180 Days) Follow Up (N=67)	
	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI
Complete Response (CR)	12 (9.0)	(4.7, 15.2)	12 (11.9)	(6.3, 19.8)	9 (13.4)	(6.3, 24.0)
Partial Response (PR)	0		0		0	
Marrow CR (mCR)	46 (34.6)	(26.6, 43.3)	46 (45.5)	(35.6, 55.8)	19 (28.4)	(18.0, 40.7)
mCR with HI	14 (10.5)	(5.9, 17.0)	14 (13.9)	(7.8, 22.2)	9 (13.4)	(6.3, 24.0)
Hematologic Improvement (HI)	7 (5.3)	(2.1, 10.5)	7 (6.9)	(2.8, 13.8)	2 (3.0)	(0.4, 10.4)
HI-E	2 (1.5)	(0.2, 5.3)	2 (2.0)	(0.2, 7.0)	1 (1.5)	(0.0, 8.0)
HI-N	1 (0.8)	(0.0, 4.1)	1 (1.0)	(0.0, 5.4)	0	—
HI-P	6 (4.5)	(1.7, 9.6)	6 (5.9)	(2.2, 12.5)	1 (1.5)	(0.0, 8.0)
Overall Response (CR+PR+mCR+HI)	65 (48.9)	(40.1, 57.7)	65 (64.4)	(54.2, 73.6)	30 (44.8)	(32.6, 57.4)
Stable Disease	28 (21.1)	(14.5, 29.0)	28 (27.7)	(19.3, 37.5)	14 (20.9)	(11.9, 32.6)
Progressive Disease	8 (6.0)	(2.6, 11.5)	8 (7.9)	(3.5, 15.0)	5 (7.5)	(2.5, 16.6)
Not Evaluable	32 (24.1)	(17.1, 32.2)	—	—	18 (26.9)	(16.8, 39.1)

Sources: ASTX727-02 CSR Table 14.3.1, Table 14.3.2, Table 14.3.3

Subgroup Analyses (Phase 3)

Subgroup analyses for efficacy endpoints based on demographic and disease-specific characteristics were not planned. However, assessment of response by disease type (MDS or CMML) was performed for the SCE after the completion of the CSR (Table 38).

Table 38. ASTX727-02 Phase 3: Best Response in MDS vs CMML

Type of Response	Phase 3 Subjects Evaluable for Response ^a N= 101	
	MDS N=87 n (%)	CMML N=14 n (%)
Complete Response (CR)	11 (12.6)	1 (7.1)
Partial Response (PR)	0	0
Marrow CR (mCR)	38 (43.7)	8 (57.1)
mCR with HI	12 (13.8)	2 (14.3)
Hematologic Improvement (HI)	6 (6.9)	1 (7.1)
HI-E	2 (2.3)	0
HI-N	0	1 (7.1)
HI-P	5 (5.7)	1 (7.1)
Overall Response (CR+PR+mCR+HI)	55 (63.2)	10 (71.4)
Stable Disease	26 (29.9)	2 (14.3)
Progressive Disease	6 (6.9)	2 (14.3)
Not Evaluable	—	—

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.

^a Excludes subjects whose response could not be evaluated by the IRC at the time of data cutoff.

Sources: Module 2.7.3, Attachment 2-Phase 3 Supplemental Efficacy Table 3.1, Table 3.2

Transfusion Independence (Phase 3)

Transfusion independence post-treatment was defined as no transfusions for ≥ 56 consecutive days while maintaining hemoglobin ≥ 8 g/dL and platelets $\geq 20 \times 10^9/L$.

Overall, of the 55 patients who were RBC or platelet transfusions dependent at baseline, 32.7% were transfusion independent post-baseline as of the cutoff date for the CSR.

One-third (32.7%) of the 52 subjects who were RBC transfusion dependent at baseline were RBC transfusion independent post-baseline. A 30% rate of platelet transfusion independence post-baseline was observed for the 10 subjects with platelet transfusion dependence at baseline.

Transfusion independence data by each response category are summarized in Table 39. Despite the limitation of the short follow-up to assess transfusion independence all patients with CR (100%) were transfusion independent post-treatment.

Table 39. ASTX727-02 Phase 3: Transfusion Dependence by Response (all patients N=133)

Best Overall Response	Baseline Transfusion	Post-Baseline Transfusion		
		Dependent n (%)	Independent n (%)	Not evaluated n (%)
Platelets				
CR (N=12)	Dependent (N=0)	0	0	0
	Independent (N=12)	0	12 (100)	0
mCR (N=46)	Dependent (N=3)	2 (66.7)	1 (33.3)	0
	Independent (N=43)	9 (20.9)	34 (79.1)	0
HI (N=7)	Dependent (N=0)	0	0	0
	Independent (N=7)	0	7 (100)	0
NR (N=68)	Dependent (N=7)	5 (71.4)	2 (28.6)	0
	Independent (N=61)	25 (41.0)	36 (59.0)	0
Overall (N=133)	Dependent (N=10)	7 (70)	3 (30)	0
	Independent (N=123)	34 (27.6)	89 (72.4)	0
Red blood cells				
CR (N=12)	Dependent (N=4)	0	4 (100)	0
	Independent (N=8)	0	8 (100)	0
mCR (N=46)	Dependent (N=21)	13 (61.9)	8 (38.1)	0
	Independent (N=25)	10 (40.0)	15 (60.0)	0
HI (N=7)	Dependent (N=3)	2 (66.7)	1 (33.3)	0
	Independent (N=4)	1 (25)	3 (75)	0
NR (N=68)	Dependent (N=24)	20 (83.3)	4 (16.7)	0
	Independent (N=44)	28 (63.6)	16 (36.4)	0
Overall (N=133)	Dependent (N=52)	35 (67.3)	17 (32.7)	0
	Independent (N=81)	39 (48.1)	42 (51.9)	0
Any platelet or red blood cell transfusion^a				
CR (N=12)	Dependent (N=4)	0	4 (100)	0
	Independent (N=8)	0	8 (100)	0
mCR (N=46)	Dependent (N=23)	14 (60.9)	9 (39.1)	0
	Independent (N=23)	11 (47.8)	12 (52.2)	0
HI (N=7)	Dependent (N=3)	2 (66.7)	1 (33.3)	0
	Independent (N=4)	1 (25)	3 (75)	0
NR (N=68)	Dependent (N=25)	21 (84)	4 (16)	0
	Independent (N=43)	31 (72.1)	12 (27.9)	0
Overall (N=133)	Dependent (N=55)	37 (67.3)	18 (32.7)	0
	Independent (N=78)	43 (55.1)	35 (44.9)	0

^a A patient was considered transfusion independent if the subject was both RBC and platelet transfusion free post-treatment for ≥56 consecutive days.

Source: Supplemental tables

The Applicant's Position:

The preliminary efficacy results in Phase 3 were secondary endpoints in the study. Only response rate and transfusions in the Phase 3 CSR were assessed at the time of the data cutoff and they provide supportive evidence of clinical benefit.

The Regulatory Authorities' Assessment:

At the time of the initial submission, the median duration of follow-up on the phase 3 Study ASTX727-02 was only 5.1 months, compared to 24.0 months for Study ASTX727-01-B. The Applicant submitted updated efficacy data for Study ASTX727-02 per the prespecified statistical analysis plan at the same time as the 120-day safety update. At that time, the median duration of follow-up was 12.6 months and the median duration on treatment was 8.1 months. FDA's analysis of the updated efficacy results on the Phase 3 trial are presented in the Table below.

ASTX727-02 Phase 3: Analysis of Best Response – 120 Day Update

	Total (N=133)
CR, n (%; 95% CI)	28 (21%; 15-29%)
Median Duration of CR, months (range)	7.5 (1.7-17.5)
Median Time to CR, months (range)	4.3 (2.1-15.2)

Source: FDA analysis

We were in agreement with the Applicant's assessment of the complete remission rate in the updated efficacy data set. FDA adjudicated CR responses based on evaluation of bone marrow and laboratory results in the submission.

Again, the acceptable response rate for MDS for regulatory decision making is ORR, defined as CR+PR responses. There were no PR responses on the Phase 3 trial of ASTX727, and therefore, only CR responses were considered for demonstration of clinical benefit. Lesser responses than CR/PR do not convey clear clinical benefit to patients. Overall, the CR responses seen on Phase 3 mirror that observed with IV decitabine.

We again note that the Phase 3 trial used IWG 2006 MDS Response Criteria, which differs from that used in the IV decitabine prescribing information (IWG 2000 MDS Response Criteria) (Cheson, Bennett et al. 2000). However, even assuming a slightly higher CR rate than the 9-15% reported in the IV decitabine USPI with the use of

updated response criteria, the results seen with ASTX727 appear to be comparable.

The following subgroup analyses were performed in patients with CR responses:

- CR rate < 65 years 8/36 (22%) and ≥ 65 years 20/97 (21%)
- CR rate females 9/46 (20%) and males 19/87 (22%)
- CR rate Canada 4/23 (17%) and US 24/110 (22%)
- CR rate White 25/121 (21%) and Non-White 3/12 (25%)
- CR rate MDS 26/117 (22%) and CMML 2/16 (13%)
- CR rate Int-1 IPSS 13/59 (22%) and Int-2 and high-risk 11/47 (23%)
- CR rate Int-2 8/26 (31%) and high-risk 3/21 (14%)

Interpretation of the subgroup analyses is limited by the small sample sizes.

FDA furthermore updated the analysis of conversion from transfusion dependence to transfusion independence and maintenance of transfusion independence using the updated efficacy data with the 120-day update (see Table below). Results were very similar to those obtained on the Phase 2 trial.

ASTX727-02 Phase 3: Transfusion Dependency by Response – 120 Day Update

Best Overall Response	Baseline Transfusion	Post-Baseline Transfusion		
		Dependent n (%)	Independent n (%)	Not evaluated n (%)
Platelets				
CR (N=28)	Dependent (N=0)	0	0	0
	Independent (N=28)	0	28(100)	0
NR (N=105)	Dependent (N=12)	7 (58)	5 (42)	0
	Independent (N=93)	25 (27)	68 (73)	0
Overall (N=133)	Dependent (N=12)	7 (58)	5 (42)	0
	Independent (N=121)	25 (21)	96 (79)	0
Red blood cells				
CR (N=28)	Dependent (N=10)	0	10 (100)	0
	Independent (N=18)	0	18 (100)	0
NR (N=105)	Dependent (N=43)	26 (60)	17 (40)	0
	Independent (N=62)	23 (37)	39 (63)	0
Overall (N=133)	Dependent (N=53)	26 (49)	27 (51)	0
	Independent (N=80)	23 (29)	57 (71)	0
Any platelet or red blood cell transfusion*				
CR (N=28)	Dependent (N=10)	0	10 (100)	0
	Independent (N= 18)	0	18 (100)	0
NR (N=105)	Dependent (N=47)	27 (57)	20 (43)	0
	Independent (N=58)	28 (48)	30 (52)	0
Overall (N=133)	Dependent (N=57)	27 (47)	30 (53)	0
	Independent (N=76)	28 (37)	48 (63)	0

Source: FDA analysis

* A patient was considered transfusion independent if the subject was both RBC and platelet transfusion free post-treatment for ≥56 consecutive days.

Dose/Dose Response (Phase 3)

Data:

A fixed dose was used in this study to produce decitabine exposure equivalent to IV decitabine at the approved dose of the 5-day regimen, and assessment of response by dose was not evaluated. The recommended dose and regimen for ASTX727 is 100 mg cedazuridine and 35 mg decitabine given orally (as the ASTX727 FDC tablet) once daily on Days 1 through 5 of each 28-day cycle. In addition, ASTX727 treatment at the recommended dose and regimen achieved almost identical demethylation to IV

decitabine, as measured by % LINE-1 demethylation (Table 8).

The Applicant's Position:

No studies were conducted to assess dose-response relationship.

The Regulatory Authorities' Assessment:

We agree with the Applicant's assessment.

Durability of Response (Phase 3)

Data:

The efficacy results presented for the Phase 3 study are preliminary and are based on available data as of the cutoff date for the primary CSR. Overall survival was not assessed in the first analysis for this study. Responses are ongoing in the study and with the K-M method median duration of response was not estimable. At the data cutoff for the first analysis in this study, all CR patients have not yet progressed and only one patient with mCR has progressed, so the duration of response for patients in CR or mCR are preliminary underestimates. With that caveat, the median (range) duration of response was 113+ days (29+, 306+) for subjects with a best response of CR, and 63+ days (range 4+, 320+) for subjects with best response of mCR.

The Applicant's Position:

Duration of response and overall survival for the Phase 3 study will be assessed in the second analysis of efficacy after all subjects have completed a minimum of 12 months of follow up. Almost all patients with CR or mCR have not yet progressed at the data cutoff of the first analysis in Phase 3. Durability of response is presented above in Section 8.1.1 for the Phase 2 study.

The Regulatory Authorities' Assessment:

FDA performed an assessment of duration of CR based on the updated efficacy data from the 120 day update (see FDA assessment Table above for Study ASTX727-02 Phase 3). The median duration of response is now 7.5 (range 1.7-17.5) months. This is similar, but slightly lower than that observed on the Phase 2 trial. It is likely that the median will increase over time with longer follow-up. Of the 28 CR responses, there were only 4 relapses to date, with most responses ongoing at the data cutoff date.

Of note, the duration of CR+PR in the IV decitabine label was 288 days (range 116-388), which is equivalent to 9.4 months (range 3.8-12.8) months on the controlled trial and 443 days (range 72-722) days or 14.6 months (range 2.4-23.7) months on the single-arm trial.

Persistence of Effect (Phase 3)

Data :

The preliminary data from Phase 3 support persistence of effect. Persistence of effect is described above in Section 8.1.1 for the Phase 2 study.

The Applicant's Position:

Preliminary data from Phase 3 are supportive of durable effect but will be updated with longer-term follow-up.

The Regulatory Authorities' Assessment:

As noted above, we determined that median duration of response for phase 3 subjects with best response of CR was 7.5 months (range 1.7 – 17.5 months) using the updated efficacy data with the 120-day safety update.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints (Phase 3)

Data:

There were no study endpoints evaluating patient-reported outcomes in this study.

The Applicant's Position:

Not applicable

The Regulatory Authorities' Assessment:

We agree with the Applicant's assessment.

Additional Analyses Conducted on the Individual Trial (Phase 3)

Data:

Assessment of response is ongoing in the Phase 3 study. As of the cutoff date, the median (range) time to response for all treated subjects (N=133) was 99 days (42-158) for CR and was 63 days (42-227) for mCR.

No additional efficacy analyses were conducted for this study.

The Applicant's Position:

Median time to best response of CR was approximately 3 months supporting the need for at least 3-4 cycles.

The Regulatory Authorities' Assessment:

Using the updated efficacy data, we determined the median time to CR was 132 days

(range 65 – 462 days), i.e., 4.3 months (range 2.1 – 15.2 months). Of note, this is similar to that observed with IV decitabine. In the USPI for IV decitabine, the median (range) time to CR+PR was 3.1 (1.8-8.9) months on the randomized trial and 5.3 (1.6-8.8) months on the single arm trial.

8.1.5. **Integrated Review of Effectiveness**

The Regulatory Authorities' Assessment:

See below sections for our integrated assessment of effectiveness.

8.1.6. **Assessment of Efficacy Across Trials**

The Applicant's Position:

The approach to establish the safety and effectiveness of ASTX727 FDC tablets (100 mg cedazuridine and 35 mg decitabine) was based primarily on a pharmacokinetic (PK) bridging approach to IV decitabine. In this application, the primary efficacy results are from the Phase 2 (ASTX727-01). Supportive efficacy results from the Phase 3 study (ASTX727-02) are provided.

All long-term efficacy endpoints, such as survival, are summarized from the Phase 2 study results only (Section 8.1.2). Due to the shorter duration of follow-up in Phase 3, only preliminary results for response rate and transfusion independence are presented here.

Complete blood counts (CBC) were completed prior to every cycle of treatment in both studies. Bone marrow was assessed every other cycle at least up to Cycle 7 until disease progression or treatment discontinuation. Transfusion needs were assessed continuously during the treatment period. In Phase 2, response was evaluated by medical review and statistical programming conducted by Astex (see implementation guide in the SAP). In Phase 3, response was assessed by an Independent Review Committee (IRC) composed of 2 disease experts (and adjudicated by a third, when necessary) who did not participate as investigators in the trial (see IRC charter). The IRC also assessed the categories of Stable Disease and Progressive Disease in the Phase 3 study, while in Phase 2 these categories were presented collectively as No Response.

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's assessment. In addition, FDA notes that the follow-up efficacy data from the Phase 3 trial received with the 120-day safety update added assurance of the clinical benefit of ASTX727, based on comparable efficacy results to the Phase 2 trial and that of IV decitabine.

Primary Endpoints

Data:

PK: Decitabine total cycle 5-day AUC was a primary endpoint in both the Phase 2 and Phase 3 studies. The results of the primary PK endpoint for Phase 2 (5-day AUC_{0-t}) and Phase 3 (5-day AUC_{0-24}) are presented in Section 6.3.1 (Table 12 and Table 13 for Phase 2 and Table 6 and Table 7 for Phase 3).

PD: LINE-1 methylation was a primary endpoint in Phase 2 and a secondary endpoint in Phase 3. The LINE-1 methylation results are presented in Section 6.3.1 (Table 8 and Table 9).

Clinical efficacy: Response rate was a primary endpoint in Phase 2 and secondary endpoint in Phase 1 and 3. Response rates for all Phases are summarized below and compared with published data from IV decitabine 5-day regimen ([Steensma et al 2009](#)), which also used IWG 2006 criteria for response (Table 40).

Table 40. Summary of Best Response and Other Key Efficacy Endpoints Across Studies

	Subjects, n (%)			
	Phase 1	Phase 2	Phase 3 (Preliminary)	Dacogen (IV decitabine)
Median (min, max) no. of treatment cycles:	5 (1-35)	7 (1-29)	4 (1-11)	5 (1-17)
Median duration of follow-up (months):	23.7 (18.9-33.6)	24.3 (12.2-29.2)	5.2 (1.9-13.2)	NR
Cedazuridine/decitabine (mg):	40-100/20-40	100/35	100/35	20 mg/m ²
Schedule:	5-day	5-day	5-day	5-day
	All Treated Subjects N=44	All Treated Subjects N=80	All Treated Subjects N=133	All Treated Subjects N=99
Type of Response				
Complete Response (CR)	5 (11.4)	17 (21.3)	12 (9.0)	17 (17)
Partial Response (PR)	0	0	0	0
Marrow CR (mCR)	2 (4.5)	18 (22.5)	46 (34.6)	15 (15)
mCR with HI	NR	6 (7.5)	14 (10.5)	NR
HI	6 (13.6)	13 (16.3)	7 (5.3)	18 (18)
HI-E	8 (18.2)	8 (10.0)	2 (1.5)	NR
HI-N	1 (2.3)	2 (2.5)	1 (0.8)	NR
HI-P	8 (18.2)	11 (13.8)	6 (4.5)	NR
Overall Response (CR+PR+mCR+HI)	13 (29.5)	48 (60.0)	65 (48.9)	50 (51)
Stable Disease	—	—	28 (21.1)	24 (24)
Progressive Disease	—	—	8 (6.0)	10 (10)
No Response ^a	31 (70.5)	32 (40.0)	32 (24.1)	15 (15)
Time to best response, median (min, max), days				NR
CR	NR	147 (29-571)	99 (42-158)	NR
mCR	NR	64 (49-218)	63 (42-227)	NR
Duration of response, median (min, max), days				NR
CR	470.00 (29.0, 672.0)	286 (32, 553)	113+ (29+, 306+)	NR
mCR	390.50 (332.0, 449.0)	143 (49, 662)	63+ (4+, 320+)	NR
K-M estimate, median (95% CI), days				
Overall survival (mo)	NE (NE, NE)	18.3 (13, NE)	NE	19.4 (15, NE)

NE: Not Estimable; NR: Not Reported; +: indicates responses are ongoing

Note: Each subject was presented only once in each of the CR, PR, mCR, and hematologic improvement (HI) categories according to their best response, in that order. mCR with HI is a subset of subjects with mCR who also achieved HI. IWG Response Criteria for MDS (Cheson et al 2006) was used for ASTX727 and Dacogen published data

^a Includes the categories of Stable Disease and Progressive Disease in Phase 1 and 2 and includes subjects who were not evaluable in Phase 3.

Sources: Phase 1 ASTX727-01-A CSR Tables 14.3.1.1 (best response), 14.3.1.2 (duration of response), 14.3.3.1 (time to AML/death), 14.3.4.1 (OS); Phase 2 ASTX727-01-B CSR Tables 14.3.1.1.1 (best response), supplemental table (time to resp), supplemental (duration of response), 14.3.4.1 (time to AML), 14.3.5.1 (OS); Phase 3 ASTX727-02 CSR Table 14.3.1 (best response), supplemental table (time to resp), Steensma 2009 (Dacogen)

The Applicant's Position:

Overall, evidence of clinical activity with ASTX727 was observed in all phases of ASTX727 studies. Response rate was relatively low for Phase 1 due to a large percentage of subjects who received prior HMA (46%). In Phase 2, the response rate was high with 21% reporting CR, and median survival of ~18 months. The data from Phase 3 are preliminary, but it is worth noting the CR rate of 9% in all treated subjects and 12% in evaluable subjects. There was also a high percentage of mCR (34.6%) that it is likely that some of them will become CR with further follow up. This would be consistent with the observation that median time to CR is usually relatively longer than time to mCR as reported above for Phase 2 and 3. The primary PK endpoint of similar or equivalent systemic decitabine exposures was consistently met in Phase 2 and Phase 3 within the limitation of the smaller sample size in Phase 2. Also, Phase 2 and 3 produced consistent data of similar effect on DNA methylation from ASTX727 and IV decitabine.

The overall response rate was 60% in Phase 2 and 49% to 64% in Phase 3 in all treated and evaluable subjects, respectively.

The response rates observed for ASTX727 in the Phase 2 and Phase 3 studies are similar to those reported for 5-day IV decitabine dosing ([Steensma et al 2009](#); [Dacogen USPI 2019](#)), suggesting that the equivalent AUC exposures and similar effect on DNA methylation observed for ASTX727 and IV decitabine produce the same meaningful clinical activity.

The Regulatory Authorities' Assessment:

FDA disagrees with the Applicant's assessment of the efficacy results from the Phase 2 trial, as noted in Section 8.1.2 above. FDA's adjudicated CR rate was 14/80 (18%; 95% CI 10-28%) with a median duration of response of 8.7 (range 1.1-18.2) months. The CR rate on the Phase 3 trial using updated efficacy data from the 120-day safety update was 28/133 (21%; 15-29%) with a median duration of response of 7.5 (range 1.7-17.5) months. Both are similar to the ORRs (CR+PR) reported in the USPI for IV decitabine, which were 17% for the randomized trial and 16% for the single arm trial.

Again, the acceptable response rate for MDS appropriate for regulatory decision making is overall response rate (ORR), defined as CR+PR responses. ORR served as the basis for approval of IV decitabine. There were no PR responses on either the Phase 2 or Phase 3 trials of ASTX727, and therefore, only CR responses are considered for demonstration of clinical benefit. Lesser responses than CR/PR do not convey clear clinical benefit to patients.

Secondary and Other Endpoints

Data:

Transfusions: Data on transfusions were available from both Phase 2 and 3. In Phase 2, 50% of subjects who were RBC or platelet transfusion dependent at baseline were transfusion independent for ≥ 56 consecutive days. In Phase 3, RBC and platelet transfusion independence for ≥ 56 consecutive days was achieved in 32.7% and 30.0% of subjects, respectively, despite the insufficient follow-up in the study at the time of this analysis. Transfusion independence for both RBCs and platelets in those who were dependent at baseline ranged from 33% in Phase 3 (short follow-up) to 49% in Phase 2. The rate of transfusion independence with IV decitabine for RBCs was 33% in the published data (Steensma et al 2009).

Table 41. Transfusion Independence for Subjects Transfusion Dependent at Baseline (Phase 2 and Phase 3)

Type of Transfusion	Status		Phase 2 (N=80)	Phase 3 (N=133)
			≥ 56 Days	≥ 56 Days
RBC or Platelet *	Baseline Dependent	N ^a	41	55
	Post-treatment Independence	n ^b	20 (48.8%)	18 (32.7%)
		95% CI ^c	(32.9, 64.9)	(20.7, 46.7)
RBC	Baseline Dependent	N ^a	38	52
	Post-treatment Independence	n ^b	19 (50.0%)	17 (32.7%)
		95% CI ^c	(33.4, 66.6)	(20.3, 47.1)
Platelet	Baseline Dependent	N ^a	12	10
	Post-treatment Independence	n ^b	6 (50.0%)	3 (30.0%)
		95% CI ^c	(21.1, 78.9)	(6.7, 65.2)

CI=confidence interval; RBC=red blood cell

^a N=Number of subjects who were transfusion dependent (i.e., received 2 or more units of transfusions within 56 days of first day of study treatment and had sufficient follow-up time).

^b n=Number of subjects who became transfusion independent (i.e., were transfusion free for ≥ 56 consecutive days in any study period post-baseline).

^c The 95% CI is the Clopper-Pearson confidence interval.

Source: ASTX727-01-B CSR Table 14.3.3.1.1 and Table 14.3.3.3.1; ASTX727-02 CSR Table 14.3.4 and Table 14.3.6

* Indicates source of data is from a supplemental table

The Applicant's Position:

The secondary efficacy endpoint of transfusion independence was supportive of clinical benefit from ASTX727 that is consistent with IV decitabine previously reported data.

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's assessment regarding the transfusion benefit of ASTX727. On the Phase 2 trial, of 41 patients who were transfusion dependent (TD) of RBCs or platelets at baseline, 49% became transfusion independent (TI) of both RBCs and platelets for at least 56 days post-baseline. Of 39 patients who were TI of RBCs and platelets at baseline, 64% remained TI of both RBCs and platelets for at least 56 days post-baseline. Using the updated efficacy data on Phase 3, the numbers were very similar. Of 57 patients TD of RBCs or platelets at baseline, 53% became TI of both RBCs and platelets for at least 56 days post-baseline and of 76 patients who were TI at baseline, 63% remained TI for at least 56 days post-baseline. This data supports a transfusion benefit of ASTX727 in patients with MDS and CMML.

Subpopulations

Data:

Due to the differences in duration of treatment and follow-up between the Phase 2 and Phase 3 studies, efficacy data were not pooled for subgroup analyses. The evaluation of the effects of major demographic factors (age, sex) and other relevant intrinsic and extrinsic factors on the PK of decitabine or cedazuridine was performed and results are presented above in Section 6.2.1. Assessment of response by different subgroups based on age, sex, race, country, disease (MDS and CMML), and different MDS IPSS categories were performed for Phase 2 and reported above in Table 25 to Table 26.

The Applicant's Position:

Subgroup analyses were performed for efficacy endpoints (e.g., response rate) by different subpopulations and clinical activity was observed in all subgroups within the limitation of the sample size. In addition age, sex, body weight, renal function, and hepatic function were assessed as potential covariates in a PopPK analysis and found no clinically meaningful effects that would require dose adjustments (see Section 6.2.1 and 6.3.2). The effects of severe hepatic impairment or severe renal impairment on the PK of decitabine and cedazuridine is unknown. Studies ASTX727-01 and ASTX727-02 did not have sufficient racial diversity to inform potential correlations with regard to race or ethnicity.

The assessment of response by disease type showed that ASTX727 was clinically active in both MDS and CMML patients. Patients with CMML tended to have better response (Table 27).

The Regulatory Authorities' Assessment:

In general, interpretation of the subgroup analyses is limited by the small sample sizes.

The Sponsor noted a better response rate in CMML patients, which was observed in Phase 2 (CR rate 5/17 [29%] CMML vs 9/63 [14%] MDS). However, the opposite was observed using the updated efficacy data from Phase 3 (CR rate 2/16 [13%] CMML vs 26/117 [22%] MDS). This indicates that the efficacy of ASTX727 is likely similar in patients with MDS and CMML.

Additional Efficacy Considerations

The Regulatory Authorities' Assessment:

Regarding considerations on benefit in the post-market setting, while patients who enroll on clinical trials tend to differ in various ways from the broader population of patients with cancer, there is no indication that efficacy would be lower in patient populations underrepresented on the Phase 2 or Phase 3 trials. Given that the therapy is oral, it will be important for prescribers to monitor compliance and adverse events closely.

8.1.7. Integrated Assessment of Effectiveness

Data:

Substantial evidence of effectiveness of ASTX727 was established primarily through the PK-bridging approach. Evidence of decitabine AUC equivalence between ASTX727 and IV decitabine was established in the Phase 3 study (ASTX727-02). The primary evidence of clinical benefit (CR) and durability of response was demonstrated in the long-term Phase 2 study with complementary clinical benefit based on preliminary efficacy results from the Phase 1 and 3 studies.

Results from the clinical development program demonstrated that ASTX727 is associated with the following benefits:

- Oral ASTX727 resulted in decitabine 5-day AUC exposure that was equivalent to IV decitabine with high certainty. The oral/IV 5-day decitabine AUC of the FDC in the Phase 3 was approximately 99% with a narrow 90% CI (92.66%, 105.6%). The oral/IV AUC comparison was robust, with all sensitivity and secondary oral/IV AUC comparisons were consistent with the primary analysis, including all 90% CIs entirely contained between 80% and 125%.
- Data from the development program also showed a similar biological effect of ASTX727 compared with IV decitabine in the first 2 cycles. Differences of DNA demethylation as measured by LINE-1 assay was approximately 1% or less between ASTX727 and IV decitabine in Phase 2 and 3.
- Since efficacy from HMA treatment requires multiple (at least 4 to 6) treatment cycles (Table 1), the long-term efficacy outcomes in the ASTX727 program were mainly driven by ASTX727, as patients received only 1 cycle of IV decitabine. While

ASTX727 would be expected to result in similar efficacy to IV decitabine based on the above equivalent decitabine systemic exposure and similar biological effect, it is reassuring that the mature data from the Phase 2 study also support that conclusion, as follows:

- CR rate of 21% with ASTX727 compared to 9% to 15% in the [Dacogen USPI 2019](#) (3-day and 5-day regimen respectively) and 17% as reported in [Steensma et al 2009](#).
- RBC and platelet transfusion independence in about 50% of patients who were transfusion-dependent at baseline compared to 33% reported in [Steensma et al 2009](#) for RBC transfusion independence.
- Median survival of 18 months compared to 19 months reported in [Steensma et al 2009](#).

The Applicant's Position:

While decitabine plasma AUC exposures are largely considered to be the principal PK determinant of both biological and clinical activity of decitabine, long interspersed nucleotide element-1 (LINE-1) demethylation and safety data were collected in a randomized design in the first 2 cycles of Phase 2 and 3 to confirm similar biological activity and safety to further support the PK bridging approach to IV decitabine. In addition, subjects continued to receive ASTX727 after the first 2 randomized cycles so that long-term efficacy and safety data were also collected in Studies ASTX727-01 and ASTX727-02. This provided additional support that clinical data from ASTX727 are consistent with the expected clinical profile of IV decitabine from published data. LINE-1 demethylation was similar between ASTX727 and IV decitabine in the first 2 cycles. The clinical safety was also generally comparable between ASTX727 and IV decitabine in the first 2 cycles. Long-term efficacy and safety results after multiple cycles of ASTX727 were consistent with the efficacy and safety reported with decitabine IV using the 5-day regimen ([Steensma et al 2009](#)). Results from studies with ASTX727 therefore support the conclusion that 5-day decitabine AUC exposure is appropriate to use as a bridge to clinical effects.

The availability of an oral HMA alternative will alleviate a significant burden to patients and patient care givers by eliminating the need for monthly 5-day IV infusions in a clinic or hospital setting that may need to continue for several months or even years in responding patients. This may also avoid premature treatment discontinuation that could occur as a result of the burden of multiple-day IV infusions every month, particularly for the most elderly patients and/or for those who live far from a treatment center. Premature HMA treatment discontinuation has been reported to result in early relapse ([Cabrerero et al 2015](#)). An oral treatment will also avoid potential safety issues due to multiple subcutaneous injections or multiple IV infusions that may require the establishment and maintenance of a central IV line, which could also result in additional

complications.

The Regulatory Authorities' Assessment:

The efficacy of ASTX727 has been established, based on the results of the Phase 2 and Phase 3 trials in adult patients with MDS and CMML (for which IV decitabine is currently approved). Patients who received ASTX727 (100 mg cedazuridine and 35 mg decitabine) achieved a CR rate of 18-21%. Duration of CR responses were sufficiently durable and roughly comparable (although slightly lower) than that reported for IV decitabine. However, many of the responses were ongoing at the time of data cutoff, and thus, the median duration of CR would be expected to increase with longer follow-up.

The CR benefit was supported by a transfusion benefit on both trials, which demonstrated that 49-53% of patients dependent on transfusions at baseline achieved at least 56 days transfusion independence post-baseline and 63-64% of patients transfusion independent at baseline were able to maintain that transfusion independence for at least 56 days post-baseline.

8.2. Review of Safety

Data:

The safety profile of ASTX727 in patients with MDS and CMML was primarily assessed based on safety results from the Phase 2 portion of ASTX727-01 study (ASTX727-01-B) and the Phase 3 study (ASTX727-02) where subjects were treated with the recommended dose of ASTX727 (100 mg cedazuridine and 35 mg decitabine). The safety data of all patients who received ASTX727 from the Phase 2 (78 patients) and Phase 3 (130 patients) studies were pooled (N=208). The key findings from the pooled analyses are provided in the following sections.

The Applicant's Position:

The safety profile of ASTX727 in patients with MDS and CMML was consistent with the known safety profile for IV decitabine, and no new safety concerns were identified.

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's approach of pooling safety data across Studies ASTX727-01-B and ASTX727-02 given the similar study designs and patient populations. Two patients from Phase 2 and three patients from Phase 3 were only treated with IV decitabine during cycle 1 (i.e. never received ASTX727), and therefore, were excluded from the safety set. This led to the total of 208 patients in the pooled population.

8.2.1. Safety Review Approach

Data:

The primary studies used to describe the safety of ASTX727 in patients with MDS or CMML include the Phase 2 portion of Study ASTX727-01 (ASTX727-01-B CSR) and the Phase 3 Study ASTX727 02.

Results from each trial are included in this submission through the data cutoff dates established for the respective clinical study reports (CSRs) (Table 42).

In addition, this submission includes relevant safety findings following medical review of all serious adverse events (SAEs) in the safety database that were reported in ongoing studies, from the CSR data cutoff dates through 12 October 2019 (approximately 60 days before the planned NDA submission).

Table 42. Summary of Clinical Studies Included in the Assessment of Safety

Study Data Contribution to NDA	CSR Cutoff Date	Number of Subjects Treated/ Ongoing Treatment^a	Median Duration of Treatment (Range)	Median Duration of Follow-up
ASTX727-01-A (Phase 1) PK, PD, supportive efficacy, safety	01 June 2017	44/6	5 cycles (1-35 cycles)	710.5 days (~24 months) (range: 566 – 1008 days)
ASTX727-01-B (Phase 2) PK, PD, primary efficacy, safety	05 June 2018	80/13	7 cycles (1-29 cycles)	729 days (~24 months) (range: 365 – 876 days)
ASTX727-02 (Phase 3) primary PK, PD, preliminary efficacy, safety	19 March 2019	133/94	4 cycles (1-11 cycles)	155 days (~5 months) (range: 57 - 397 days)
ASTX727-04 (Food effect) PK, safety	08 July 2019	17/13	2 cycles (1-6 cycles)	Not available
E7727-01 (ADME) PK for cedazuridine, safety	01 April 2019	8/0	2 single doses	NA (healthy subjects)

ADME=absorption, distribution, metabolism, excretion; NA=not applicable; PK=pharmacokinetics.

^a As of the data cutoff date for the respective CSRs.

Source: ASTX727-01-A CSR Table 14.1.2.1, 14.1.1.1; ASTX727-01-B CSR Table 14.1.2.1.3, 14.1.1.3; ASTX727-02 CSR Table 14.1.8, 14.1.4, 14.1.6; ASTX727-04 CSR Table 14.1.1.3, 14.1.2; E7727-01 CSR Section 12.1.

The safety profile of ASTX727 was assessed based on the incidence of AEs, deaths, other SAEs, and other significant AEs (e.g., AEs leading to permanent treatment discontinuation, AEs leading to drug interruption or dose reduction, clinical laboratory assessments, and ECGs) as well as clinical laboratory evaluations, vital signs, and ECGs.

Comparison of AE incidence rates were limited to comparison of ASTX727 to IV decitabine during the first 2 cycles of treatment only (during the crossover portion of

the study). In Cycle 3 and beyond, subjects only received ASTX727. IV decitabine was only administered for 1 cycle in both the Phase 2 and Phase 3 studies.

The Applicant’s Position:

The safety review focuses on safety based on overall treatment exposure of ASTX727 in patients with MDS or CMML from 208 patients. Safety is expected to be similar between ASTX727 and IV decitabine based on equivalent decitabine systemic exposure and similar biological effect on DNA methylation from the 2 treatments as assessed in the randomized comparison of PK and PD in the first 2 cycles of Phase 2 and 3. In addition, a limited randomized comparison of ASTX727 vs IV decitabine in the first 2 cycles provided a useful assessment of potential of safety issues as a result of oral decitabine administration (mainly GI effects) or for detecting safety signals that may be attributed to cedazuridine. Safety review issues were not identified during drug development and there were no clinical holds for safety during the development program.

The Regulatory Authorities’ Assessment:

FDA agrees with the Applicant’s assessment of median duration of exposure across Studies ASTX727-01-A, ASTX727-01-B, ASTX727-02, ASTX727-04, and E7727-01. FDA performed an updated analysis of exposure based on the data submitted with the 120-day safety update received on 4/6/2020. The 120-day safety update included updated safety data from Studies ASTX727-01-A, ASTX727-01-B, ASTX727-02, and ASTX727-04, with a cutoff date of 11/1/2019. FDA utilized the safety data from the 120-day safety update for all safety analyses.

Updated Exposure and Follow-up Durations (120-Day Safety Update)

Study	Number of Subjects Treated/ Ongoing Treatment	Median Duration of Treatment (Range)	Median Duration of Follow-up
ASTX727-01-A (Phase 1)	44/1	4.3 months (0.03-54.6)	52.4 months (range: 47.6 – 62.2)
ASTX727-01-B (Phase 2)	80/1	6.6 months (0.03-43.5)	40.9 months (range: 28.9 – 45.7)
ASTX727-02 (Phase 3)	133/60	8.1 months (0.1-19.7)	12.6 months (range: 9.3 – 20.5 days)
ASTX727-04 (Food effect)	17/8	3.6 months (0.03-7.1)	6.3 months (range: 4.7 – 8.9)

Source: FDA analysis

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Overall, 208 subjects were exposed to ASTX727 in the Phase 2 (78 subjects) and Phase 3 (130 subjects) studies and 69 subjects were exposed to cedazuridine and/or decitabine in the Phase 1 studies (Table 42 and Table 43). In the controlled clinical trials a total of 208 subjects were exposed to at least 1 dose of 100 mg cedazuridine plus 35 mg decitabine administered concomitantly as separate capsules or as the ASTX727 FDC tablet and a total of 159 subjects were exposed to the ASTX727 FDC tablet (Table 44).

It is important to note that the first 2 cycles of the Phase 2 and Phase 3 controlled clinical trials consisted of a 2-way crossover. Subjects received both ASTX727 and IV decitabine in these trials. A total of 207 subjects received IV decitabine (Table 48).

Table 43. Safety Population, Size, and Denominators

Safety Database for the ASTX727 Individuals exposed to the study drug in this development program for the indication under review (MDS and CMML) N=277			
Clinical Trial Groups	New Drug ASTX727 (n=277)	Active Control IV decitabine (n=207)	Placebo Not applicable
Controlled trials conducted for this indication	208	207	0
All other than controlled trials conducted for this indication	69 ^a	0	0
Controlled trials conducted for other indications	0	0	0

^a Includes 8 healthy volunteers exposed to cedazuridine only in the E7727-01 ADME study

Safety Population: The safety population includes all subjects exposed to at least one dose of study drug. Adverse events are summarized by treatment based on the onset date of the AE.

Pooling strategy: Phase 2 and Phase 3 safety data (Phase 2 stages of ASTX727-01 and Phase 3 ASTX727-02) were pooled for the integrated safety analysis as discussed and agreed at the pre-NDA meeting. All subjects who received ASTX727 in the pooled population received the recommended dose (100 mg cedazuridine and 35 mg decitabine) either as separate capsules (Phase 2 dose confirmation stage) or as FDC tablet (Phase 2 FDC stage and Phase 3). Both studies (the Phase 2 of ASTX727-01 and ASTX727-02) had very similar treatment frequency, study assessments, efficacy and safety endpoints.

Duration of exposure to ASTX727 in the integrated population is summarized in Table 44. In the 208 subjects treated with ASTX727 in the Phase 2 and Phase 3 studies, the median number of cycles received was 5 and the total number was 1342 cycles, including 20 subjects (9.6%) who had received long-term treatment with ≥ 12 cycles.

Table 44. Study Drug Exposure in ASTX727 Integrated Population

		Cedazuridine and Decitabine		
		Capsules or ASTX727 FDC Tablet ^a (N=208)	ASTX727 FDC Tablet (N=159)	All Subjects ^b (N=213)
Number of Subjects Treated		208 ^c	159	213
Total Number of Cycles	Total	1342	862	1347
Number of Cycles Received ^c	Mean	6.5	5.4	6.3
	SD	5.00	2.89	5.01
	Median	5.0	5.0	5.0
	Min, Max	1, 29	1, 16	1, 29
Number (%) of Subjects Receiving Exactly	1 cycle	6 (2.9)	4 (2.5)	11 (5.2)
	2 cycles	20 (9.6)	13 (8.2)	20 (9.4)
	3-5 cycles	93 (44.7)	83 (52.2)	93 (43.7)
	6-8 cycles	42 (20.2)	33 (20.8)	42 (19.7)
	9-11 cycles	27 (13.0)	21 (13.2)	27 (12.7)
	≥ 12 cycles	20 (9.6)	5 (3.1)	20 (9.4)

NOTE: Exposure data are included through the data cutoff dates for the respective CSRs.

^a Includes all subjects who received 100 mg cedazuridine and 35 mg decitabine, either administered concomitantly as separate capsules or as the ASTX727 FDC tablet.

^b Includes all subjects who received any treatment in Study ASTX727-01 Phase 2 or Study ASTX727-02, including 5 subjects who only received IV decitabine.

^c Completed or partially completed cycles.

Source: ISS Table 1.1.1

Table 45. Study Drug Exposure in Phase 2 and Phase 3 (Safety Analysis Set)

		Cedazuridine and Decitabine	
		Phase 2 (N=80)	Phase 3 (N=133)
Number of Subjects Treated		80 ^c	133
Total Number of Cycles		702	645
Number of Cycles Received ^a	Mean	8.8	4.8
	SD	7.0	2.23
	Median	7.0	4.0
	Min, Max	1, 29	1, 11
Number (%) of Subjects Receiving Exactly *	1 cycle	7 (8.8)	4 (3.0)
	2 cycles	10 (12.5)	10 (7.5)
	3-5 cycles	13 (16.3)	80 (60.2)
	6-8 cycles	16 (20.0)	26 (19.5)
	9-11 cycles	14 (17.5)	13 (9.8)
	≥12 cycles	20 (25.0)	0 (0.0)

NOTE: Exposure data are included through the data cutoff dates for the respective CSRs.

^a Completed or partially completed cycles including the IV cycle

Source: ASTX727-01-B CSR Table 14.1.2.1.3, ASTX727-02 CSR Table 14.1.6

* Indicates source of data is from a supplemental table

Treatment intensity was calculate based on exposure data and number of days of treatment received. If a subject received <4 of the 5 days of dosing, the subject was counted in the <80% intensity column. As per the Phase 2 and 3 study design, dose reduction was not allowed in the first 2 cycles, however one subject in each of Cycle 1 and 2 did not receive the full 5 days of treatment (one in an ASTX727 cycle and one in an IV decitabine cycle).

Table 46. Treatment Intensity of ASTX727 Safety Population (includes the IV cycle)

Cycle	Phase 2		Phase 3		Combined	
	Number of patients N	Dose intensity < 80% n (%)	Number of patients N	Dose intensity < 80% n (%)	Number of patients N	Dose intensity < 80% n (%)
1	78	1 (1.3)	130	0	208	1 (0.5) ^a
2	73	1 (1.4)	129	0	202	1 (0.5) ^b
3	63	1 (1.6)	119	6 (5.0)	182	7 (3.8)
4	59	4 (6.8)	96	11 (11.5)	155	15 (9.7)
5	55	3 (5.5)	64	7 (10.9)	119	10 (8.4)
6	50	4 (8.0)	39	9 (23.1)	89	13 (14.6)
7	41	3 (7.3)	26	5 (19.2)	67	8 (11.9)
8	37	2 (5.4)	17	0	54	2 (3.7)
9	34	2 (5.9)	13	1 (7.7)	47	3 (6.4)
10	28	2 (7.1)	5	0	33	2 (6.1)
11	25	0	4	1 (25.0)	29	1 (3.4)
12	20	0	0	0	20	0
> 12	20	8 (40.0)	0	0	20	8 (40.0)

^a Subject (b) (6) (Phase 2) discontinued treatment during Cycle 1.

^b Subject (b) (6) (Phase 2) received IV decitabine during Cycle 2 and only received 2 days of IV treatment.

Source: Supplemental table

The Applicant's Position:

The number of patients exposed to the study drug in the integrated analysis (208 patients) and the total number of cycles (1342 cycles) with median of 5 cycles (range 1 to 29) is adequate for safety review. The duration of follow-up in the Phase 2 (minimum: 12 months; median: ~24 months) and Phase 3 (minimum: 2 months; median: ~5 months) studies and the extent of exposure (i.e., number of cycles) are sufficient to assess the long-term safety of ASTX727. In the Phase 2 study with the longer follow-up, dose intensity was 80% or higher in over 90% of the patients in each cycle up to cycle 12. The data from Phase 3 show lower dose intensity beyond 5 cycles, but the number of patients beyond 5 cycles are small due to the shorter follow-up.

This pooling strategy was chosen because it provides the largest dataset for safety assessment and includes subjects who received multiple cycles of the same dose of cedazuridine and decitabine, and because there were similar exposure profiles (based on decitabine AUC) and adverse event (AE) profiles in ASTX727-01 Phase 2 and ASTX727-02 Phase 3. In addition, both studies provided a safety comparison between ASTX727 and IV decitabine in the first 2 cycles of treatment. Because Study ASTX727-01 Phase 2 was started earlier, the duration of treatment and follow up (median 7 cycles and 24 months, respectively) is longer than in Study ASTX727-02 (median 4 cycles of treatment and 5 months follow up) (Table 42).

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's assessment of the pooled safety analysis set (SAS) of 208

subjects exposed to ASTX727 in the Phase 2 (n=78) and Phase 3 (n=130) studies, excluding the 5 subjects treated with IV decitabine in cycle 1 who never received ASTX727. However, given that the one cycle of IV decitabine was part of the larger treatment regimen on these studies, FDA analyzed safety during all cycles of therapy, including the IV decitabine cycles. This differed from the Applicant's analyses, where TEAEs with onset during the IV decitabine cycle were not included in the "All Cycles" columns.

Furthermore, FDA focused its review of comparative safety between ASTX727 and IV decitabine in the first cycle of therapy, so as to avoid the possibility of overlapping toxicities between the first and second cycles of therapy. In these comparative analyses, we included the 5 subjects treated with IV decitabine in cycle 1 only. A total of 106 subjects received IV decitabine during Cycle 1 and a total of 107 subjects received ASTX727 during Cycle 1.

FDA performed an analysis of exposure in the pooled SAS based on the data from the 120-day safety update.

Exposure – ASTX727 Pooled SAS (120-Day Safety Update)

<u>Duration of Therapy (months)</u>	<u>Pooled SAS (N=208)</u>
Median (range)	8.0 (0.03-43.5)
0-3	41 (20%)
>3-6	41 (20%)
>6-9	30 (14%)
>9-12	47 (23%)
>12	49 (24%)

Source: FDA analysis

The Applicant provided updated data on treatment intensity in the 120-day safety update.

Treatment Intensity – ASTX727 Pooled SAS (120-Day Safety Update)

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Cycle	Pooled SAS	
	Number of patients N	Dose intensity < 80% n (%)
1	208	1 (0.5)
2	202	1 (0.5)
3	186	7 (3.8)
4	171	16 (9.4)
5	152	11 (7.2)
6	137	18 (13.1)
7	119	24 (20.2)
8	108	20 (18.5)
9	96	18 (18.8)
10	81	17 (21)
11	71	13 (18.3)
12	54	12 (22.2)
> 12	41	19 (46.3)

Source: 120-Day Safety Update

ASTX727 appeared to be relatively well tolerated with the majority of patients able to receive $\geq$ 80% of the planned doses for the majority of the treatment cycles. Later in the course of therapy, treatment intensity went down somewhat.

Relevant characteristics of the safety population:

Data:

The safety and efficacy population in the Phase 2 and Phase 3 studies were the same including all treated subjects. A summary of demographic and disease characteristics is provided above in the efficacy sections: Section 8.1.2 for Phase 2 (Table 21 and Table 22), and Section 8.1.4 for Phase 3 (Table 34 and Table 35).

The median age of subjects evaluated for safety in the integrated population was 71 years (range 32 to 90 years), subjects were predominantly male (69.5%) and White (91.5%). The median weight was 83.0 kg (range 39.8-157.9 kg) and the median body surface area (BSA) was 1.99 m² (range 1.3-2.9 m²).

Table 47. Subject Demographics in the Integrated Population (Phase 2 and Phase 3 Subjects)

Characteristic	Cedazuridine and Decitabine		All Subjects ^b (N=213)
	Capsules or ASTX727 FDC Tablet ^a (N=208)	ASTX727 FDC Tablet (N=159)	
Age (Years)			
n	208	159	213
Mean	69.6	69.5	69.7
SD	9.86	9.61	9.82
Median	71.0	71.0	71.0
Min, Max	32, 90	40, 90	32, 90
Age Category (years), n (%)			
<65	52 (25.0)	43 (27.0)	53 (24.9)
≥65 - <75	82 (39.4)	62 (39.0)	84 (39.4)
≥75	74 (35.6)	54 (34.0)	76 (35.7)
Sex, n (%)			
Male	144 (69.2)	104 (65.4)	148 (69.5)
Female	64 (30.8)	55 (34.6)	65 (30.5)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	4 (1.9)	3 (1.9)	4 (1.9)
Black or African American	6 (2.9)	4 (2.5)	6 (2.8)
Native Hawaiian or Other Pacific Islander	0	0	0
White	190 (91.3)	145 (91.2)	195 (91.5)
More than One Race	0	0	0
Not Reported	5 (2.4)	5 (3.1)	5 (2.3)
Other	3 (1.4)	2 (1.3)	3 (1.4)
Ethnicity, n (%)			
Hispanic or Latino	11 (5.3)	9 (5.7)	11 (5.2)
Not Hispanic or Latino	192 (92.3)	147 (92.5)	197 (92.5)
Not Reported	3 (1.4)	3 (1.9)	3 (1.4)
Unknown	2 (1.0)	0	2 (0.9)
Country, n (%)			
USA	170 (81.7)	128 (80.5)	174 (81.7)
Canada	38 (18.3)	31 (19.5)	39 (18.3)
Weight (kg)			
Mean	83.13	82.88	83.02
SD	17.713	17.677	17.894
Median	83.05	81.60	83.00
Min, Max	39.8, 157.9	45.0, 157.9	39.8, 157.9
BSA (m²)			
n	206	157	211
Mean	1.97	1.97	1.97
SD	0.247	0.243	0.251
Median	1.99	1.98	1.99
Min, Max	1.3, 2.9	1.4, 2.9	1.3, 2.9

^a Includes all subjects who received 100 mg cedazuridine and 35 mg decitabine, either administered concomitantly as separate capsules or as the ASTX727 FDC tablet.

^b Includes all subjects who received any treatment in Study ASTX727-01 Phase 2 or Study ASTX727-02, including 5 subjects who only received only IV decitabine.

Source: ISS Table 3.1.1, Table 3.1.2

All MDS IPSS types were represented in the study, and 15.5% of subjects had CMML. IPSS low-risk MDS was included in Study ASTX727-02 as it corresponded to eligibility by FAB disease criteria from the Dacogen USPI indication. The median time since diagnosis was 66 days (range 5 days to 15 years). Just over 20% of subjects had had prior anticancer therapy, with under 5% having had 1 previous cycle of HMA therapy. Just over 40% of subjects were dependent on RBC transfusions at baseline and just over 10% were dependent on platelet transfusions at baseline. Low hemoglobin (<80 g/L) was present at baseline in 17.8% of subjects, 14.6% had low platelets (<25×10⁹/L), and 22.5% had low neutrophils (<0.5×10⁹/L). Half of the subjects had >5% blasts in baseline bone marrow.

The Applicant’s Position:

The demographic and disease characteristics of the integrated population were representative of the general disease population for MDS of all IPSS scores and CMML.

The Regulatory Authorities’ Assessment:

FDA agrees with the Applicant’s assessment of baseline demographics, except for the statement that under 5% had 1 previous cycle of HMA therapy. Reviewing the data in the submission, we determined that 17 (8%) of patients in the pooled SAS received up to 1 prior cycle of HMA therapy.

FDA assessed baseline demographics according to whether patients received ASTX727 or IV decitabine in Cycle 1, in order to better understand comparative safety analyses between the arms in the first Cycle of therapy. Results are displayed in the Table below.

Demographics in the Pooled SAS per Treatment Received during Cycle 1

Variable		IV decitabine Cy1 (N=106)	ASTX727 Cy1 (N=107)
Age	Median (range)	72 (41-88)	70 (32-90)
Gender	Male	74 (70%)	74 (69%)
	Female	32 (30%)	33 (31%)
Site	United States	86 (81%)	88 (82%)
	Canada	20 (19%)	19 (18%)
ECOG PS	Median (range)	1 (0-2)	1 (0-2)

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Disease	MDS	86 (81%)	94 (88%)
	CMML	20 (19%)	13 (12%)
IPSS	Low risk	7 (7%)	4 (4%)
	Intermediate-1	46 (43%)	48 (45%)
	Intermediate-2	22 (21%)	23 (22%)
	High risk	11 (10%)	19 (18%)
	N/A	20 (19%)	13 (12%)
Cytogenetic risk	Better	36 (34%)	41 (38%)
	Intermediate	35 (33%)	25 (23%)
	Poor	25 (24%)	23 (22%)
	Missing/unknown	10 (9%)	18 (17%)
Prior HMA	Yes	8 (8%)	9 (8%)
Baseline blasts	Median (range)	5% (0-18%)	5.5% (0-19%)
Baseline ANC	< 1000/ μ L	43 (41%)	49 (46%)

Source: FDA analysis

Slightly more patients exposed to ASTX727 in the first cycle had MDS, high-risk IPSS score, less had intermediate risk cytogenetics, more had missing/unknown cytogenetics, and more had ANC < 1000 at baseline.

Adequacy of the safety database:

Data:

The safety profile of cedazuridine has been evaluated in 208 subjects treated in the Phase 2 and Phase 3 studies and in 69 subjects treated in the Phase 1 studies (Table 48). The integrated population included 208 subjects with MDS or CMML who were exposed to at least 1 dose of 100 mg cedazuridine and 35 mg decitabine administered concomitantly as separate capsules or as the ASTX727 FDC tablet, and 159 subjects were exposed to at least 1 dose of the ASTX727 FDC tablet.

A summary of the duration of treatment and follow-up by study is provided in Table 42 and the

duration of treatment for the integrated population is provided in Table 44. Treated subjects in the Phase 1 and Phase 2 portions of ASTX727-01 were followed for a minimum of 18 months and 12 months, respectively, with a median follow-up duration of approximately 24 months in both Phase 1 and Phase 2. The Phase 3 study had a shorter duration of follow-up (minimum: 2 months; median: approximately 5 months), in order to assess the primary endpoint of decitabine area under the plasma concentration-time curve (AUC) equivalence after all treated subjects completed assessments in Cycles 1 and 2.

Table 48. Summary of Exposure by Study

Study Identifier	Phase	Patient Population	Number of Subjects Treated ^a			Oral Treatment		
			Overall	Oral	IV ^b	Dosage Form	Cedazuridine/ Decitabine (mg)	Schedule (28-day cycles)
Phase 2-3								
ASTX727-02	3	MDS, CMML	133	130	132	ASTX727 FDC tablet	100/35	Daily×5
ASTX727-01 Phase 2 stage	2	MDS, CMML	50	49	48	Capsules ^c	100/35	Daily×5
			30	29	27	ASTX727 FDC tablet	100/35	Daily×5
Total # treated in Phase 2-3 (Integrated Population for Safety Analysis)			213	208	207			
Total # treated w/FDC tablet			--	159	--			
Phase 1								
ASTX727-01 Phase 1 stage (Dose Escalation)	1	MDS, CMML	44	44 ^d	--	Capsules ^c	40/20 (n=7) 60/20 (n=6) 100/20 (n=6) 100/40 (n=6) 100/30 (n=19)	See notes ^e
ASTX727-04 (Food Effect)	1b	MDS, CMML ^f	17	17	--	ASTX727 FDC tablet	100/35	Daily×5
E7727-01 ^g (ADME)	1	Healthy volunteers	8	8	--	Non-labelled cedazuridine capsules	100	Single dose
						3 h later ¹⁴ C-cedazuridine IV	100 µg	Single dose
						¹⁴ C-cedazuridine capsules	100	Single dose
Total # treated in Phase 1				69	--			

^a ASTX727-02 and the Phase 2 stages of ASTX727-01 were crossover studies.

^b IV=decitabine 20 mg/m² IV (1-hour infusion).

^c Cedazuridine and decitabine administered concomitantly as separate capsules.

^d One of the 44 subjects only received oral decitabine and did not receive oral cedazuridine.

^e **Cycle 1:** oral decitabine Day -3, decitabine 1-hour IV infusion (20 mg/m²) Day 1, cedazuridine capsules + decitabine capsules Days 2-5; **Cycle 2:** single-dose cedazuridine Day -3, cedazuridine capsules + decitabine capsules Days 1-5; **Cycle ≥3:** cedazuridine capsules + decitabine capsules Days 1-5.

^f Subjects with AML were eligible but none were enrolled.

^g ADME study (non-US IND study) conducted in the Netherlands.

The Applicant's Position:

The size of the database for the integrated population is adequate to assess the safety of

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ASTX727 in patients with MDS/CMML. The length of treatment, dose intensity, and follow-up were adequate to assess the long-term safety of the recommended dose in this population.

The Regulatory Authorities' Assessment:
FDA agrees with the Applicant's assessment.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
None

The Applicant's Position:
No issues relating to data integrity or quality were identified that may affect the safety review.

The Regulatory Authorities' Assessment:
The data integrity and submission quality are sufficient for FDA review.

Categorization of Adverse Event

The Applicant's Position:
The definitions for AEs and SAEs are provided in the individual study protocols. Disease progression was not considered to be an AE or serious adverse event (SAE).

- AEs that occurred during screening (prior to dosing) were recorded. Any new AEs from the start of study treatment to the earliest of the following were recorded: Until 30 days after the last dose of study treatment or
- Until the subject starts new MDS/CMML treatment (including new investigational treatment)

AEs were collected spontaneously and were elicited at scheduled visits using an open-ended non-leading question such as "Have you had any new symptoms, injuries, illnesses since your last visit?".

AEs and SAEs that occurred during the protocol-specified reporting period were followed until 1.) resolution, 2.) the investigator assesses the subject as stable and the event is following a clinically expected outcome, or 3.) the subject is lost to follow-up or withdraws consent.

Verbatim descriptions of all AEs were mapped to MedDRA thesaurus terms for all studies in the individual CSRs. For the integrated analyses, AEs from Phase 2 Study ASTX727-01 were re-mapped using MedDRA version 22.0 (up-versioned from the versions used in the CSR) to be

consistent with the version used for coding AEs in Phase 3 Study ASTX727-02. Verbatim terms as well as the preferred terms are provided in by-subject listings of Adverse Events.

Adverse event severity was graded using NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.3 for Phase 3 Study ASTX727-02. For Study ASTX727-01, CTCAE version 4.0 was used to grade AE severity. No re-grading of AE severity was performed.

All AEs summarized in the submission and summarized below are TEAEs. A treatment-emergent adverse event (TEAE) was 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 (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 subsequent leukemia), 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 subsequent leukemia) that were both serious and related to the study treatment were also considered treatment emergent. AEs with unknown onset date were considered to be treatment-emergent unless the stop date/time was known to be before first administration of the study drug (C1D1).

All AE data collected in the clinical study database with an AE start date on or before the CSR data cutoff dates were included in the data listings. However, only TEAEs are included in the AE summary tables. The number and percentage of subjects who had AEs are summarized by MedDRA system organ class (SOC) and preferred term (PT). AEs were not summarized based on per patient-year).

Summary tables that provide the causality of AEs are based on the investigator's assessment of relationship to study drug.

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's assessment. FDA evaluated the mapping of verbatim AE terms to MedDRA terms and is in agreement with the mapping.

We created a grouped terms dictionary based on common related terms (see Appendix 19.5). The grouped terms are included in safety analyses throughout the review and will be indicated with a "*" in safety tables and the text of the review.

Routine Clinical Tests

The Applicant's Position:

Chemistry and hematology laboratory parameters were assessed prior to each cycle (at a minimum); hematology parameters were assessed more frequently in the first 2 cycles. The schedule of assessments is provided in Table 18 for Phase 2 and in Table 31 for Phase 3.

The Regulatory Authorities' Assessment:
 FDA agrees with the Applicant's assessment.

8.2.4. Safety Results

Deaths

Data:

All deaths were recorded in the ASTX727 clinical studies in order to assess the efficacy endpoint of survival. In the Phase 2 and 3 studies, 13 subjects died within 30 days of the last dose of study drug; 11 subjects due to AEs and 1 subject due to progressive disease.

Table 49. Summary of Deaths Occurring in the Integrated Population (Phase 2 and Phase 3 Subjects)

Cause of Death	Number (%) of Subjects		
	All Cycles		
	Cedazuridine and Decitabine		
	Capsules or ASTX727 FDC Tablet (N=208)	ASTX727 FDC Tablet (N=159)	All Subjects ^a (N=213)
All Deaths	49 (23.6)	25 (15.7)	51 (23.9)
Progressive Disease	2 (1.0)	2 (1.3)	2 (0.9)
Adverse Event	18 (8.7)	11 (6.9)	20 (9.4)
Other ^b	2 (1.0)	2 (1.3)	2 (0.9)
Unknown ^c	27 (13.0)	10 (6.3)	27 (12.7)
Deaths During Treatment Period ^d	12 (5.8)	10 (6.3)	13 (6.1)
Progressive Disease	1 (0.5)	1 (0.6)	1 (0.5)
Adverse Event	10 (4.8)	8 (5.0)	11 (5.2)
Other	0	0	0
Unknown ^c	1 (0.5)	1 (0.6)	1 (0.5)
Deaths After Treatment Period ^e	37 (17.8)	15 (9.4)	38 (17.8)
Progressive Disease	1 (0.5)	1 (0.6)	1 (0.5)
Adverse Event	8 (3.8)	3 (1.9)	9 (4.2)
Other ^b	2 (1.0)	2 (1.3)	2 (0.9)
Unknown ^c	26 (12.5)	9 (5.7)	26 (12.2)

^a Includes the 5 subjects who received only IV decitabine.

^b "Other" causes of death included pneumonia, fulminant liver failure, and unknown.

^c For subjects in Study ASTX727-01, if the cause of death was not attributed to an AE, it was reported as unknown.

^d Date of death on or after the first dose date up to 30 days after the last dose date.

^e Date of death more than 30 days after the last dose.

Source: ISS Table 5.3.1, ASTX727-02 CSR Table 37

During Cycle 1 (N=213), the 30-day all-cause mortality (30 days from start of treatment) was the same (0.9%) for patients treated with ASTX727 and for subjects treated with IV decitabine. One subject in each group died within the first 30 days: one subject on ASTX727 from Phase 2 died

from respiratory failure considered unrelated to treatment by the investigator on C1 D29 (Subject (b) (6)); and one subject on IV decitabine from Phase 3 died from septic shock considered related to treatment by the investigator on C1 D28 (Subject (b) (6)).

TEAEs with and Outcome of Death

A total of 17 subjects in the integrated population (3 in the IV decitabine cycle and 14 in the overall ASTX727 population) had a treatment-emergent AE with an onset date within 30 days of the last study treatment and an outcome of death (Table 50), including subjects who died more than 30 days after last treatment, but the event started within 30 days.

Table 50. Treatment-Emergent Adverse Events with an Outcome of Death in ASTX727 Integrated Population

	Number (%) of Subjects			
	Cycle 1 or 2		Cycles ≥3	All Cycles
	Cedazuridine and Decitabine			
	IV Decitabine (N=207)	Capsules or FDC Tablet ASTX727 (N=208)	Capsules or FDC Tablet ASTX727 (N=182)	Capsules or FDC Tablet ASTX727 (N=208)
Number of subjects who reported at least one TEAE with an outcome of death	3 (1.4)	4 (1.9)	10 (5.5)	14 (6.7)
Sepsis	0	1 (0.5)	3 (1.6)	4 (1.9)
Septic shock ^a	1 (0.5)	2 (1.0)	1 (0.5)	3 (1.4)
Cardiac arrest	0	0	1 (0.5)	1 (0.5)
Myocarditis	0	0	1 (0.5)	1 (0.5)
Sudden death	0	0	1 (0.5)	1 (0.5)
Pneumonia	2 (1.0)	0	1 (0.5)	1 (0.5)
Small cell lung cancer	0	0	1 (0.5)	1 (0.5)
Cerebral haemorrhage	0	0	1 (0.5)	1 (0.5)
Respiratory failure	0	1 (0.5)	0	1 (0.5)

Treatment-emergent AEs included those occurring up to 30 days after the last dose and events that occurred more than 30 days after the last dose that were both serious and related to study treatment.

^a One event of septic shock reported with ASTX727 in Cycle 2 was considered by the investigator to be related to IV decitabine received in Cycle 1 (Subject (b) (6)) (ASTX727-02 CSR Section 12.2.4).

Source: ISS Table 5.4.1

Table 51. Summary of Treatment-Emergent Adverse Events with an Outcome of Death - Cycle 1 and Cycle 2 Separately in the Integrated Population (Phase 2 and Phase 3 Subjects)

Preferred Term	Number (%) of Subjects			
	Cycle 1		Cycle 2	
	IV Decitabine (N=106)	Cedazuridine and Decitabine Capsules or FDC Tablet (N=107)	IV Decitabine (N=101)	Cedazuridine and Decitabine Capsules or FDC Tablet (N=101)
Number of subjects who reported at least one TEAE with an outcome of death	2 (1.9)	2 (1.9)	1 (1.0)	2 (2.0)
Pneumonia	1 (0.9)	0	1 (1.0)	0
Respiratory failure	0	1 (0.9)	0	0
Sepsis	0	0	0	1 (1.0)
Septic shock	1 (0.9)	1 (0.9)	0	1 (1.0)

Source: Supplemental table

Phase 1 Studies

As of the 01 June 2017 data cutoff date for the Phase 1 stage of Study ASTX727-01, 4 of 44 subjects died from AEs occurring up to 30 days from the last study treatment, all were considered unrelated to treatment by the investigator. TEAEs with an outcome of death in this study included:

- cardiac arrest (2 patients): died C7 D20; and C12 D10
- multiple organ dysfunction syndrome (died C1 D31), and sepsis (died C1 D20)

In Study ASTX727-04 (food effect), 1 of 17 treated subjects had an AE with an outcome of death as of the 08 July 2019 CSR data cutoff. TEAEs with an outcome of death in this study included:

- atrial fibrillation (died C1 D25) considered unrelated to study treatment

In the E7727-01 ADME study in healthy volunteers there were no deaths or SAEs during the study.

The Applicant's Position:

In general, AEs with an outcome of death were primarily infections that likely occurred as a result of prolonged neutropenia, which are typical for this patient population. A few other events, such as cardiac arrest, respiratory failure, and cancer were also observed, which are not unusual given the age of the subjects in the study population. Fatal AEs reported in >1 subject were sepsis and septic shock. In Cycles 1 and 2, there was no difference in the incidence of fatal AEs between treatments. In the IV decitabine 5-day published study ([Steensma et al 2009](#)), 11 patients of 99 treated died within 30 days of study treatment (11%). The 6.7% deaths within 30 days of treatment in the pooled safety data set is consistent with data from IV decitabine.

The Regulatory Authorities' Assessment:

Using the data from the 120-day safety update, FDA identified a total of 94 deaths among 277

subjects exposed to ASTX727 in the ISS dataset listed in the Table below. Most deaths occurred more than 30 days after the last dose of ASTX727 (73 subjects, 26%), leaving 21 (8%) on-treatment deaths.

Deaths in the Integrated Summary of Safety

Population / Treatment	On or within 30 days of last dose	More than 30 days after last dose
Phase 2 and Phase 3 Subjects (N=208)*	16 (8%)	65 (31%)
Phase 1 Subjects (N=44)	4 (9%)	7 (16%)
Food Effect Subjects (N=17)	1 (6%)	1 (6%)
Healthy volunteers (N=8)	0	0
Total (N=277)	21 (8%)	73 (26%)

Source: FDA analysis

*Excludes the 5 subjects who received only IV decitabine during Cycle 1.

The Applicant identified the underlying malignancy as the cause of death in 2 of the 21 on-treatment deaths (10%) in subjects exposed to ASTX727. A total of 18 (86%) were due to an adverse reaction and one had an unknown cause. Fatal adverse reactions occurring in 2 or more patients included sepsis (n=4), pneumonia (n=3), septic shock (n=3), cardiac arrest (n=2), and respiratory failure (n=2).

FDA performed a detailed assessment of deaths in patients on the Phase 2 and 3 trials (the pooled SAS population), including a comparison of deaths between the IV decitabine and ASTX727 arms in the first cycle of therapy (see Table below).

Deaths in the Pooled SAS Population – 120 Day Safety Update

	Cycle 1		All cycles ¹
	ASTX727 (N=107)	IV decitabine (N=106)	ASTX727 (N=208)
Total deaths	2 (2%)	2 (2%)	81 (39%)
30-day mortality²	1 (1%)	1 (1%)	1 (0.5%)
On-treatment deaths³	2 (2%)	1 (1%)	16 (8%)
On-treatment fatal ARs⁴	2 (2%)	2 (2%)	12 (6%)

Source: FDA analysis

¹Excludes the 5 patients who received IV decitabine during cycle 1 and never received ASTX727

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²Within 30 days following the first dose of treatment

³On or within 30 days after the last dose of treatment

⁴Includes patients with fatal AR that started within the window

Reviewer comments: It is notable that the 30-day mortality rate was quite low and consistent between ASTX727 and IV decitabine.

FDA reviewed individual patient narratives from the 16 patients in the pooled SAS (N=208) with on-treatment deaths to confirm the causes of death. In general, the narratives were well-written.

Of the 16 on-treatment deaths in the pooled SAS, FDA-adjudicated causes of death were primary disease (n=4) and adverse drug reactions (n=12), including sepsis (n=3), septic shock (n=3), pneumonia (n=2), respiratory failure (n=2), and one each of cerebral hemorrhage and sudden death. FDA agreed with the Applicant’s assessment of causality for most deaths, except for the two bolded in the Table below.

Deaths within 30 Days in the Pooled SAS – 120 Day Safety Update

Subject	Death Day	Days since last dose	FDA Root COD	Applicant Root COD
(b) (6)	29	24	Adverse reaction (respiratory failure)	Adverse reaction (respiratory failure)
	32	27	Adverse reaction (septic shock)	Adverse reaction (septic shock)
	56	23	Adverse reaction (septic shock)	Adverse reaction (septic shock)
	61	28	Adverse reaction (pneumonia)	Adverse reaction (pneumonia)
	99	21	Adverse reaction (septic shock)	Adverse reaction (septic shock)
	134	27	Adverse reaction (cerebral hemorrhage)	Adverse reaction (cerebral hemorrhage)
	157	25	Adverse reaction (pneumonia)	Adverse reaction (pneumonia)
	161	16	Adverse reaction (sepsis)	Adverse reaction (sepsis)
	161	30	Adverse reaction (sepsis)	Adverse reaction (sepsis)
	294	12	Adverse reaction (sudden death)	Adverse reaction (sudden death)
	300	28	Adverse reaction (respiratory failure)	Adverse reaction (respiratory failure)
	664	26	Adverse reaction (sepsis)	Adverse reaction (sepsis)

NDA Multi-disciplinary Review and Evaluation
 NDA 212576, Original
 INQOVI (decitabine and cedazuridine)

Subject	Death Day	Days since last dose	FDA Root COD	Applicant Root COD
(b) (6)	59	26	Primary disease	Adverse reaction (pneumonia)
224	14		Primary disease	Primary disease
261	14		Primary disease	Primary disease
274	19		Primary disease	Unknown

Source: FDA analysis

Abbreviations: COD, cause of death

As per the Table above, two cases that the Applicant designated as due to adverse reaction (pneumonia) (n=1) and unknown (n=1) were deemed related to primary disease by FDA. These case narratives are described in detail below.

Subject (b) (6): This was an 86-year-old man with CMML enrolled on the Phase 2 trial in Stage 2, Sequence A. On Study day 57, 24 days after the last dose of IV decitabine, the patient presented to the hospital for bilateral pneumonia. The patient had pneumonia prior to starting on the study, as well. He was found to have leukocytosis of 139.9 and was started on antibiotics. He clinically deteriorated and was transferred to the intensive care unit for respiratory failure and hyperleukocytosis and was intubated. Acute kidney injury, tumor lysis syndrome, and severe coagulopathy were also noted. White blood cell count further increased to 225.7. The patient died on Study day 57. The investigator assessed the event of bilateral pneumonia as Grade 5 and not related. The Applicant concurred but noted that the cause of death was the AE in the NDA dataset. FDA deemed the root cause of death to be the underlying disease, as evidenced by the hyperleukocytosis and tumor lysis syndrome.

Subject (b) (6): This was a 66-year-old man with CMML enrolled on the Phase 2 trial in Stage 3 Sequence B. He was hospitalized on study day 264, 5 days after the last dose, with an unrelated SAE of abdominal pain. On day 267, 12 days after the last dose, while still hospitalized, bone marrow showed progression of CMML. He was transitioned to comfort care and remained in the hospital for pain management. On Day 274, the patient died, with an immediate cause of death reported as disease progression. Increasing peripheral blasts and pancytopenia may have contributed. The Applicant listed the cause of death as unknown, but given the report of suspected disease progression in the narrative along with increasing peripheral blasts, FDA considered this death to be related to the primary disease.

Lastly, FDA reviewed the two deaths that occurred in patients treated with IV decitabine during Cycle 1 (Subjects (b) (6) and (b) (6)) who never received ASTX727. The first patient died of an adverse reaction of septic shock on Day 28, 23 days after the last dose of IV decitabine and the second patient died of an adverse reaction of pneumonia on Day 48, 43 days after the last dose of IV decitabine.

Serious Adverse Events

Data:

The most common non-fatal SAEs in the integrated population across all cycles were febrile neutropenia, pneumonia, and sepsis (Table 52).

In Cycles 1 and 2, the incidence of non-fatal SAEs was higher in the ASTX727 cycle (31.7% for the overall pooled AST727 population) compared to IV decitabine cycle (21.3%). There was no single AE responsible for this difference; however, small differences in the AEs of febrile neutropenia (11.5% for overall ASTX727, 7.7% for IV decitabine), pneumonia (5.8% for overall ASTX727, 3.9% for IV decitabine), and sepsis (3.4% for overall ASTX727, 1.0% for IV decitabine) were observed. All 3 AE terms are associated with one another, since pneumonia and sepsis are common in subjects with febrile neutropenia. In addition, the incidence of SAEs of pneumonia and sepsis on ASTX727 during Cycles ≥ 3 decreased compared with the incidence on ASTX727 in Cycle 1 or 2, to a comparable incidence with IV decitabine (3.8% for SAE of pneumonia in ASTX727 Cycles ≥ 3 vs 3.9% for IV decitabine; 2.7% for SAE of sepsis in ASTX727 Cycles ≥ 3 vs 1% for IV decitabine).

Table 52. Non-fatal Serious Adverse Events Occurring in $\geq 1\%$ of Subjects in Any Group in ASTX727 Integrated Population (Phase 2 and Phase 3 Subjects)

	Number (%) of Subjects			
	Cycle 1 or 2	Cycles ≥ 3		All Cycles
	Cedazuridine and Decitabine			
	IV Decitabine (N=207)	Capsules or ASTX727 FDC Tablet (N=208)	Capsules or ASTX727 FDC Tablet (N=182)	Capsules or ASTX727 FDC Tablet (N=208)
Number of subjects who reported at least one non-fatal serious TEAE ^a	44 (21.3)	66 (31.7)	64 (35.2)	102 (49.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	19 (9.2)	26 (12.5)	29 (15.9)	46 (22.1)
Febrile neutropenia	16 (7.7)	24 (11.5)	28 (15.4)	43 (20.7)
Anaemia	0	1 (0.5)	2 (1.1)	3 (1.4)
CARDIAC DISORDERS	1 (0.5)	1 (0.5)	4 (2.2)	5 (2.4)
Myocardial infarction	0	1 (0.5)	1 (0.5)	2 (1.0)
GASTROINTESTINAL DISORDERS	4 (1.9)	2 (1.0)	10 (5.5)	11 (5.3)
Gastrointestinal haemorrhage	1 (0.5)	1 (0.5)	3 (1.6)	4 (1.9)
Abdominal pain	0	0	2 (1.1)	2 (1.0)
Nausea	1 (0.5)	0	2 (1.1)	2 (1.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.5)	2 (1.0)	8 (4.4)	10 (6.8)
Pyrexia	1 (0.5)	2 (1.0)	4 (2.2)	6 (2.9)
Asthenia	0	0	3 (1.6)	3 (1.4)
Oedema peripheral	0	0	2 (1.1)	2 (1.0)
INFECTIONS AND INFESTATIONS	17 (8.2)	30 (14.4)	25 (13.7)	49 (23.6)
Pneumonia	8 (3.9)	12 (5.8)	7 (3.8)	17 (8.2)
Sepsis	2 (1.0)	7 (3.4)	5 (2.7)	12 (5.8)
Cellulitis	2 (1.0)	4 (1.9)	2 (1.1)	6 (2.9)

	Number (%) of Subjects			
	Cycle 1 or 2		Cycles ≥3	All Cycles
	Cedazuridine and Decitabine			
	IV Decitabine (N=207)	Capsules or ASTX727 FDC Tablet (N=208)	Capsules or ASTX727 FDC Tablet (N=182)	Capsules or ASTX727 FDC Tablet (N=208)
Bacteraemia	0	2 (1.0)	2 (1.1)	4 (1.9)
Urinary tract infection	1 (0.5)	1 (0.5)	3 (1.6)	4 (1.9)
Influenza	0	1 (0.5)	2 (1.1)	3 (1.4)
Upper respiratory tract infection	0	0	3 (1.6)	3 (1.4)
Diverticulitis	0	1 (0.5)	1 (0.5)	2 (1.0)
Pharyngitis	0	2 (1.0)	0	2 (1.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (1.0)	3 (1.4)	1 (0.5)	4 (1.9)
Fall	0	2 (1.0)	1 (0.5)	3 (1.4)
METABOLISM AND NUTRITION DISORDERS	2 (1.0)	4 (1.9)	1 (0.5)	5 (2.4)
Failure to thrive	0	2 (1.0)	0	2 (1.0)
Dehydration	2 (1.0)	0	1 (0.5)	1 (0.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.5)	1 (0.5)	3 (1.6)	4 (1.9)
Back pain	0	0	2 (1.1)	2 (1.0)
NERVOUS SYSTEM DISORDERS	2 (1.0)	2 (1.0)	4 (2.2)	6 (2.9)
Syncope	1 (0.5)	1 (0.5)	3 (1.6)	4 (1.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (2.9)	2 (1.0)	4 (2.2)	6 (2.9)
Dyspnoea	2 (1.0)	1 (0.5)	1 (0.5)	2 (1.0)
VASCULAR DISORDERS	2 (1.0)	0	5 (2.7)	5 (2.4)
Hypertension	1 (0.5)	0	2 (1.1)	2 (1.0)

^a Excluding AEs with an outcome of death but including the non-fatal SAEs of subjects who had AEs with outcome of death.
Source: ISS Table 5.5.1

Due to the crossover design of the Phase 2 and 3 studies, there was a potential for AEs that began and were reported in Cycle 2 to be a consequence of Cycle 1 treatment. This made the Cycle 1 comparison more reliable as it is not affected by prior treatment. Therefore, an analysis was performed to summarize SAEs by treatment for Cycle 1 and Cycle 2 separately (Table 53). This allowed the assessment of AEs for Cycle 1, which was the principal randomized comparison before the crossover, and the potential for carryover effects. The data suggest that the overall higher incidence of SAEs reported in Cycles 1 or 2 for ASTX727 compared with IV decitabine was mainly driven by a difference in the incidence of SAEs in Cycle 2 (35.6% for ASTX727, 19.8% for IV decitabine) with a much smaller difference in SAE incidence in Cycle 1 (29.9% for ASTX727, 23.6% for IV decitabine). The small difference in SAE incidence in Cycle 1 may simply reflect small differences in the population of subjects randomized to Sequence A (ASTX727 in Cycle 1) compared with Sequence B (IV decitabine in Cycle 1). In Study ASTX727-02, subjects randomized to ASTX727 in Cycle 1 (Sequence A) had a higher proportion with high risk MDS and higher proportion with low baseline neutrophil count (<1000 µL) compared to Sequence B (Table 35).

Table 53. Serious Adverse Events Occurring in >1% of Subjects - Cycles 1 or 2 Separately in the Integrated Population (Phase 2 and Phase 3 Subjects)

System Organ Class Preferred Term	Number (%) of Subjects			
	Cycle 1		Cycle 2	
	IV Decitabine (N=106)	Cedazuridine and Decitabine Capsules or FDC Tablet (N=107)	IV Decitabine (N=101)	Cedazuridine and Decitabine Capsules or FDC Tablet (N=101)
Total number of serious TEAES	39	44	30	50
Number of subjects who reported at least one serious TEAE	25 (23.6)	32 (29.9)	20 (19.8)	36 (35.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	13 (12.3)	10 (9.3)	6 (5.9)	16 (15.8)
Febrile neutropenia	12 (11.3)	9 (8.4)	4 (4.0)	15 (14.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	2 (1.9)	1 (1.0)	0
Pyrexia	0	2 (1.9)	1 (1.0)	0
INFECTIONS AND INFESTATIONS	8 (7.5)	15 (14.0)	11 (10.9)	18 (17.8)
Pneumonia	4 (3.8)	6 (5.6)	6 (5.9)	6 (5.9)
Sepsis	1 (0.9)	5 (4.7)	2 (2.0)	4 (4.0)
Septic shock ^a	1 (0.9)	1 (0.9)	0	1 (1.0)
Cellulitis	1 (0.9)	2 (1.9)	1 (1.0)	2 (2.0)
Bacteraemia	0	0	0	2 (2.0)
METABOLISM AND NUTRITION DISORDERS	2 (1.9)	3 (2.8)	0	1 (1.0)
Dehydration	2 (1.9)	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (3.8)	2 (1.9)	2 (2.0)	1 (1.0)
Dyspnoea	2 (1.9)	0	0	1 (1.0)
Respiratory failure	0	2 (1.9)	1 (1.0)	0

^a Septic shock is included despite occurring at an incidence below the cut-off for this table because of its medical relatedness to sepsis.

Source: ISS Table 6.1.2.1

Table 54 below shows the most common SAEs (including fatal SAEs) from the Phase 2 and Phase 3 separately in Cycles 1 or 2. A summary of all SAEs in Phase 2 and Phase 3 separately by Cycle 1 or 2 separately is provided in Appendix 19.6, Table 84 and Table 85).

Table 54. Most Common SAEs ≥5% (including fatal SAEs) in Cycles 1 or 2 for Phase 2 and 3

Preferred Term	Phase 2		Phase 3	
	Cycle 1 or 2		Cycle 1 or 2	
	IV decitabine N=75	ASTX727 N=78	IV decitabine N=132	ASTX727 N=130
Subjects with any SAEs	21 (28%)	28 (35.9%)	24 (18.2%)	40 (30.8%)
Febrile Neutropenia	9 (12%)	8 (10.3%)	7 (5.3%)	16 (12.3%)
Pneumonia	5 (6.7%)	5 (6.4%)	5 (3.8%)	7 (5.4%)
Sepsis or Septic Shock	1 (1.3%)	5 (6.4%)	1 (0.8%)	5 (3.8%)

Source: ASTX727-01-B CSR, 14.4.2.4.3; ASTX727-02 CSR, 14.4.1.4

The Applicant’s Position:

Non-fatal SAEs from oral ASTX727 are mainly related to myelosuppression and infections related to neutropenia, which is consistent with IV decitabine data from [Steensma et al 2009](#) and [Dacogen USPI 2019](#), and also consistent with expected complications of the disease itself. The incidence was higher in ASTX727 Cycle 1 or 2 vs IV decitabine Cycles 1 or 2 in some of those events such as febrile neutropenia, pneumonia, and sepsis (Table 52). However, the difference was small and mostly in Cycle 2 for febrile neutropenia (Table 53). The differences were mainly driven by Phase 3 population and may be related to lower baseline neutrophil count and higher % of high-risk MDS in Sequence A (ASTX727 in Cycle 1) compared to Sequence B (IV decitabine in Cycle 1) in the Phase 3 population. In Phase 2, the 2 most common SAEs of febrile neutropenia and pneumonia occurred at similar or lower incidence in ASTX727 compared to IV decitabine (Table 54). Only sepsis SAEs occurred at higher incidence in both Phase 2 and Phase 3.

The most common SAEs (febrile neutropenia, pneumonia, and sepsis) were identical in both Phase 2 and Phase 3 and highly consistent with both the expected complications of the disease population and the mechanism of action of decitabine. Myelosuppression and infections are common complications in MDS and CMML and are also expected pharmacological effects from decitabine. Since ASTX727 achieves equivalent systemic exposure and the same DNA demethylation effect compared to IV decitabine, it is unlikely that the incidence of these events are substantially different between ASTX727 and IV decitabine.

The Regulatory Authorities’ Assessment:

FDA performed an analysis of all treatment-emergent SAEs (TESAEs) and TESAEs in the first cycle of therapy between ASTX727 and IV decitabine based on the data from the 120-day safety update.

A TESAE occurring within 30 days after the last dose of ASTX727 or IV decitabine in the pooled SAS (N=208) was reported for 142 (68%) of patients. Considering the first Cycle of therapy, TESAEs occurred in 32 (30%) of patients treated with ASTX727 and 25 (24%) patients treated

with IV decitabine. The most frequently occurring ($\geq 2\%$) TESAEs are presented in the Table below.

SAEs in the Pooled SAS Population – 120 Day Safety Update

PT/Grouped term	Cycle 1		All cycles
	ASTX727 (N=107)	IV decitabine (N=106)	ASTX727 (N=208)
Total TESAEs	32 (30%)	25 (24%)	142 (68%)
Febrile neutropenia	9 (8%)	13 (12%)	62 (30%)
Pneumonia*	6 (6%)	6 (6%)	30 (14%)
Sepsis*	6 (6%)	2 (2%)	28 (13%)
Cellulitis	2 (2%)	1 (1%)	9 (4%)
Dyspnea*	2 (2%)	2 (2%)	9 (4%)
Pyrexia	2 (2%)	0	6 (3%)
Mucositis	1 (1%)	0	5 (2%)
Syncope	1 (1%)	1 (1%)	6 (3%)
Thrombosis*	0	0	6 (3%)
Fatigue*	0	0	5 (2%)

Source: FDA analysis

*Grouped term (see Appendix 19.5).

SAEs were slightly lower in patients treated with IV decitabine during Cycle 1 for unclear reasons. It is possible that variations in baseline characteristics may have contributed. Sepsis was slightly more common in patients treated with ASTX727 during Cycle 1, while febrile

neutropenia was slightly less common. The numbers are sufficiently low that firm conclusions cannot be made. Overall, the SAEs observed are in line with the known safety profile of IV decitabine.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Overall, the incidence of AEs leading to discontinuation of treatment in the integrated population was low (3.8%). During Cycles 1 and 2, two subjects each permanently discontinued treatment with ASTX727 or IV decitabine due to an AE. Across all cycles, the only AE leading to treatment discontinuation of ASTX727 that was reported in >1 subject was febrile neutropenia.

The Applicant's Position:

Discontinuation of treatment due to AEs in ASTX727 is low and do not represent an impediment to treatment compliance.

The Regulatory Authorities' Assessment:

FDA performed an analysis of all TEAEs leading to withdrawal of study therapy in the pooled SAS and by treatment arm during Cycle 1 using the data from the 120-day safety update.

TEAEs leading to withdrawal occurred in 11 (5%) of patients, including 3 (3%) of patients treated with ASTX727 and 1 (1%) of patients treated with IV decitabine during Cycle 1. The only TEAEs leading to discontinuation in more than one subject were febrile neutropenia (n=2) and pneumonia (n=2). Overall, permanent discontinuation due to adverse reactions was quite low.

Dose Interruption/Reduction Due to Adverse Effects

Data:

The most common AEs that led to drug interruption or dose reduction of ASTX727 were expected myelosuppression events, including neutropenia, febrile neutropenia, and thrombocytopenia.

During IV decitabine treatment, there was one subject in Phase 2 who received 2 of the 5 days of IV treatment during Cycle 2; dosing was interrupted due to an AE of sepsis.

Table 55. Adverse Events Leading to Drug Interruption in >1% of Subjects in the ASTX727 Integrated Population

SYSTEM ORGAN CLASS Preferred Term	Number (%) of Subjects	
	All Cycles	
	Cedazuridine and Decitabine	
	Capsules or ASTX727 FDC Tablet (N=208)	ASTX727 FDC Tablet (N=159)
Total number of TEAEs leading to drug interruption	118	73
Number of subjects who reported at least one TEAE leading to drug interruption	46 (22.1)	34 (21.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	33 (15.9)	23 (14.5)
Neutropenia	20 (9.6)	13 (8.2)
Febrile neutropenia	9 (4.3)	6 (3.8)
Anaemia	5 (2.4)	3 (1.9)
Thrombocytopenia	5 (2.4)	4 (2.5)
Leukopenia	3 (1.4)	2 (1.3)
GASTROINTESTINAL DISORDERS	6 (2.9)	5 (3.1)
Stomatitis	2 (1.0)	2 (1.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (1.4)	1 (0.6)
Pyrexia	2 (1.0)	1 (0.6)
INFECTIONS AND INFESTATIONS	11 (5.3)	7 (4.4)
Sepsis	2 (1.0)	1 (0.6)
Pneumonia	2 (1.0)	2 (1.3)

Source: Supplemental table

Table 56. Adverse Events Leading to Dose Reduction in >1% of Subjects in the ASTX727 Integrated Population

SYSTEM ORGAN CLASS Preferred Term	Number (%) of Subjects	
	All Cycles	
	Cedazuridine and Decitabine	
	Capsules or ASTX727 FDC Tablet (N=208)	ASTX727 FDC Tablet (N=159)
Total number of TEAEs leading to dose reduction	30	16
Number of subjects who reported at least one TEAE leading to dose reduction	21 (10.1)	12 (7.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	16 (7.7)	10 (6.3)
Neutropenia	11 (5.3)	6 (3.8)
Thrombocytopenia	4 (1.9)	3 (1.9)
Febrile neutropenia	2 (1.0)	1 (0.6)
Leukopenia	2 (1.0)	2 (1.3)

Source: Supplemental table

The Applicant's Position:

Dose interruptions or reduction are an important tool to manage myelosuppression, infections, or other complications. Dose reductions due to AEs occurred in 10% or less of patients

suggesting that the recommended dose and intensity are appropriate for the majority of patients.

The Regulatory Authorities' Assessment:

FDA performed an analysis of TEAEs leading to dose interruption and reduction in the pooled SAS and by treatment arm during Cycle 1 using the data from the 120-day safety update.

Dose interruption

TEAEs leading to dose interruption occurred in 86 (41%) of patients in the pooled SAS, including 7 (7%) with ASTX727 and 9 (8%) with IV decitabine during Cycle 1. The most common TEAEs leading to interruption of study therapy are shown in the Table below in descending order. The Table includes only those events that occurred in > 2% of subjects.

TEAEs leading to dose interruption (> 2%) in the pooled SAS – 120 day safety update

PT/Grouped term	Cycle 1		All Cycles
	ASTX727 (N=107)	IV decitabine (N=106)	ASTX727 (N=208)
Neutropenia	2 (1%)	2 (2%)	38 (18%)
Febrile neutropenia	1 (1%)	2 (2%)	17 (8%)
Thrombocytopenia	0	1 (1%)	12 (6%)
Anemia	0	0	11 (5%)
Leukopenia*	0	0	10 (5%)
Pneumonia*	1 (1%)	0	8 (4%)
Sepsis*	0	1 (1%)	5 (2%)

Source: FDA analysis

*Grouped term (see Appendix 19.5)

Overall, the number of treatment interruptions are as expected for the patient population. The most common interruptions were for cytopenia-related complications. Interruptions in the first treatment cycle were uncommon with both ASTX727 and IV decitabine.

Dose reduction

Dose reduction due to TEAEs occurred in 39 (19%) of patients in the pooled SAS, including 1 (1%) with ASTX727 (thrombocytopenia) and 1 (1%) with IV decitabine (anemia) during Cycle 1. TEAEs leading to dose reduction of study therapy in > 1% of subjects during all cycles were neutropenia (12%), anemia (3%), and thrombocytopenia (3%).

Significant Adverse Events

Data:

Myelosuppression

The most common Grade ≥ 3 AEs across all cycles in the overall ASTX727 integrated population (N=208) were the expected myelosuppression-related events that could be related to either disease or treatment with ASTX727, including thrombocytopenia (41.8%), neutropenia (42.3%), anemia (28.4%), febrile neutropenia (23.6%), and leukopenia (20.7%) (Table 59). In Cycles 1 or 2 the incidence was generally similar between IV decitabine and ASTX727 (Table 59 and Table 60).

Infections

The most common Grade ≥ 3 infection AEs in the integrated population (N=208) was pneumonia (10.1%) and sepsis (7.7%) for all ASTX727 cycles (Table 59). The incidence of pneumonia was slightly higher for ASTX727 than IV decitabine in Cycle 1 but not in Cycle 2 (Table 60). Grade ≥ 3 sepsis was higher in ASTX727 Cycles 1 or 2, which is consistent with data from SAEs.

Phase 1

In Study ASTX727-01 Phase 1 (N=44), Grade ≥ 3 myelosuppression AEs included thrombocytopenia (40.9%), neutropenia (29.5%), anemia (25.0%), febrile neutropenia (15.9%), and leukopenia (15.9%). Most common Grade ≥ 3 infection AEs in Study ASTX727-01 Phase 1 included pneumonia (15.9%), and sepsis (6.8%).

In Study ASTX727-04 (N=17), Grade ≥ 3 myelosuppression AEs included neutropenia (58.8%), thrombocytopenia (35.3%), anemia (29.4%), leukopenia (29.4%), and febrile neutropenia (11.8%). There was 1 patient in this study with Grade ≥ 3 sepsis but no cases of Grade ≥ 3 pneumonia.

In Study E7727-01 (N=8), there were no myelosuppression AEs.

The Applicant's Position:

The significant AEs of Grade ≥ 3 were the expected events of myelosuppression and infections. They were consistent in all studies and as expected from the disease patient population and the pharmacological effect of decitabine. The incidences were generally similar between IV decitabine and ASTX727 in Cycles 1 or 2. A slightly higher incidence on ASTX727 mainly in cycle 1 was observed in some events, which may have also been related to the imbalance between Sequence A and B in Phase 3. As discussed above patients randomized to Sequence A (ASTX727 vs IV decitabine in Cycle 1 in Phase 3) had worse baseline characteristics than Sequence B (higher % of high risk MDS, lower % of CMML, and higher % of low baseline neutrophils $< 1000/\mu\text{L}$) (See Table 35 of patients characteristics in Phase 3). Many cases with sepsis occurred in patients with Grade 3 or 4 neutropenia at baseline (Appendix 19.6, Table 86).

The Regulatory Authorities' Assessment:

FDA performed an analysis of AESIs of cytopenias, infections, and hemorrhage in the pooled SAS, including the comparison of ASTX727 and IV decitabine during Cycle 1 using the data from

the 120-day safety update (see Table below).

AESIs in pooled SAS – 120 day safety update

PT/grouped term	Cycle 1				All Cycles	
	ASTX727 (N=107)		IV decitabine (N=106)		ASTX727 (N=208)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Ang Grade	Grade ≥ 3
Cytopenias¹	78 (73%)	70 (65%)	72 (68%)	68 (64%)	179 (86%)	175 (84%)
Thrombocytopenia	55 (51%)	45 (42%)	43 (41%)	36 (34%)	128 (62%)	113 (54%)
Neutropenia	41 (38%)	39 (36%)	39 (37%)	33 (31%)	118 (57%)	113 (54%)
Anemia*	33 (31%)	27 (25%)	35 (33%)	30 (28%)	99 (48%)	88 (42%)
Febrile neutropenia	11 (10%)	11 (10%)	14 (13%)	14 (13%)	68 (33%)	67 (32%)
Leukopenia	27 (25%)	20 (19%)	15 (14%)	13 (12%)	59 (28%)	54 (26%)
Infections²	35 (33%)	16 (15%)	22 (21%)	9 (8%)	139 (67%)	78 (38%)
URI*	6 (6%)	0	3 (3%)	0	47 (23%)	3 (1%)
Pneumonia*	8 (7%)	7 (7%)	7 (7%)	6 (6%)	44 (21%)	35 (17%)
Sepsis*	6 (6%)	6 (6%)	2 (2%)	2 (2%)	29 (14%)	29 (14%)
Cellulitis*	4 (4%)	1 (1%)	3 (3%)	2 (2%)	24 (12%)	11 (5%)
Hemorrhage³	27 (25%)	3 (3%)	21 (20%)	0	95 (46%)	14 (7%)
Contusion	10 (9%)	0	2 (2%)	0	35 (17%)	0
Epistaxis	5 (5%)	1 (1%)	8 (8%)	0	26 (13%)	2 (1%)

FDA analysis

*Grouped term (see Appendix 19.5)

¹Cytopenias: defined as hematopoietic cytopenias broad SMQ term

²Infections: defined as the infections and infestations SOC

³Hemorrhage: defined as the haemorrhage terms (excl laboratory terms) narrow SMQ

To put things in perspective with these AESIs, the USPI for IV decitabine using the 15 mg/m² q8h x 3 days every 6 weeks dosing regimen reports an incidence of neutropenia of 90%, thrombocytopenia 89%, anemia 82%, febrile neutropenia 29%, and leukopenia 28%. Results in the USPI for the 20 mg/m² qday x 5 days every 4 weeks dosing regimen were neutropenia 38%, thrombocytopenia 27%, anemia 31%, febrile neutropenia 20%, and leukopenia 6%. However, it was noted that in this single-arm study, investigators reported AEs based on clinical signs and symptoms rather than predefined laboratory abnormalities. Given that laboratory AEs often under-report laboratory abnormalities, it is difficult to make the comparison across trials. However, the cytopenias seen with ASTX727 are roughly the same (in terms of febrile neutropenia and leukopenia) or less (neutropenia, thrombocytopenia, anemia) than what was observed with the 15 mg/m² regimen of decitabine.

For the 3-day and 5-day regimens, the IV decitabine USPI describes pneumonia in 22% and 20% of patients and cellulitis in 12% and 9%, respectively. With the 3-day regimen, 7% had Staphylococcal infection and 5% had bacteremia and with the 5-day regimen, 8% had Staphylococcal bacteremia. These infectious AEs are of similar incidence to what is reported here with ASTX727. In terms of hemorrhage, the IV decitabine USPI notes petechiae in 39%, ecchymosis in 22%, and hematoma in 5% for the 3-day regimen and epistaxis in 13%, petechiae in 12%, contusion in 9%, and ecchymosis in 9% for the 5-day regimen. Therefore, the numbers

for hemorrhage also appear similar to what is reported here for ASTX727.

Overall, the AEs appear to be more common in patients treated with ASTX727 compared to IV decitabine in the first cycle of therapy. It is possible, again, that this may have been due to imbalances in baseline demographics. It will be important for clinicians to closely monitor patients while on this oral form of decitabine given the possibility for significant cytopenias, infection, and hemorrhage. Despite this being an oral therapy that will allow patients to spend more time at home and away from the clinic, it will be important to have close follow-up for laboratory testing and clinical monitoring.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Common AEs (All Grades)

The most common AEs across all cycles in the overall ASTX727 integrated population were consistent with the known AE profile of decitabine and included thrombocytopenia, neutropenia, anemia, fatigue, nausea, constipation, leukopenia, febrile neutropenia, diarrhea, and dyspnea (Table 57). The incidence of these events was similar during randomized treatment with ASTX727 and IV decitabine in Cycles 1 and 2. There were also no clinically notable differences in the proportion of subjects with AEs in the different System Organ Classes (SOCs), with the exception of the Infections and Infestations SOC. However, the most common AE in this SOC (pneumonia) occurred at a similar incidence for ASTX727 and IV decitabine.

Table 57. All Grade Adverse Events Occurring in ≥10% of Subjects in Any Group in ASTX727 Integrated Population (Phase 2 and Phase 3 Subjects)

System Organ Class Preferred Term	Number (%) of Subjects			
	Cycle 1 or 2		Cycles ≥3	
	Cedazuridine and Decitabine			
	IV Decitabine (N=207)	Capsules or ASTX727 FDC Tablet (N=208)	Capsules or ASTX727 FDC Tablet (N=182)	Capsules or ASTX727 FDC Tablet (N=208)
Number of subjects who reported at least one TEAE	193 (93.2)	198 (95.2)	162 (89.0)	203 (97.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	119 (57.5)	130 (62.5)	102 (56.0)	155 (74.5)
Thrombocytopenia	74 (35.7)	80 (38.5)	54 (29.7)	102 (49.0)
Neutropenia	64 (30.9)	63 (30.3)	57 (31.3)	91 (43.8)
Anaemia	53 (25.6)	58 (27.9)	36 (19.8)	71 (34.1)
Febrile neutropenia	22 (10.6)	27 (13.0)	32 (17.6)	49 (23.6)
Leukopenia	31 (15.0)	35 (16.8)	32 (17.6)	50 (24.0)
GASTROINTESTINAL DISORDERS	104 (50.2)	110 (52.9)	87 (47.8)	144 (69.2)
Nausea	32 (15.5)	36 (17.3)	21 (11.5)	55 (26.4)
Constipation	37 (17.9)	35 (16.8)	22 (12.1)	53 (25.5)
Diarrhoea	23 (11.1)	29 (13.9)	25 (13.7)	48 (23.1)

System Organ Class Preferred Term	Number (%) of Subjects			
	Cycle 1 or 2		Cycles ≥3	
	Cedazuridine and Decitabine			
	IV Decitabine (N=207)	Capsules or ASTX727 FDC Tablet (N=208)	Capsules or ASTX727 FDC Tablet (N=182)	Capsules or ASTX727 FDC Tablet (N=208)
GENERAL DISORDERS AND ADMINISTRATION	64 (30.9)	76 (36.5)	70 (38.5)	116 (55.8)
SITE CONDITIONS				
Fatigue	32 (15.5)	46 (22.1)	34 (18.7)	70 (33.7)
Asthenia	8 (3.9)	11 (5.3)	22 (12.1)	32 (15.4)
Oedema peripheral	16 (7.7)	12 (5.8)	15 (8.2)	26 (12.5)
Pyrexia	15 (7.2)	12 (5.8)	15 (8.2)	24 (11.5)
INFECTIONS AND INFESTATIONS	37 (17.9)	67 (32.2)	68 (37.4)	107 (51.4)
Pneumonia	13 (6.3)	15 (7.2)	11 (6.0)	24 (11.5)
INVESTIGATIONS	36 (17.4)	42 (20.2)	48 (26.4)	71 (34.1)
Alanine aminotransferase increased	9 (4.3)	14 (6.7)	17 (9.3)	26 (12.5)
METABOLISM AND NUTRITION DISORDERS	47 (22.7)	58 (27.9)	60 (33.0)	92 (44.2)
Decreased appetite	11 (5.3)	19 (9.1)	20 (11.0)	38 (18.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	38 (18.4)	35 (16.8)	60 (33.0)	84 (40.4)
Arthralgia	9 (4.3)	11 (5.3)	23 (12.6)	32 (15.4)
Back pain	13 (6.3)	6 (2.9)	15 (8.2)	21 (10.1)
NERVOUS SYSTEM DISORDERS	51 (24.6)	51 (24.5)	45 (24.7)	84 (40.4)
Dizziness	19 (9.2)	23 (11.1)	16 (8.8)	39 (18.8)
Headache	23 (11.1)	26 (12.5)	15 (8.2)	35 (16.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	62 (30.0)	65 (31.3)	65 (35.7)	102 (49.0)
Dyspnoea	16 (7.7)	26 (12.5)	19 (10.4)	43 (20.7)
Cough	16 (7.7)	14 (6.7)	20 (11.0)	29 (13.9)

Source: ISS Table 5.1.2

Table 58. All Grade Adverse Events Occurring in ≥10% of Subjects - Cycle 1 or 2 Separately in the Integrated Population (Phase 2 and Phase 3 Subjects)

Preferred Term	Number (%) of Subjects			
	Cycle 1		Cycle 2	
	Cedazuridine and Decitabine Capsules or FDC		Cedazuridine and Decitabine Capsules or FDC	
	IV Decitabine (N=106)	Tablet (N=107)	IV Decitabine (N=101)	Tablet (N=101)
Number of subjects who reported at least one TEAE	103 (97.2)	106 (99.1)	90 (89.1)	92 (91.1)
Thrombocytopenia	41 (38.7)	53 (49.5)	33 (32.7)	27 (26.7)
Neutropenia	36 (34.0)	41 (38.3)	28 (27.7)	22 (21.8)
Anaemia	29 (27.4)	32 (29.9)	24 (23.8)	26 (25.7)
Nausea	16 (15.1)	27 (25.2)	16 (15.8)	9 (8.9)
Leukopenia	15 (14.2)	26 (24.3)	16 (15.8)	9 (8.9)
Fatigue	21 (19.8)	25 (23.4)	11 (10.9)	21 (20.8)
Constipation	24 (22.6)	21 (19.6)	13 (12.9)	14 (13.9)

Preferred Term	Number (%) of Subjects			
	Cycle 1		Cycle 2	
	Cedazuridine and Decitabine Capsules or FDC		Cedazuridine and Decitabine Capsules or FDC	
	IV Decitabine (N=106)	Tablet (N=107)	IV Decitabine (N=101)	Tablet (N=101)
Number of subjects who reported at least one TEAE	103 (97.2)	106 (99.1)	90 (89.1)	92 (91.1)
Headache	14 (13.2)	22 (20.6)	9 (8.9)	4 (4.0)
Dyspnoea	9 (8.5)	18 (16.8)	7 (6.9)	8 (7.9)
Diarrhoea	12 (11.3)	17 (15.9)	11 (10.9)	12 (11.9)
Dizziness	12 (11.3)	17 (15.9)	7 (6.9)	6 (5.9)
Febrile neutropenia	15 (14.2)	11 (10.3)	7 (6.9)	16 (15.8)
Oropharyngeal pain	12 (11.3)	8 (7.5)	7 (6.9)	3 (3.0)
Decreased appetite	6 (5.7)	11 (10.3)	5 (5.0)	8 (7.9)

Source: Supplemental table

Grade ≥ 3 AEs

In Cycles 1 and 2, the overall incidence of Grade ≥ 3 AEs was generally similar in the ASTX727 cycle and the IV decitabine cycle in Cycles 1 or 2 (Table 59). This was also generally true for all SOCs with the exception of Infections SOC, but no large differences in the incidence of individual infection events, with the exception of sepsis (1.0% IV decitabine, 3.8% ASTX727). Of note is that GI AEs of Grade ≥ 3 were $< 2\%$ and therefore not represented in the table. The most common myelosuppression AEs Grade ≥ 3 tended to be higher on ASTX727 in Cycle 1 (thrombocytopenia, neutropenia, and anemia), but higher on IV decitabine in Cycle 2 (Table 60). However, febrile neutropenia Grade ≥ 3 occurred at a higher incidence on IV decitabine in Cycle 1 and higher on ASTX727 in Cycle 2 (Table 60).

Table 59. Grade ≥ 3 Adverse Events Occurring in $\geq 2\%$ of Subjects in the ASTX727 Integrated Population

	Number (%) of Subjects			
	Cycle 1 or 2		Cycles ≥ 3	All Cycles
	Cedazuridine and Decitabine			
	IV Decitabine (N=207)	Capsules or ASTX727 FDC Tablet (N=208)	Capsules or ASTX727 FDC Tablet (N=182)	Capsules or ASTX727 FDC Tablet (N=208)
Number of subjects who reported at least one Grade ≥ 3 TEAE	128 (61.8)	132 (63.5)	121 (66.5)	168 (80.8)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	107 (51.7)	114 (54.8)	95 (52.2)	148 (71.2)
Thrombocytopenia	58 (28.0)	61 (29.3)	44 (24.2)	87 (41.8)
Neutropenia	55 (26.6)	59 (28.4)	54 (29.7)	88 (42.3)
Anaemia	43 (20.8)	46 (22.1)	29 (15.9)	59 (28.4)
Febrile neutropenia	20 (9.7)	26 (12.5)	32 (17.6)	49 (23.6)
Leukopenia	25 (12.1)	28 (13.5)	28 (15.4)	43 (20.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.5)	7 (3.4)	6 (3.3)	12 (5.8)

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	Number (%) of Subjects			
	Cycle 1 or 2	Cycles ≥3		All Cycles
	Cedazuridine and Decitabine			
	IV Decitabine (N=207)	Capsules or ASTX727 FDC Tablet (N=208)	Capsules or ASTX727 FDC Tablet (N=182)	Capsules or ASTX727 FDC Tablet (N=208)
Fatigue	1 (0.5)	4 (1.9)	3 (1.6)	6 (2.9)
INFECTIONS AND INFESTATIONS	19 (9.2)	34 (16.3)	30 (16.5)	58 (27.9)
Pneumonia	10 (4.8)	13 (6.3)	9 (4.9)	21 (10.1)
Sepsis	2 (1.0)	8 (3.8)	8 (4.4)	16 (7.7)
Septic shock ^a	1 (0.5)	2 (1.0)	1 (0.5)	3 (1.4)
Cellulitis	4 (1.9)	4 (1.9)	2 (1.1)	6 (2.9)
METABOLISM AND NUTRITION DISORDERS	7 (3.4)	9 (4.3)	15 (8.2)	21 (10.1)
Hyponatraemia	1 (0.5)	4 (1.9)	2 (1.1)	5 (2.4)
Hypokalaemia	1 (0.5)	2 (1.0)	3 (1.6)	4 (1.9)
NERVOUS SYSTEM DISORDERS	2 (1.0)	3 (1.4)	6 (3.3)	9 (4.3)
Syncope	2 (1.0)	1 (0.5)	4 (2.2)	5 (2.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	7 (3.4)	8 (3.8)	8 (4.4)	15 (7.2)
Dyspnoea	3 (1.4)	5 (2.4)	2 (1.1)	6 (2.9)

^a Septic shock is included because of its medical relatedness to sepsis despite occurring at an incidence below the cut-off for this table.

Source: ISS Table 5.1.6

Table 60. Grade ≥3 Adverse Events Occurring in ≥2% of Subjects - Cycle 1 or 2 Separately in the Integrated Population (Phase 2 and Phase 3 Subjects)

System Organ Class Preferred Term	Number (%) of Subjects			
	Cycle 1		Cycle 2	
	IV Decitabine (N=106)	Cedazuridine and Decitabine Capsules or FDC Tablet (N=107)	IV Decitabine (N=101)	Cedazuridine and Decitabine Capsules or FDC Tablet (N=101)
Number of subjects who reported at least one Grade ≥3 TEAE	71 (67.0)	78 (72.9)	57 (56.4)	54 (53.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Thrombocytopenia	34 (32.1)	43 (40.2)	24 (23.8)	18 (17.8)
Neutropenia	30 (28.3)	38 (35.5)	25 (24.8)	21 (20.8)
Anaemia	22 (20.8)	26 (24.3)	21 (20.8)	20 (19.8)
Febrile neutropenia	13 (12.3)	11 (10.3)	7 (6.9)	15 (14.9)
Leukopenia	13 (12.3)	20 (18.7)	12 (11.9)	8 (7.9)
Lymphopenia	1 (0.9)	0	2 (2.0)	1 (1.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	0	1 (0.9)	1 (1.0)	3 (3.0)
INFECTIONS AND INFESTATIONS				
Pneumonia	4 (3.8)	7 (6.5)	6 (5.9)	6 (5.9)
Sepsis	1 (0.9)	5 (4.7)	2 (2.0)	4 (4.0)
Cellulitis	2 (1.9)	1 (0.9)	2 (2.0)	3 (3.0)
Septic shock ^a	1 (0.9)	1 (0.9)	0	1 (1.0)
Bacteraemia	0	0	0	2 (2.0)
INVESTIGATIONS				
Alanine aminotransferase increased	0	2 (1.9)	0	1 (1.0)
METABOLISM AND NUTRITION DISORDERS				
Hyponatraemia	0	1 (0.9)	1 (1.0)	3 (3.0)
Hypokalaemia	0	0	1 (1.0)	2 (2.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Dyspnoea	3 (2.8)	3 (2.8)	0	2 (2.0)
Respiratory failure	0	3 (2.8)	1 (1.0)	0

^a Septic shock is included because of its medical relatedness to sepsis despite occurring at an incidence below the cut-off for this table.

Source: ISS Table 6.1.3.1

Phase 1 Studies

A summary of adverse events occurring in >1 subject by dose cohort or ≥10% of subjects overall in supportive study ASTX727-01 Phase 1 Dose Escalation is presented in Table 61. Adverse events (all grades) that occurred with the highest incidence included thrombocytopenia (52.3%), fatigue (43.2%), and constipation (36.4%).

Table 61. ASTX727-01 Phase 1: All Grade Adverse Events Occurring in >10% of Subject Overall by Dose Cohort

System Organ Class Preferred Term	Number (%) of Subjects					Total (N=44)
	Dose Cohort					
	Cohort 1 40/20 (N=7)	Cohort 2 60/20 (N=6)	Cohort 3 100/20 (N=6)	Cohort 4 100/40 (N=6)	Cohort 5 100/30 (N=19)	
Number (%) of Subjects who Reported any TEAE	6 (85.7%)	6 (100.0%)	6 (100.0%)	5 (83.3%)	19 (100.0%)	42 (95.5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
Anaemia	4 (57.1%)	1 (16.7%)	3 (50.0%)	2 (33.3%)	4 (21.1%)	14 (31.8%)
Febrile Neutropenia	1 (14.3%)	1 (16.7%)	1 (16.7%)	2 (33.3%)	3 (15.8%)	8 (18.2%)
Leukopenia	1 (14.3%)	2 (33.3%)	1 (16.7%)	0	3 (15.8%)	7 (15.9%)
Neutropenia	3 (42.9%)	2 (33.3%)	4 (66.7%)	1 (16.7%)	4 (21.1%)	14 (31.8%)
Thrombocytopenia	4 (57.1%)	3 (50.0%)	4 (66.7%)	3 (50.0%)	9 (47.4%)	23 (52.3%)
GASTROINTESTINAL DISORDERS						
Abdominal Pain	0	1 (16.7%)	1 (16.7%)	2 (33.3%)	2 (10.5%)	6 (13.6%)
Constipation	2 (28.6%)	5 (83.3%)	1 (16.7%)	1 (16.7%)	7 (36.8%)	16 (36.4%)
Diarrhoea	2 (28.6%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	2 (10.5%)	8 (18.2%)
Haemorrhoids	1 (14.3%)	1 (16.7%)	0	0	3 (15.8%)	5 (11.4%)
Nausea	1 (14.3%)	4 (66.7%)	3 (50.0%)	2 (33.3%)	4 (21.1%)	14 (31.8%)
Stomatitis	1 (14.3%)	0	0	2 (33.3%)	2 (10.5%)	5 (11.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Fatigue	2 (28.6%)	5 (83.3%)	3 (50.0%)	4 (66.7%)	5 (26.3%)	19 (43.2%)
Oedema	1 (14.3%)	2 (33.3%)	0	1 (16.7%)	1 (5.3%)	5 (11.4%)
Oedema Peripheral	0	2 (33.3%)	1 (16.7%)	2 (33.3%)	4 (21.1%)	9 (20.5%)
Pyrexia	1 (14.3%)	2 (33.3%)	1 (16.7%)	2 (33.3%)	1 (5.3%)	7 (15.9%)
INFECTIONS AND INFESTATIONS						
Pneumonia	0	2 (33.3%)	0	3 (50.0%)	4 (21.1%)	9 (20.5%)
Sepsis ^a	0	0	0	0	3 (15.8%)	3 (6.8%)
INVESTIGATIONS						
Alanine Aminotransferase Increased	1 (14.3%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	5 (26.3%)	9 (20.5%)
Aspartate Aminotransferase Increased	1 (14.3%)	2 (33.3%)	0	2 (33.3%)	4 (21.1%)	9 (20.5%)
Weight Decreased	0	1 (16.7%)	0	0	4 (21.1%)	5 (11.4%)
METABOLISM AND NUTRITION DISORDERS						
Hyperkalaemia	0	1 (16.7%)	0	1 (16.7%)	4 (21.1%)	6 (13.6%)
Hypoalbuminaemia	1 (14.3%)	1 (16.7%)	0	1 (16.7%)	5 (26.3%)	8 (18.2%)
Hypokalaemia	2 (28.6%)	1 (16.7%)	0	2 (33.3%)	3 (15.8%)	8 (18.2%)
Hypomagnesaemia	2 (28.6%)	1 (16.7%)	1 (16.7%)	3 (50.0%)	2 (10.5%)	9 (20.5%)
Hyponatraemia	1 (14.3%)	1 (16.7%)	0	1 (16.7%)	2 (10.5%)	5 (11.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
Back Pain	0	1 (16.7%)	0	1 (16.7%)	3 (15.8%)	5 (11.4%)
Muscle Spasms	2 (28.6%)	0	1 (16.7%)	0	2 (10.5%)	5 (11.4%)
NERVOUS SYSTEM DISORDERS						
Headache	0	0	2 (33.3%)	0	4 (21.1%)	6 (13.6%)
PSYCHIATRIC DISORDERS						
	1 (14.3%)	2 (33.3%)	0	1 (16.7%)	3 (15.8%)	7 (15.9%)

System Organ Class Preferred Term	Number (%) of Subjects					Total (N=44)
	Dose Cohort					
	Cedazuridine (mg) / Decitabine (mg)					
	Cohort 1 40/20 (N=7)	Cohort 2 60/20 (N=6)	Cohort 3 100/20 (N=6)	Cohort 4 100/40 (N=6)	Cohort 5 100/30 (N=19)	
Insomnia	1 (14.3%)	2 (33.3%)	0	1 (16.7%)	3 (15.8%)	7 (15.9%)
RENAL AND URINARY DISORDERS	0	3 (50.0%)	1 (16.7%)	1 (16.7%)	6 (31.6%)	11 (25.0%)
Acute Kidney Injury	0	3 (50.0%)	0	1 (16.7%)	1 (5.3%)	5 (11.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (57.1%)	4 (66.7%)	1 (16.7%)	2 (33.3%)	9 (47.4%)	20 (45.5%)
Cough	1 (14.3%)	2 (33.3%)	1 (16.7%)	2 (33.3%)	2 (10.5%)	8 (18.2%)
Dyspnoea	1 (14.3%)	0	1 (16.7%)	0	4 (21.1%)	6 (13.6%)
Oropharyngeal Pain	3 (42.9%)	0	0	0	2 (10.5%)	5 (11.4%)

^a Sepsis is included despite occurring at an incidence below the cutoff.

Source: ASTX727-01-A CSR Table 14.4.2.4.1

Common all grades AEs in supporting study ASTX727-04 (food effect) included neutropenia (58.8%), anemia (41.2%), thrombocytopenia (35.3%), fatigue (29.4%), leukopenia (29.4%), nausea (29.4%), and constipation (23.5%).

Grade ≥ 3 AEs in supporting studies ASTX727-01 Phase 1 and ASTX727-04 were generally similar to those in the integrated population. Overall (N=44) the most common Grade ≥ 3 AEs in ASTX727-01 Phase 1 included thrombocytopenia (40.9%), neutropenia (29.5%), and anemia (25.0%). In ASTX727-04 (food effect), the most common Grade ≥ 3 AEs (N=17) were neutropenia (58.8%), thrombocytopenia (35.3%), anemia (29.4%), and leukopenia (29.4%).

The Applicant's Position:

The common all grade AEs and Grade ≥ 3 AEs were consistent with the expected AEs from IV decitabine and are the common complications of the disease population. The overall incidence of all grade AEs and Grade ≥ 3 AEs was generally similar between IV decitabine and ASTX727 in Cycles 1 or 2 with few exceptions.

GI AEs either as a system organ class or individually were very similar between IV decitabine and ASTX727 in the first 2 randomized cycles and the GI SOC incidence did not increase with subsequent cycles (Cycles ≥ 3). GI AEs of Grade ≥ 3 were <2%.

In Phase 1, there was no obvious difference in AEs particularly mechanism related myelosuppression between the lowest dose cohort 1 in Phase 1 (cedazuridine 40 mg/ decitabine 20 mg) and the highest dose cohort 4 in Phase 1 (cedazuridine 100 mg/ decitabine 40 mg) suggesting a broad therapeutic index across all doses tested.

The Regulatory Authorities' Assessment:

FDA performed an analysis TEAEs based on the data from the 120-day safety update, focusing

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on the pooled SAS and the comparative safety data between ASTX727 and IV decitabine in Cycle 1 of the pooled Phase 2 and Phase 3 trials.

A total of 208/208 (100%) of patients experienced a TEAE in the pooled SAS. In Cycle 1, 106/107 (99%) treated with ASTX727 and 105/106 (99%) treated with IV decitabine experienced a TEAE. A total of 195/208 (94%) experienced a grade 3 or higher TEAE, including 79/107 (74%) treated with ASTX727 in Cycle 1 and 76/106 (72%) treated with IV decitabine in Cycle 1.

TEAEs occurring either on study treatment or within 30 days after discontinuation of study treatment in the pooled SAS and in the comparative safety population between ASTX727 and IV decitabine during Cycle 1 are summarized by PT/grouped term in the Table below. TEAEs occurring in at least 10% of patients are included in the Table.

TEAEs in ≥ 10% of patients in the pooled SAS and in Cycle 1 between ASTX727 and IV decitabine – 120 day safety update

PT/grouped term	Cycle 1				All Cycles	
	ASTX727 (N=107)		IV decitabine (N=106)		ASTX727 (N=208)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Thrombocytopenia	55 (51%)	45 (42%)	43 (41%)	36 (34%)	128 (62%)	113 (54%)
Neutropenia	41 (38%)	39 (36%)	39 (37%)	33 (31%)	118 (57%)	113 (54%)
Fatigue*	31 (29%)	2 (2%)	26 (25%)	0	114 (55%)	11 (5%)
Anemia*	33 (31%)	27 (25%)	35 (33%)	30 (28%)	99 (48%)	88 (42%)
Constipation	21 (20%)	0	24 (23%)	0	91 (44%)	0
Myalgias*	10 (9%)	2 (2%)	17 (16%)	1 (1%)	88 (42%)	6 (3%)
Mucositis*	19 (18%)	1 (1%)	25 (24%)	2 (2%)	86 (41%)	8 (4%)
Arthralgias*	10 (9%)	1 (1%)	14 (13%)	1 (1%)	84 (40%)	6 (3%)
Nausea	27 (25%)	0	17 (16%)	0	84 (40%)	1 (0.5%)
Dyspnea*	18 (17%)	3 (3%)	10 (9%)	3 (3%)	79 (38%)	13 (6%)
Diarrhea*	17 (16%)	0	12 (11%)	0	77 (37%)	3 (1%)
Rash*	13 (12%)	1 (1%)	12 (11%)	1 (1%)	69 (33%)	1 (0.5%)
Febrile neutropenia	11 (10%)	11 (10%)	14 (13%)	14 (13%)	68 (33%)	67 (32%)
Dizziness*	17 (16%)	1 (1%)	12 (11%)	0	68 (33%)	4 (2%)
Edema*	11 (10%)	0	12 (11%)	0	63 (30%)	1 (0.5%)
Cough*	7 (7%)	0	9 (8%)	0	58 (28%)	0
Headache	23 (22%)	0	14 (13%)	0	62 (30%)	0
Leukopenia	27 (25%)	20 (19%)	15 (14%)	13 (12%)	59 (28%)	54 (26%)
Decreased appetite	11 (10%)	1 (1%)	6 (6%)	0	50 (24%)	4 (2%)
URI*	6 (6%)	0	3 (3%)	0	47 (23%)	3 (1%)
Pneumonia*	8 (7%)	7 (7%)	7 (7%)	5 (5%)	44 (21%)	31 (15%)
Transaminase increased*	13 (12%)	1 (1%)	3 (3%)	0	43 (21%)	6 (3%)
Abdominal pain*	10 (9%)	0	7 (7%)	0	40 (19%)	2 (1%)
Pyrexia	8 (7%)	0	7 (7%)	0	39 (19%)	2 (1%)
Contusion	10 (9%)	0	2 (2%)	0	35 (17%)	0
Renal impairment*	8 (7%)	0	9 (8%)	1 (1%)	35 (17%)	0
Vomiting	5 (5%)	0	5 (5%)	0	32 (15%)	0
Hypokalemia	2 (2%)	0	7 (7%)	0	29 (14%)	6 (3%)
Sepsis*	6 (6%)	6 (6%)	2 (2%)	1 (1%)	29 (14%)	23 (11%)

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Neuropathy*	4 (4%)	0	8 (8%)	0	28 (13%)	0
Epistaxis	5 (5%)	1 (1%)	8 (8%)	0	26 (13%)	2 (1%)
Fall	4 (4%)	0	1 (1%)	0	25 (12%)	3 (1%)
Hypoalbuminemia	9 (8%)	0	3 (3%)	0	25 (12%)	1 (0.5%)
Insomnia	6 (6%)	0	2 (2%)	0	25 (12%)	1 (0.5%)
Cellulitis*	4 (4%)	1 (1%)	3 (3%)	2 (2%)	24 (12%)	11 (5%)
Hyperbilirubinemia*	5 (5%)	0	5 (5%)	0	23 (11%)	4 (2%)
Hypocalcemia	6 (6%)	0	2 (2%)	0	23 (11%)	0
Hypomagnesemia	3 (3%)	0	5 (5%)	0	23 (11%)	1 (0.5%)
Hypotension*	4 (4%)	0	6 (6%)	1 (1%)	23 (11%)	5 (2%)
Arrhythmia*	3 (3%)	0	2 (2%)	0	22 (11%)	2 (1%)
Hyperglycemia	3 (3%)	0	2 (2%)	0	21 (10%)	5 (2%)
Weight decreased	5 (5%)	0	3 (3%)	0	21 (10%)	2 (1%)

FDA analysis

*Grouped term (see Appendix 19.5)

FDA agrees with the Applicant's assessment that the common all-grade and Grade ≥ 3 TEAEs are consistent with the expected AEs from IV decitabine and are common complications in the disease population. TEAEs $\geq 5\%$ more common with ASTX727 in the first cycle of therapy included thrombocytopenia, neutropenia, nausea, dyspnea, diarrhea, dizziness, headache, leukopenia, transaminase increased, contusion, and hypoalbuminemia. TEAEs $\geq 5\%$ more common with IV decitabine in the first cycle included arthralgias, myalgias, mucositis, and hypokalemia. Again, the increased cytopenias seen with ASTX727 during Cycle 1 may have been due to some baseline imbalances between the two treatment sequences. The increased nausea, diarrhea, and transaminase elevation with ASTX727 could be associated with the oral administration. However, almost all of the gastrointestinal toxicity was Grade 1-2 in severity.

FDA conducted an analysis of cases of acute febrile neutrophilic dermatosis (AFND, also known as Sweet's syndrome) given that this TEAE has been reported in the postmarketing setting for Dacogen. There were two cases of Grade 2 AFND noted in the submission – one in an 80-year-old man with MDS on the Phase 2 trial on Cycle 2, Day 24 of ASTX727 (Subject ^{(b) (6)}) and one in a 66-year-old man with MDS on the Phase 3 trial on Cycle 2, Day 1 of IV decitabine (Subject ^{(b) (6)}). Therefore, FDA agrees with the Applicant to include this adverse reaction in Section 6 of labeling.

Lastly, FDA evaluated TEAEs on the healthy volunteer Study E7727-01. Of the 8 healthy volunteers enrolled and treated with two single doses of cedazuridine 100 mg separated by a washout, 5 (63%) experienced a TEAE. Two (25%) experienced nasopharyngitis, and one each experienced anal hemorrhage, back pain, diarrhea, and headache. All were of Grade 1 severity, except for back pain, which was Grade 2.

Laboratory Findings

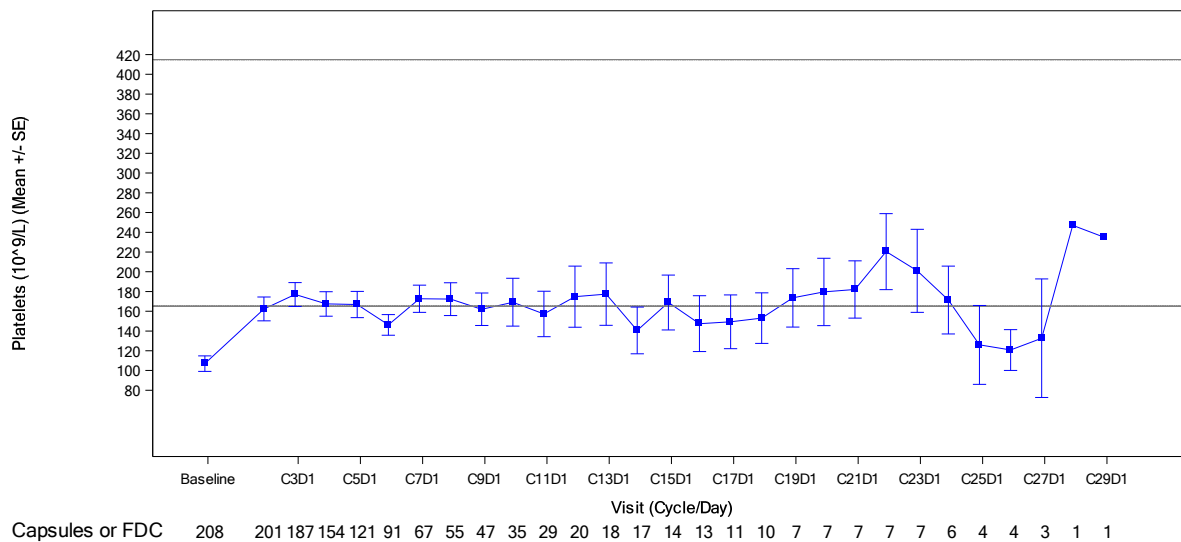
Data:

In both Study ASTX727-01 Phase 2 and Study ASTX727-02 Phase 3, hematology was evaluated on Days 1 (Screening and/or Day 1 of Cycle 1), 8, 15 and 22 for the first 2 treatment cycles; and at least on Day 1 of all following treatment cycles; and at study treatment discontinuation. Baseline values of neutrophils, hemoglobin, and platelets were defined as the average of all values obtained during screening up to and including the first dosing date. If there was only one value available before treatment, it was used as the baseline value. In both studies, serum chemistry was evaluated at Screening (for Cycle 1 treatment), then predose on Day 1 of Cycles ≥ 2 , and at treatment discontinuation.

There were no clinically notable trends over time in central tendency for alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, bilirubin, alkaline phosphatase, or electrolytes (potassium, sodium, and magnesium).

Analysis of central tendency for selected hematology parameters (Figure 22 through Figure 24) showed a decrease in mean neutrophils over the first 2 cycles followed by an increase, an increase in mean platelets over the first 3 cycles followed by stable levels, and an increase in mean hemoglobin over the first 8 cycles.

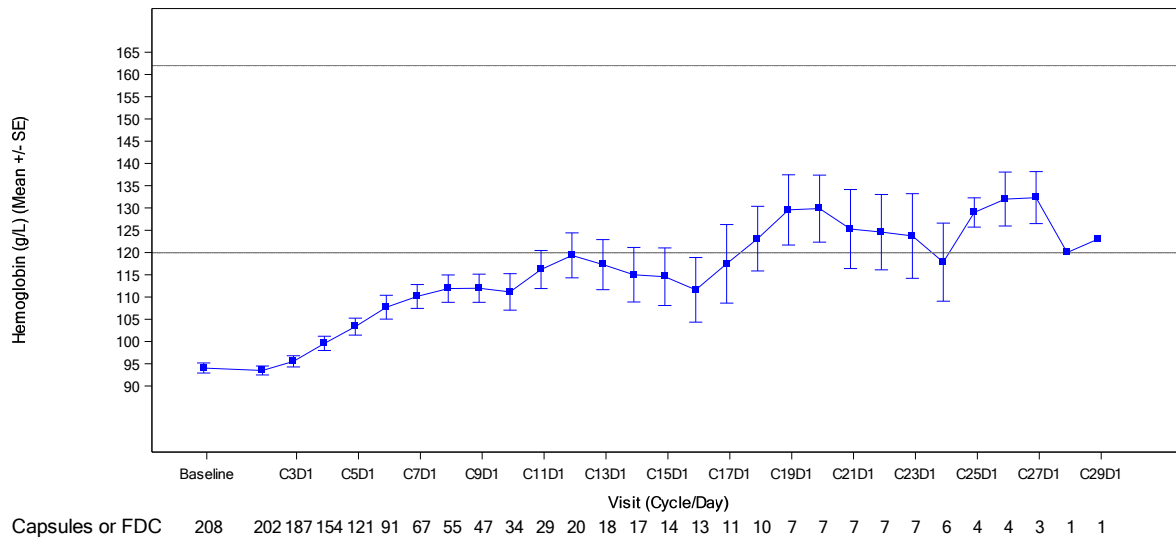
Figure 22. Plot of Platelet Counts by Visit (Phase 2 and Phase 3 Subjects)



Source: ISS Figure 9.1.6

The reference lines represent the lower limit and upper limit of the lab normal range used for CTCAE grading of platelet counts.

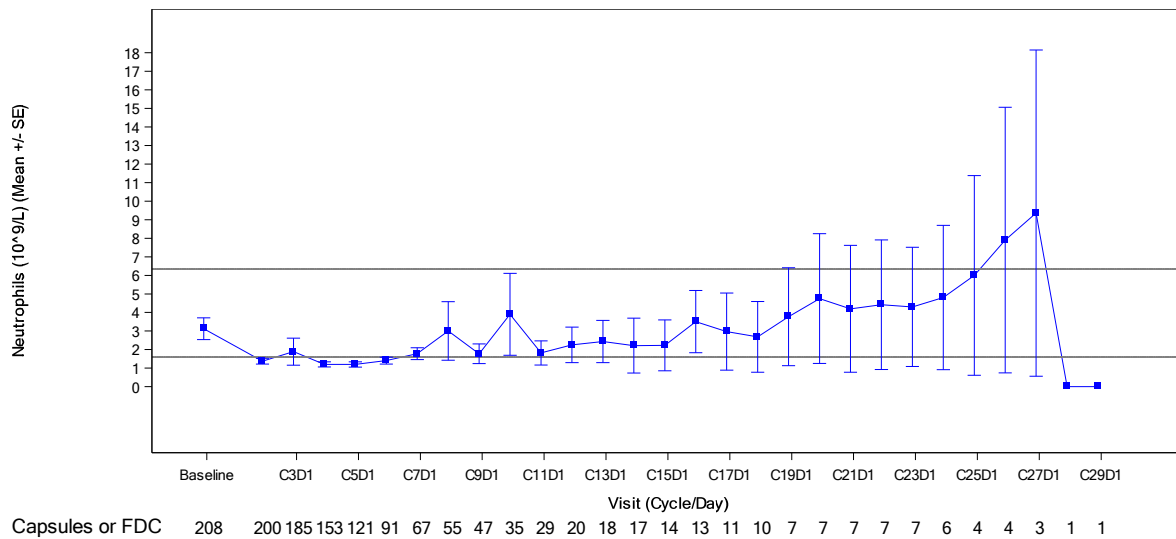
Figure 23. Plot of Hemoglobin Values by Visit (Phase 2 and Phase 3 Subjects)



Source: ISS Figure 9.1.4

The normal range for males is <133, 162> and for females is <120, 158>. The reference lines represent the minimum of the lower limits and the maximum of the upper limits.

Figure 24. Plot of Neutrophil Counts by Visit (Phase 2 and Phase 3 Subjects)



Source: ISS Figure 9.1.5

The reference lines represent the lower limit and upper limit of the lab normal range used for CTCAE grading of neutrophil counts.

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The reference lines represent the lower limit and upper limit of the lab normal range used for CTCAE grading of neutrophil counts.

The incidence of Common Terminology Criteria for Adverse Events (CTCAE) Grade $\geq$ 3 laboratory abnormalities for renal and hepatic function parameters was low, typically occurring in 1-3 subjects (<2%). Shifts of 2 or more CTCAE grades for renal and hepatic function parameters were infrequent during treatment. Only 2 subjects had Grade 4 abnormalities (increased ALT and AST), both of which occurred in the setting of fatal AEs.

Laboratory data were also evaluated for potential Hy's Law cases. Three subjects met the Hy's Law laboratory criteria, but all 3 cases also occurred in the setting of fatal AEs of myocarditis or sepsis. Narratives for each of these subjects were provided in the submission.

Common new or worsening laboratory abnormalities are summarized below in Table 62 (all grades) and Table 63 (Grade $\geq$ 3).

Table 62. Common ($\geq$ 10%) All CTCAE Grade New or Worsening Laboratory Abnormalities by Cycle 1 and 2 Separately and Overall (Phase 2 and 3)

Parameter	Number (%) of Subjects				
	Cycle 1		Cycle 2		All Cycles
	IV Decitabine (N=106)	Capsules or FDC Tablet (N=107)	IV Decitabine (N=101)	Capsules or FDC Tablet (N=101)	Capsules or FDC Tablet (N=208)
Alanine aminotransferase increased	7 (6.6%)	13 (12.1%)	17 (16.8%)	17 (16.8%)	64 (30.8%)
Albumin hypoalbuminemia	21 (19.8%)	21 (19.6%)	18 (17.8%)	29 (28.7%)	79 (38.0%)
Alkaline phosphatase increased	12 (11.3%)	22 (20.6%)	16 (15.8%)	19 (18.8%)	71 (34.1%)
Aspartate aminotransferase increased	2 (1.9%)	4 (3.7%)	10 (9.9%)	11 (10.9%)	47 (22.6%)
Bilirubin increased	7 (6.6%)	4 (3.7%)	8 (7.9%)	7 (6.9%)	32 (15.4%)
Calcium hypocalcemia	12 (11.3%)	17 (15.9%)	13 (12.9%)	11 (10.9%)	56 (26.9%)
Creatinine increased	8 (7.5%)	5 (4.7%)	9 (8.9%)	11 (10.9%)	43 (20.7%)
Glucose hyperglycemia	11 (10.4%)	20 (18.7%)	22 (21.8%)	21 (20.8%)	93 (44.7%)
Glucose hypoglycemia	17 (16.0%)	13 (12.1%)	9 (8.9%)	13 (12.9%)	69 (33.2%)
Hemoglobin decreased	63 (59.4%)	61 (57.0%)	54 (53.5%)	60 (59.4%)	144 (69.2%)
Leukocytes decreased	82 (77.4%)	85 (79.4%)	76 (75.2%)	81 (80.2%)	180 (86.5%)
Magnesium hypermagnesemia	2 (1.9%)	3 (2.8%)	1 (1.0%)	7 (6.9%)	26 (12.5%)
Neutrophils decreased	66 (62.3%)	74 (69.2%)	71 (70.3%)	66 (65.3%)	149 (71.6%)
Platelets decreased	82 (77.4%)	84 (78.5%)	54 (53.5%)	58 (57.4%)	169 (81.3%)
Potassium hyperkalemia	2 (1.9%)	1 (0.9%)	3 (3.0%)	2 (2.0%)	25 (12.0%)
Sodium hyponatremia	8 (7.5%)	9 (8.4%)	7 (6.9%)	14 (13.9%)	49 (23.6%)

Source: Supplemental table

Table 63. Most Common (≥5%) Grade ≥3 Laboratory Abnormalities by Cycle 1 and 2 Separately and Overall (Phase 2 and 3)

Parameter	Number (%) of Subjects				
	Cycle 1		Cycle 2		All Cycles
	IV Decitabine (N=106)	Capsules or FDC Tablet (N=107)	IV Decitabine (N=101)	Capsules or FDC Tablet (N=101)	Capsules or FDC Tablet (N=208)
Glucose hyperglycemia	0 (0.0%)	0 (0.0%)	3 (3.0%)	0 (0.0%)	12 (5.8%)
Hemoglobin decreased	38 (35.8%)	43 (40.2%)	38 (37.6%)	39 (38.6%)	109 (52.4%)
Leukocytes decreased	62 (58.5%)	70 (65.4%)	62 (61.4%)	70 (69.3%)	163 (78.4%)
Neutrophils decreased	62 (58.5%)	69 (64.5%)	63 (62.4%)	62 (61.4%)	144 (69.2%)
Platelets decreased	71 (67.0%)	70 (65.4%)	38 (37.6%)	45 (44.6%)	152 (73.1%)

Source: Supplemental table

The Applicant's Position:

No clinically meaningful trends in laboratory values were observed other than the trends in hematology parameters as a result of the effects of continued treatment and also response to treatment (increased platelets and hemoglobin). Laboratory abnormalities of any grade occurred in both IV and oral cycles and in all ASTX727 cycles with no clinically meaningful trend as incidence was somewhat higher on ASTX727 cycles for some laboratory abnormalities (decrease albumin and sodium, increase glucose and alkaline phosphatase) but somewhat higher on IV decitabine for others (bilirubin). Grade ≥3 abnormalities ≥5% were all hematological with the exception of increase glucose in all ASTX727 cycles which was not present in the first 2 cycles for ASTX727. This is probably reflective of the elderly disease population and underlying comorbidities. The hematological laboratory abnormalities of Grade ≥3 were generally similar for IV and ASTX727 in Cycles 1 and 2.

The Regulatory Authorities' Assessment:

The Applicant's analyses of platelets, hemoglobin, and neutrophils over time indicates that treatment with ASTX727 improved hematologic parameters with continued treatment. Of course, this assessment is somewhat biased, as patients on continued therapy are more likely to have responded to the therapy. However, the data is in-line with the demonstrated transfusion benefit of ASTX727 in a subset of patients (see Sections 8.1.2 and 8.1.4).

The below table contains post-baseline laboratory abnormalities in patients in the pooled SAS and comparative safety population during Cycle 1 using the data from the 120-day safety update.

New or worsening laboratory abnormalities (≥ 10%) in the pooled SAS and in Cycle 1 between ASTX727 and IV decitabine – 120 day safety update

Laboratory parameter	Cycle 1				All Cycles	
	ASTX727*		IV decitabine*		ASTX727*	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4

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Leukocytes decreased	79	65	77	59	87	81
Platelet count decreased	79	65	77	67	82	76
Neutrophil count decreased	70	65	62	59	73	71
Hemoglobin decreased	58	41	59	36	71	55
Glucose increased	19	0	11	0	54	7
Albumin decreased	22	1	20	0	45	2
Alkaline phosphatase increased	22	1	12	0	42	0.5
Glucose decreased	14	0	17	0	40	1
ALT increased	13	1	7	0	37	2
Calcium decreased	16	0	12	0	30	2
Sodium decreased	9	2	8	0	30	4
AST increased	6	1	2	0	30	2
Creatinine increased	7	0	8	0	29	0.5

(b) (4)

*The denominator used to calculate the rate varied from 103 to 107 for ASTX727 Cycle 1, from 102 to 106 for IV decitabine Cycle, and from 203 to 208 for All Cycles based on the number of patients with a baseline value and at least one post-treatment value.

As expected, the predominate laboratory abnormalities were cytopenias. Again, the Grade 3-4 cytopenias were slightly more pronounced during Cycle 1 with ASTX727 compared to IV decitabine, with the exception of platelet count decreased. The fact that the opposite was true for the AE of thrombocytopenia (i.e. Grade 3-4 thrombocytopenia appeared worse for ASTX727 during cycle 1), and that the incidences of cytopenias were considerably lower using AE data, illustrates that the AE data incompletely captures the incidence of cytopenias compared to the more accurate and complete laboratory results. Therefore, cytopenias will be indicated in labeling with the laboratory data.

A total of 3 patients (1%) in the pooled SAS experienced ALT and/or AST values > 3 x ULN combined with a total bilirubin value $\geq$ 2 x ULN and alkaline phosphatase < 2 x ULN. FDA reviewed narratives for all of the potential Hy's law cases and ruled out drug-induced liver injury based on plausible alternative causes, including sepsis (n=2) and myocarditis (n=1).

Vital Signs

Data:

In Study ASTX727-01, assessment of vital signs was performed at Screening, before dosing on Day 1 of all treatment cycles, and at study treatment discontinuation. In Study ASTX727-02, assessment of vital signs was performed at Screening, before dosing on all dosing days (Days 1-5), on Days 8, 15 and 22 of the first 2 treatment cycles, on Day 1 of all following treatment cycles, and at study treatment discontinuation. Vital signs were summarized for the integrated population by visit using proportion of subjects with each vital sign being above or below conventionally accepted vital sign normal ranges. In addition, for each vital sign parameter, a figure of mean values by visit was provided.

There were no clinically notable trends in the central tendency for vital signs parameters over time, including heart rate, diastolic blood pressure, systolic blood pressure, respiration rate, or temperature.

The most frequently occurring post-baseline vital signs finding outside the normal limits was respiration rate, which was ≥ 20 breaths per minute on one or more occasions for approximately 75% of subjects, and diastolic blood pressure, which was ≤ 55 mmHg on one or more occasions for approximately 50% of subjects.

The most common vital signs AEs were dyspnea and pyrexia (20.7% and 11.5%, respectively, across all cycles in the overall ASTX727 population), which were likely associated with the occurrence of pneumonia and other infections.

The Applicant's Position:

The vital signs findings are not unexpected in a relatively sick population with myelosuppression who are receiving treatment for infections.

The Regulatory Authorities' Assessment:

FDA agrees with the Sponsor's assessment.

Electrocardiograms (ECGs)

Data:

The Phase 3 study included ECG assessment at screening then at Day 3 (predose and at t_{max} of decitabine or cedazuridine post dose) in Cycles 1 or 2 (Table 64).

Table 64. ASTX727-02 Phase 3: Mean change from Baseline to Postdose on Day 3 of Cycles 1 or 2 (ASTX727 vs IV)

Treatment	ASTX727 Cycles 1 or 2	IV Decitabine Cycles 1 or 2
Total N	130	129
Heart Rate in bpm, (LCI, UCI)	1.0 (-0.5, 2.5)	-3.0 (-4.3, -1.7)
PR in ms, (LCI, UCI)	1.5 (-0.5, 3.5)	1.9 (-0.6, 4.3)
QRS in ms, (LCI, UCI)	1.9 (-0.3, 4.2)	0.1 (-1.3, 1.5)
QT in ms, (LCI, UCI)	4.1 (0.4, 7.8)	11.7 (8.0, 15.3)
QTcF in ms, (LCI, UCI)	5.0 (1.7, 8.3)	5.8 (2.7, 8.9)
QTcB in ms, (LCI, UCI)	5.6 (1.6, 9.7)	2.7 (-1.0, 6.5)

Source: ASTX727-02 CSR, Appendix 16.1.13.6 (in-text Table 2-1)

The Applicant's Position:

(b) (4)

QT

Data:

A dedicated thorough QT study to evaluate the QT prolongation potential of ASTX727 has not been conducted. Analyses of QTc from the pooled population and the Phase 2 and Phase 3 studies individual are presented in Table 65.

The pooled population (N=208) in Table 65 below includes QTcF interval data from both the Phase 2 and Phase 3 studies. It is important to note that ECGs were collected at different time points in the Phase 2 and Phase 3 studies. In the Phase 2 study ECGs were collected at Screening and predose on Day 1 of each cycle (i.e., more than 3 weeks after last dose), and at the Treatment Termination Visit. In the Phase 3 study, ECGs were collected at Screening and on Day 3 (predose and 3 hours after ASTX727 and within 10 min before end of IV infusion for decitabine) of Cycle 1 and 2. Due to the differences in ECG collection times between the studies, an analysis of QTcF was also provided below for each study individually.

Maximum post-baseline absolute QT findings in Phase 2 and 3 presented in Table 65 probably reflect the background noise of the disease population (elderly age, comorbidities, concomitant medication) rather than a treatment effect as they do not indicate which cycle or day of cycle they were recorded. Table 66 shows adverse events of QT prolonged in Phase 2. All patients, except 2 had the QTc increase on Day >15 from start of cycle and almost all continued treatment with no recurrence of events supporting that it is not related to drug exposure. The two patients who had the event recorded on Day 1 of a cycle received multiple cycles (12 and 16) and the event has not been recorded in other cycles.

A summary of the QTcF analysis from the Phase 3 study is provided below in Table 67. This tables shows the subjects with a new QTcF outlier value above 480 msec and above 500 msec and the maximum post-baseline increase in QTcF done at the time of maximum drug exposure on Day 3 of Cycles 1 and 2.

Table 65. Analysis of Maximum Post-Baseline Absolute QTcF and Increase in QTcF

Parameter	N (%) of Subjects		
	Phase 2 ASTX727 (N=78)	Phase 3 ASTX727 (N=130)	ASTX727 (N=208)*
Maximum post-baseline absolute QTcF, n (%)			
≤450 msec	41 (52.6)	93 (71.5)	134 (64.4)
>450 to ≤480 msec	22 (28.2)	25 (29.2)	47 (22.6)
>480 to ≤500 msec	4 (5.1)	9 (6.9)	13 (6.3)
>500 msec	2 (2.6)	3 (2.3)	5 (2.4)
Missing	9 (11.5)	0	9
Maximum post-baseline increase in QTcF, n (%)			
≤30 msec	49 (62.8)	106 (81.5)	155 (74.5)
>30 to ≤60 msec	11 (14.1)	17 (13.1)	28 (13.5)
>60 msec	6 (7.7)	7 (5.4)	13 (6.5)
Missing	12 (15.4)	0	12

* A total of 9 subjects were missing post-baseline QTcF values; 12 subjects were missing post-baseline increase in QTcF (3 of subjects having post-baseline QTcF were missing baseline QTcF).

Source: Supplemental tables

Table 66. ASTX727-01 Phase 2: Subjects with AEs of QT Prolongation

Subject	Onset of AEs of ECG QT Prolonged (Cx/Dy)	Most Recent Treatment	CTCAE Grade	Serious	Related	Last Cycle of ASTX727 Treatment
(b) (6)	C13D36	ASTX727	Grade 1	No	No	Cycle 14
	C2D29	ASTX727	Grade 2	No	No	Cycle 6
	C4D28	ASTX727	Grade 1	No	No	
	C10D1	ASTX727	Grade 1	No	No	Cycle 12
	C3D16	ASTX727	Grade 1	No	No	Cycle 9
	C4D36	ASTX727	Grade 1	No	No	
	C1D1	ASTX727	Grade 1	No	No	Cycle 16
	C9D1	ASTX727	Grade 1	No	No	

Source: ASTX727-01-B CSR Listing 16.2.5.1, Listing 16.2.7.1

Table 67. ASTX727-02 Phase 3: Analysis of Maximum Post-Baseline Absolute QTcF

Parameter	Cycle 1 or 2	
	ASTX727 (N=130)	IV Decitabine (N=129)
Maximum post-baseline absolute QTcF, n (%)		
>480 msec (new)	5 (4%)	5 (4%)
>500 msec (new)	1 (1%)	1 (1%)
Missing	0	0
Maximum post-baseline increase in QTcF, n (%)		
≤30 msec	118 (91%)	115 (89%)
>30 to ≤60 msec	7 (5%)	12 (9%)
>60 msec	5 (4%)	2 (2%)
Missing	0	0

Source: ASTX727-02 CSR, Appendix 16.1.13.6 (Appendix A, Table 5)

The Applicant's Position:



(b) (4)

The Regulatory Authorities' Assessment:

As of the 120-day safety update, the incidence of all-grade PTs in the broad SMQ for Torsade de pointes/QT prolongation was 16/208 (8%). This included 7 (3%) patients with electrocardiogram QT prolonged, 7 (3%) with syncope, and one patient each with cardiac arrest, multiple organ dysfunction syndrome, and sudden death. Of note, there were no Grade 3 or higher TEAEs of electrocardiogram QT prolonged. No further ECG data were available from the 120-day safety update.

Overall, the data presented are not adequate to determine whether there is an effect of ASTX727 on post-baseline QTcF. Given the similar exposures to IV decitabine, the decitabine component is unlikely to contribute to increases in QTcF, but there are no clinical data to conclude that cedazuridine does not have an independent effect on QTcF. A PMR study will be requested to evaluate the QT prolongation potential of cedazuridine.

Immunogenicity

Data:

No findings from overall safety AE assessments to suggest immunogenicity from ASTX727.

The Applicant's Position:

No immunogenic reactions are expected with decitabine and were not observed with ASTX727.

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's assessment.

8.2.5. Analysis of Submission-Specific Safety Issues

Data:

No specific safety issues were observed in this submission that are not consistent with decitabine reported data and its mechanism of action.

The Applicant's Position:

No specific safety issues or new safety signals were identified with ASTX727.

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's assessment.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

No specific patient reported outcomes were analyzed in the clinical trials for this application.

The Applicant's Position:

Not applicable

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's assessment.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Adverse events were analyzed by subgroups for a variety of intrinsic (age, sex, race, renal impairment, hepatic impairment, BSA, study disease) and extrinsic factors (country) in the integrated population.

Age

There was no consistent and clinically notable pattern of increasing AE incidence either overall or in the different SOCs from between the younger age group (<65 years) to the oldest age group (≥75 years) particularly in the SOCs of interest such as Blood and Lymphatic System Disorders and Infections and Infestations (Table 68).

Individual AEs that were notably higher (more than double) in the oldest age group (≥75 years) compared to the youngest age group (<65 years) included:

- sepsis (12.2% vs 3.8%)
- contusion (14.9% vs 3.8%), which were reported as bruises, some of which may have been due to multiple venipuncture for PK draws
- blood creatinine increase (12.2% vs 3.8%)

Individual AEs that were notably higher (more than double) in the youngest age group (<65 years) compared to the oldest group (≥75 years) included:

- nausea (48.1% vs 17.6%)
- vomiting (19.2% vs 5.4%)
- headache (26.9% vs 10.8%)
- insomnia (13.5% vs 5.4%)
- oropharyngeal pain (15.4% vs 4.1%)

Table 68. Adverse Events in ≥10% of Subjects by Age Group (Phase 2 and Phase 3 Subjects)

System Organ Class Preferred Term	Number (%) of Subjects		
	All Cycles		
	Capsules or ASTX727 FDC Tablet (N=208)		
	<65 (N=52)	≥65 to <75 (N=82)	≥75 (N=74)
Number of subjects with at least one TEAE	49 (94.2)	82 (100.0)	72 (97.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	43 (82.7)	55 (67.1)	57 (77.0)
Anaemia	20 (38.5)	23 (28.0)	28 (37.8)
Febrile neutropenia	18 (34.6)	17 (20.7)	14 (18.9)
Leukopenia	17 (32.7)	17 (20.7)	16 (21.6)
Neutropenia	22 (42.3)	35 (42.7)	34 (45.9)
Thrombocytopenia	29 (55.8)	39 (47.6)	34 (45.9)
GASTROINTESTINAL DISORDERS	36 (69.2)	57 (69.5)	51 (68.9)
Constipation	13 (25.0)	21 (25.6)	19 (25.7)
Diarrhoea	13 (25.0)	17 (20.7)	18 (24.3)
Nausea	25 (48.1)	17 (20.7)	13 (17.6)
Vomiting	10 (19.2)	4 (4.9)	4 (5.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	27 (51.9)	42 (51.2)	47 (63.5)
Asthenia	8 (15.4)	10 (12.2)	14 (18.9)
Fatigue	14 (26.9)	25 (30.5)	31 (41.9)
Oedema peripheral	5 (9.6)	9 (11.0)	12 (16.2)
Pyrexia	7 (13.5)	9 (11.0)	8 (10.8)
INFECTIONS AND INFESTATIONS	27 (51.9)	44 (53.7)	36 (48.6)
Pneumonia	6 (11.5)	7 (8.5)	11 (14.9)
Sepsis	2 (3.8)	6 (7.3)	9 (12.2)
Septic shock ^a	1 (1.9)	2 (2.4)	0
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS	11 (21.2)	19 (23.2)	25 (33.8)
Contusion	2 (3.8)	6 (7.3)	11 (14.9)
Fall	3 (5.8)	6 (7.3)	9 (12.2)
INVESTIGATIONS	15 (28.8)	29 (35.4)	27 (36.5)
Alanine aminotransferase increased	7 (13.5)	9 (11.0)	10 (13.5)
Blood creatinine increased	2 (3.8)	6 (7.3)	9 (12.2)
Weight decreased	3 (5.8)	7 (8.5)	8 (10.8)
METABOLISM AND NUTRITION DISORDERS	24 (46.2)	30 (36.6)	38 (51.4)
Decreased appetite	11 (21.2)	9 (11.0)	18 (24.3)
Hypocalcaemia	3 (5.8)	7 (8.5)	9 (12.2)
Hypomagnesaemia	3 (5.8)	11 (13.4)	3 (4.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	17 (32.7)	36 (43.9)	31 (41.9)
Arthralgia	8 (15.4)	15 (18.3)	9 (12.2)
Back pain	3 (5.8)	8 (9.8)	10 (13.5)
NERVOUS SYSTEM DISORDERS	23 (44.2)	28 (34.1)	33 (44.6)
Dizziness	9 (17.3)	12 (14.6)	18 (24.3)
Headache	14 (26.9)	13 (15.9)	8 (10.8)
PSYCHIATRIC DISORDERS	13 (25.0)	12 (14.6)	9 (12.2)
Insomnia	7 (13.5)	7 (8.5)	4 (5.4)

System Organ Class Preferred Term	Number (%) of Subjects		
	All Cycles		
	Capsules or ASTX727 FDC Tablet (N=208)		
	<65 (N=52)	≥65 to <75 (N=82)	≥75 (N=74)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	23 (44.2)	39 (47.6)	40 (54.1)
Cough	6 (11.5)	10 (12.2)	13 (17.6)
Dyspnoea	8 (15.4)	15 (18.3)	20 (27.0)
Oropharyngeal pain	8 (15.4)	9 (11.0)	3 (4.1)
SKIN AND SUBCUTANEOUS DISORDERS	21 (40.4)	29 (35.4)	18 (24.3)
Rash maculo-papular	3 (5.8)	3 (3.7)	8 (10.8)

^a Septic shock is included despite occurring at an incidence below the cutoff because of its medical relatedness to sepsis.

Source: ISS Table 5.1.2.1

Sex:

There was no overall difference in the incidence of AEs based on sex but for most SOCs the incidence of AEs was slightly higher in females than males (Table 69).

Individual AEs that were notably higher (more than double) in females compared with males:

- vomiting (14.1% vs 6.3%)
- urinary tract infection (15.6% vs 1.4%)
- hypokalemia (15.6% vs 5.6%)
- headache (26.6% vs 12.5%)
- insomnia (14.1% vs 6.3%)
- myalgia (10.9% vs 4.9%)
- oropharyngeal pain (17.2% vs 6.3%)

Individual AEs that were notably higher (more than double) in males than females:

- stomatitis (11.8% vs 1.6%)

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Table 69. Adverse Events in $\geq 10\%$ of Subjects by Sex for All Cycles for the Overall ASTX727 Population (Phase 2 and Phase 3 Subjects)

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System Organ Class Preferred Term	Number (%) of Subjects	
	All Cycles	
	Capsules or ASTX727 FDC Tablet (N=208)	
	Male (N=144)	Female (N=64)
Number of subjects with at least one TEAE	139 (96.5)	64 (100.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	107 (74.3)	48 (75.0)
Anaemia	45 (31.3)	26 (40.6)
Febrile neutropenia	35 (24.3)	14 (21.9)
Leukopenia	28 (19.4)	22 (34.4)
Neutropenia	61 (42.4)	30 (46.9)
Thrombocytopenia	64 (44.4)	38 (59.4)
GASTROINTESTINAL DISORDERS	97 (67.4)	47 (73.4)
Constipation	35 (24.3)	18 (28.1)
Diarrhoea	31 (21.5)	17 (26.6)
Nausea	30 (20.8)	25 (39.1)
Stomatitis	17 (11.8)	1 (1.6)
Vomiting	9 (6.3)	9 (14.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	79 (54.9)	37 (57.8)
Asthenia	20 (13.9)	12 (18.8)
Fatigue	48 (33.3)	22 (34.4)
Oedema peripheral	16 (11.1)	10 (15.6)
Pyrexia	17 (11.8)	7 (10.9)
INFECTIONS AND INFESTATIONS	70 (48.6)	37 (57.8)
Pneumonia	15 (10.4)	9 (14.1)
Sepsis	9 (6.3)	8 (12.5)
Septic shock ^a	2 (1.4)	1 (0.6)
Urinary tract infection	2 (1.4)	10 (15.6)
INVESTIGATIONS	51 (35.4)	20 (31.3)
Alanine aminotransferase increased	18 (12.5)	8 (12.5)
METABOLISM AND NUTRITION DISORDERS	61 (42.4)	31 (48.4)
Decreased appetite	25 (17.4)	13 (20.3)
Hypocalcaemia	15 (10.4)	4 (6.3)
Hypokalaemia	8 (5.6)	10 (15.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	56 (38.9)	28 (43.8)
Arthralgia	20 (13.9)	12 (18.8)
Back pain	14 (9.7)	7 (10.9)
Myalgia	7 (4.9)	7 (10.9)
NERVOUS SYSTEM DISORDERS	55 (38.2)	29 (45.3)
Dizziness	27 (18.8)	12 (18.8)
Headache	18 (12.5)	17 (26.6)
PSYCHIATRIC DISORDERS	18 (12.5)	16 (25.0)
Insomnia	9 (6.3)	9 (14.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	57 (39.6)	45 (70.3)
Cough	18 (12.5)	11 (17.2)
Dyspnoea	26 (18.1)	17 (26.6)
Oropharyngeal pain	9 (6.3)	11 (17.2)

^a Septic shock is included despite occurring at an incidence below the cutoff because of its medical relatedness to sepsis.

Source: ISS Table 5.1.2.2

Body Surface Area:

In addition, since ASTX727 contains a fixed dose of decitabine (35 mg), it is important to note that the safety analysis by BSA quartiles showed no consistent trend of higher AEs for ASTX727 in subjects in the smallest BSA quartile compared with BSA-based dosing of IV decitabine. While subjects in the smallest BSA quartile had a higher incidence of certain AEs with ASTX727 in Cycles 1 or 2, the results were similar to IV decitabine, indicating that the higher AE incidence is probably related to other intrinsic baseline patients characteristics factors in that cohort compared with subjects in the larger BSA quartiles. Subjects in the smallest BSA quartile had lower baseline neutrophils and a higher incidence of transfusion dependence at baseline.

Other

There was no consistent clinically notable pattern of a higher incidence of AEs in one race group versus the other (White vs non-White).

There were no notable safety differences in subjects with mild to moderate renal or hepatic impairment. Anemia and febrile neutropenia tended to have similar or lower incidence in the moderately impaired versus normal subjects while neutropenia, leukopenia, and thrombocytopenia tended to be higher in the moderately impaired compared to normal subjects. No clinically notable increase in AEs in other SOCs was observed in hepatically impaired subjects compared to normal subjects. The interpretation is limited due to the small sample size of hepatically impaired subjects (N=22) and the fact that most of them had only mild impairment. There was also no notable difference in AEs between MDS and CMML patients; however, there was a general trend toward lower incidence of AEs in CMML subjects compared to MDS subjects in most SOCs.

The Applicant's Position:

The subgroup analyses of safety data did not show marked or notable differences in the safety profile of ASTX727 for any individual subgroup.

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's assessment.

8.2.8. Specific Safety Studies/Clinical Trials

Data:

No specific studies were conducted with ASTX727 to evaluate a specific safety concern.

The Applicant's Position:

Not applicable

The Regulatory Authorities' Assessment:
 FDA confirms the Applicant's assessment.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

There were 8 subjects with neoplasms reported in all ASTX727 Cycles (N=208) and 1 subject in the 1 cycle of IV decitabine (N=207).

ASTX727-01 Phase 1 Dose Escalation (N=44):

- basal cell carcinoma (1 subject)
- squamous cell carcinoma (2 subjects)

In the Phase 1 food effect study (ASTX727-04) and in the Phase 1 ADME study in healthy volunteers (E7727-01) no adverse events were reported in the neoplasm SOC.

Table 70. Summary of Secondary Malignancies in Integrated Population (Phase 2 and Phase 3 Subjects)

	Number (%) of Subjects			
	Cycle 1 or 2		Cycles ≥3	All Cycles
	Cedazuridine and Decitabine			
	IV Decitabine (N=207)	Capsules or FDC Tablet (N=208)	Capsules or FDC Tablet (N=182)	Capsules or FDC Tablet (N=208)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.5)	1 (0.5)	7 (3.8)	8 (3.8)
Basal cell carcinoma	0	0	2 (1.1)	2 (1.0)
Adenocarcinoma gastric	0	0	1 (0.5)	1 (0.5)
Melanocytic naevus	0	0	1 (0.5)	1 (0.5)
Refractory cytopenia with unilineage dysplasia	0	0	1 (0.5)	1 (0.5)
Seborrhoeic keratosis	0	1 (0.5)	0	1 (0.5)
Small cell lung cancer	0	0	1 (0.5)	1 (0.5)
Squamous cell carcinoma of skin	0	0	1 (0.5)	1 (0.5)
Squamous cell carcinoma	1 (0.5)	0	0	0

Source: ISS Table 5.1.2

The Applicant's Position:

While decitabine has carcinogenic potential, the reported neoplasms in the study were consistent with the elderly disease population including non-malignant neoplasms.

The Regulatory Authorities' Assessment:

In addition, FDA performed an analysis of secondary malignancies using data from the 120-day safety update. In the pooled SAS, there were 15/208 (7%) patients with a TEAE in the

Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC. This included 2 (1%) with squamous cell carcinoma, 2 (1%) with squamous cell carcinoma of skin, 2 (1%) with basal cell carcinoma, 2 (1%) with seborrheic keratosis, and one each of adenocarcinoma gastric, hypergammaglobulinaemia benign monoclonal, melanocytic naevus, pancreatic carcinoma metastatic, refractory cytopenia with unilineage dysplasia, small cell lung cancer, and squamous cell carcinoma of the tongue. The median time to first event was 148.5 days (range 12-1285) days. Given the short median time to onset, these malignancies are less likely to be related to treatment with ASTX727.

Excluding the cases of seborrheic keratosis, hypergammaglobulinaemia benign monoclonal, melanocytic naevus, and refractory cytopenia with unilineage dysplasia (the disease under study), the incidence of second malignancies was 10 (5%). Two patients with second malignancies of basal and squamous cell carcinoma had a prior history of skin cancer (basal carcinoma) and had relatively short drug exposure at the time of the event (Cycle 4 and Cycle 7). Another 4 patients had their second malignancy after < 6 cycles of decitabine (Cycles 2, 3, 4, and 5). Therefore, the second malignancies observed are most likely unrelated to ASTX727.

Human Reproduction and Pregnancy

Data:

No pregnancies were reported in the clinical trials.

Based on its mechanism of action and findings in animals, decitabine (one of the active ingredients in the ASTX727 FDC tablet) can cause fetal harm when administered to a pregnant woman. Decitabine alters DNA synthesis and is expected to result in adverse reproductive effects. In nonclinical studies with decitabine in mice and rats, decitabine was teratogenic, fetotoxic, and embryotoxic ([Dacogen USPI 2019](#)).

Due to the known adverse reproductive effects of decitabine, no reproductive or developmental toxicity studies have been conducted with ASTX727 or cedazuridine alone.

Pregnant and breast-feeding women were excluded from enrollment in ASTX727 clinical studies. ASTX727 or its components (cedazuridine and decitabine) have not been administered orally to women who were pregnant or breast-feeding in the ASTX727 clinical program and no information is available on the use of ASTX727 in pregnant women.

There are no data on the effects of oral administration of cedazuridine or decitabine or its metabolites in human milk, the effects on the breastfed child, or on milk production.

The Applicant's Position:

Based on findings from human data, animal studies, and the mechanism of action for decitabine, ASTX727 may cause fetal harm when administered to a pregnant woman.

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Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from ASTX727 in a nursing child, advise lactating women to avoid breastfeeding during treatment with ASTX727 and for at least 1 week after the last dose.

The Regulatory Authorities' Assessment:

Lactating women are advised to avoid breastfeeding during treatment with ASTX727 and for at least 2 weeks after the last dose, consistent with the recommendation for IV decitabine.

Pediatrics and Assessment of Effects on Growth

Data:

ASTX727 has not been investigated in pediatric patients.

The Applicant's Position:

Not applicable

The Regulatory Authorities' Assessment:

FDA confirms the Applicant's assessment.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

There were no reports of overdose.

There is no known antidote for overdosage with ASTX727 FDC tablets. Higher doses of decitabine may be associated with increased myelosuppression, including prolonged neutropenia and thrombocytopenia.

There is no evidence that ASTX727 is habit forming or could lead to dependence.

ASTX727 can be stopped abruptly with no withdrawal effects. Potential clinical benefit may be lost if ASTX727 is stopped too early. Once treatment is stopped, blood levels of decitabine, cedazuridine, and cedazuridine-epimer should be non-detectable within 24, 72, and 72 hours, respectively.

The Applicant's Position:

Overdose of ASTX727 should be managed with supportive care of expected adverse events of myelosuppression and infection.

The Regulatory Authorities' Assessment:

FDA confirms the Applicant's assessment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

ASTX727 FDC tablets are not currently marketed in any country.

The Applicant's Position:

Postmarketing data from IV decitabine are included in ASTX727 proposed labelling.

The Regulatory Authorities' Assessment:

The Applicant added differentiation syndrome (DS) and interstitial lung disease (ILD) to the post-marketing experience section of the proposed drug label. DS is in the USPI for IV decitabine, but ILD is not. The Sponsor responded to a labeling query on 5/13/2020 indicating that ILD is included in the Canadian PM and the EMA SmPC of Dacogen. However, given that ILD was not in the USPI for IV decitabine, the IV decitabine label was updated via a labeling supplement to include the risk of ILD. Both DS and ILD are now included in the post-marketing experience section. Sweet's syndrome (acute febrile neutrophilic dermatosis), which is related to DS, is listed in the post-marketing section for IV decitabine, but Sweet's syndrome occurred in ASTX727 clinical trials (1%), so was included in Section 6.1.

Expectations on Safety in the Postmarket Setting

Data:

The safety profile of decitabine from the approved indication and long-term use in clinical setting both in MDS and off label in other myeloid malignancies have been extensively studied and reported in the literature together with substantial postmarketing experience globally. It is unlikely that ASTX727 use will result in additional safety concerns than what is already known for decitabine, considering the equivalent systemic exposure to IV decitabine and long-term safety assessment in the application (up to 29 cycles in Phase 2 and up to 35 cycles in Phase 1).

The Applicant's Position:

Use of ASTX727 is not expected to result in new safety concerns that were not already described for IV decitabine and ASTX727 NDA submission.

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's assessment but notes that it is unknown whether cedazuridine and/or the oral route of administration may contribute to certain adverse effects of ASTX727 that may yet be unknown.

8.2.11. Integrated Assessment of Safety

Data:

Decitabine in ASTX727 has known risks of cytotoxicity, mainly myelosuppression (hematologic toxicity), and infection consequences due to neutropenia; however, these complications are also common in the disease population. In addition, ASTX727 has a fixed dose of decitabine as opposed to IV decitabine, which is dosed based on BSA. ASTX727 also contains an NCE, the CDA inhibitor cedazuridine, and is dosed orally. This could result in added risks to those already known for IV decitabine, which are discussed below:

- As expected, ASTX727 was associated with common AEs of thrombocytopenia, neutropenia, anemia, and febrile neutropenia. The overall incidence of these AEs (all grades and Grade ≥ 3 AEs) was generally similar between ASTX727 and IV decitabine in Cycle 1 or 2. Infection SAEs of pneumonia and sepsis were less common in both treatments, with pneumonia occurring at a similar incidence in the ASTX727 and IV decitabine cycles but with sepsis reported at a higher incidence for ASTX727. The slightly higher incidence of SAEs of sepsis may have been more related to baseline characteristics in Cycle 1 and 2 since the incidence was generally lower with ASTX727 in Cycles ≥ 3 with continued treatment where patients may have been stabilized by treatment response. There was some imbalance in baseline disease characteristics between Sequence A (ASTX727 in Cycle 1) and B (IV decitabine in Cycle 1) in Phase 3. The risks of cytopenias and associated infections/bleeding are the same risks as the target disease of MDS and CMML ([Steensma 2018](#); [Parikh and Tefferi 2012](#)). These complications are easily monitored with blood counts and manageable with the use of appropriate standard of care therapies (e.g., growth factors and anti-infectives) by physicians experienced in the treatment of this disease. ASTX727 treatment can also be delayed and/or dose reduced to manage these complications.
- Analyses of safety data by BSA quartiles did not show any notable safety profile differences between quartiles that was not also present for IV decitabine. In addition, analyses of exposure-safety for certain hematological AEs showed that incidence of the selected AEs were similar across the full range of decitabine exposures achieved with the fixed dose treatment with ASTX727.
- Analysis of GI disorders SOC showed no differences in the overall incidence of GI AEs between ASTX727 and IV decitabine. Notably, incidence of individual GI AEs of Grade ≥ 3 was $< 2\%$ for ASTX727 and IV decitabine. No additional risk from the oral administration of ASTX727 was identified.
- Overview of the safety profile of ASTX727 did not identify a safety risk associated with cedazuridine. The relatively short and intermittent (5 days per month) CDA inhibition only had the desired effect of enabling oral delivery of decitabine with no other safety consequences apparent from the safety data. However, other nucleosides that are also metabolized by CDA should not be co-administered on the same day as cedazuridine.

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Table 71. Major Safety Events in the First Two Cycles (Phase 2 and Phase 3)

Safety parameter	Number (%) of Subjects			
	Cycle 1		Cycle 2	
	IV decitabine (N=106)	ASTX727 (N=107)	IV decitabine (N=101)	ASTX727 (N=101)
Total deaths	1 (0.9)	2 (1.9)	2 (2.0)	1 (1.0)
On-treatment deaths ¹	1 (0.9)	2 (1.9)	2 (2.0)	1 (1.0)
On-treatment fatal ARs ^{1, *}	2 (1.9)	2 (1.9)	1 (1.0)	2 (2.0)
All grade TEARs*	103 (97.2)	106 (99.1)	90 (89.1)	92 (91.1)
Gr ≥ 3 TEARs	71 (67.0)	78 (72.9)	57 (56.4)	54 (53.5)
TESARs	25 (23.6)	32 (29.9)	20 (19.8)	36 (35.6)
All-cause treatment discontinuation ^{2, *}	5 (4.7)	6 (5.6)	8 (7.9)	8 (7.9)
TEAR with treatment discontinuation ^{2, *}	1 (0.9)	2 (1.9)	1 (1.0)	0

ARs, adverse reactions; TEARs, treatment-emergent adverse reactions; TESARs, treatment-emergent serious adverse reactions

Note: All ARs above include all TEAEs

¹ On or within 30 days after the last dose. Grouping of on-treatment deaths were based on the date of death and on-treatment fatal ARs (AEs with fatal outcome) were based on the onset of the AE.

² All-cause treatment discontinuation was based on the date of treatment discontinuation and TEAR with treatment discontinuation (AEs with action taken with study drug = treatment discontinuation) was based on the onset date of the AE.

Source: ISS Table 6.1.3.1 (Gr ≥3 TEARS), ISS Table 6.1.2.1 (TESARS)

* Indicates source is a supplemental table

Table 72. Major Safety Events over the Entire Treatment Period

Safety parameter	ASTX727 (N=208)
Total deaths	49 (23.6%)
30-day mortality ^{1, *}	1 (0.5)
60-day mortality ^{2, *}	5 (2.4)
On-treatment deaths ³	12 (5.8%)
Fatal TEARs	14 (6.7%)
All-grade TEARs	203 (97.6%)
Grade ≥3 TEARs	168 (80.8%)
TESARs	106 (51.0%)
All-cause treatment discontinuation	101 (48.6%)
TEAR with treatment discontinuation	8 (3.8%)

TEARs, treatment-emergent adverse reactions; TESARs, treatment-emergent serious adverse reactions
 Note: All ARs above include all TEAEs

¹ Within 30 days following the first dose of treatment

² Within 60 days following the first dose of treatment

³ On or within 30 days after the last dose of ASTX727

Source: SCS Table 20 (deaths), SCS Table 11 (overview of AEs), SCS Table 5 (disposition)

* Indicates source is a supplemental table

The Applicant's Position:

IV decitabine is already approved for the treatment of MDS and CMML with a known positive benefit-risk profile. Based on the above data, ASTX727 is expected to provide similar benefits to those achieved with IV decitabine. ASTX727 treatment involves similar risks to those known for IV decitabine. There was no notable added risk observed as a result of cedazuridine treatment or the oral administration of ASTX727. The decitabine exposures from ASTX727 fixed-dose administration were largely overlapping with those of IV decitabine in individual patients). The fixed decitabine dose in ASTX727 did not result in added risk particularly for patients with smaller body weight/body size. The range of decitabine exposures across the different body weights were also largely overlapping (Figure 8) and exposure-safety analyses showed similar AE incidence across the range of decitabine exposures). The data support the conclusion that ASTX727 (cedazuridine 100 mg and decitabine 35 mg; Daily×5) is associated with a similar positive benefit-risk to that of the approved IV decitabine dose and regimen of 20 mg/m² Daily×5 in patients with intermediate or high-risk MDS or CMML.

The Regulatory Authorities' Assessment:

FDA performed an updated analysis of the overall safety profile of ASTX727 based on data from the 120-day safety update. The on-treatment fatal TEARs listed are as per FDA adjudication.

Major safety events in the pooled SAS and in Cycle 1 between ASTX727 and IV decitabine – 120 day safety update

Safety parameter	Cycle 1		All cycles
	ASTX727 (N=107)	IV decitabine (N=106)	ASTX727 (N=208)
Total deaths	2 (2%)	2 (2%)	81 (39%)
On-treatment deaths ¹	2 (2%)	1 (1%)	16 (8%)
On-treatment fatal TEARs ²	2 (2%)	2 (2%)	12 (6%)
30-day mortality ³	1 (1%)	1 (1%)	1 (0.5%)
All-grade TEARs	106 (99%)	105 (99%)	208 (100%)
Gr ≥ 3 TEARs	79 (74%)	76 (72%)	195 (94%)
TESARs	32 (30%)	25 (24%)	142 (68%)
All-cause treatment discontinuation	5 (4.7)	6 (5.6)	147 (71%)
TEAR with treatment discontinuation	3 (3%)	1 (1%)	11 (5%)

Source: FDA analysis

¹On or within 30 days after the last dose of treatment

²At least possibly related to treatment with ASTX727 or IV decitabine as per FDA adjudication. Includes patients with fatal AR that started within the window

³Within 30 days following the first dose of treatment

Overall, the pooled SAS demonstrated the already known safety profile of IV decitabine. The study population was monitored for deaths, SAEs, common AEs, and common laboratory tests.

A total of 16 (8%) of patients treated with ASTX727 died during or within 30 days after study treatment. Considering only the first cycle of therapy, on-treatment deaths were similarly low (1-2%) in patients treated with ASTX727 or IV decitabine. The most frequent cause of death was primary disease. Treatment-related fatal ARs included sepsis, septic shock, pneumonia, respiratory failure, cerebral hemorrhage, and sudden death. Treatment-related fatal ARs in the first cycle were due to septic shock, pneumonia, and respiratory failure in patients treated with ASTX727 and IV decitabine.

ASTX727 was generally well-tolerated. The most common TEARs (incidence ≥ 15% and ≥ 2% more frequent with ASTX727 compared to IV decitabine) during Cycle 1 were thrombocytopenia, fatigue, nausea, dyspnea, diarrhea, dizziness, headache, and leukopenia. The most frequent Grade ≥ 3 TEARs (incidence ≥ 5% and ≥ 2% more frequent with ASTX727 compared to IV decitabine) were thrombocytopenia, neutropenia, dyspnea, leukopenia, and sepsis. The most frequent serious AE during the first cycle was febrile neutropenia, which occurred at a lower rate with ASTX727 (8%) compared to IV decitabine (12%). However, the SAR of sepsis was more common with ASTX727 (6%) compared to IV decitabine (2%) during Cycle 1.

The most common TEAR during all cycles of ASTX727 was thrombocytopenia, with 62% incidence of all-grade and 54% incidence of Grade 3 or higher thrombocytopenia. Other ARs occurring in $\geq 20\%$ of patients were neutropenia, fatigue, anemia, arthralgias, constipation, myalgias, mucositis, nausea, dyspnea, diarrhea, rash, febrile neutropenia, dizziness, edema, cough, headache, leukopenia, decreased appetite, URI, pneumonia, and transaminase increased. Additional Grade ≥ 3 TEARs ($\geq 10\%$) included neutropenia, anemia, febrile neutropenia, leukopenia, pneumonia, and sepsis.

Discontinuation due to AR occurred in only 5% of patients in the pooled SAS. The most frequent ARs leading to discontinuation were febrile neutropenia (1%) and pneumonia (1%).

The important risks of myelosuppression and embryo-fetal toxicity are unchanged from IV decitabine based on the data presented in the submission.

Overall, given the historically poor outcomes of patients with MDS who are candidates for hypomethylating agent therapy, the level of toxicity observed with ASTX727 is acceptable for the clinical benefit observed. The toxicity profile is very similar to that observed with IV decitabine, with perhaps more myelosuppression, which can be managed with close monitoring and dose interruption or reduction, if required.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The Regulatory Authorities' Assessment:

The submitted clinical data from studies ASTX727-01-B (phase 2) and ASTX727-02 (phase 3) demonstrated:

- 1) a CR rate of 18-21% with median duration of CR responses of 7.5 – 8.7 months. These results are similar to the ORRs (CR+PR) reported in the USPI for IV decitabine, which were 17% for the randomized trial and 16% for the single arm trial.
- 2) 49-53% of patients dependent on transfusions at baseline achieved at least 56 days transfusion independence post-baseline and 63-64% of patients transfusion independent at baseline were able to maintain that transfusion independence for at least 56 days post-baseline.

Of note,

- 1) both studies ASTX727-01-B (phase 2) and ASTX727-02 (phase 3) are considered as single arm trial in terms of efficacy assessment, therefore results of time to event endpoints are not interpretable.

- 2) Study ASTX727-02 (phase 3) will be updated when all subjects complete a minimum of at least 12 months of follow-up.

8.4. Conclusions and Recommendations

The Regulatory Authorities' Assessment:

The review team was able to verify or clarify the efficacy and safety endpoints as provided by the Applicant. The review team recommends approval of the NDA.

X

X

Haiyan Chen, PhD
Primary Statistical Reviewer
OB/DBIX

Jonathon Vallejo, PhD
Acting Statistical Team Leader
OB/DBIX

X

X

Kelly Norsworthy, MD
Primary Clinical Reviewer
OOD/DHM1

Lori Ehrlich, MD, PhD
Acting Clinical Team Leader
OOD/DHM1

9 Advisory Committee Meeting and Other External Consultations

The Regulatory Authorities' Assessment:

No Oncology Drug Advisory Committee (ODAC) Meeting or other external consultations are required for the current application.

10 Pediatrics

The Applicant's Position:

ASTX727 was granted waiver from conducting pediatric studies due to the extreme rarity of the target disease in the pediatric population.

The Regulatory Authorities' Assessment:

FDA agrees with the Applicant's assessment. Pediatric study plan was agreed with the FDA which included a waiver for all pediatric age groups.

11 Labeling Recommendations

The table below summarizes changes to the proposed prescribing information made by FDA. See the final approved prescribing information for INQOVI (decitabine and cedazuridine) accompanying the approval letter for more information.

Section	Applicant's Proposed Labeling	FDA Proposed Labeling
General	Proposed a product title of INQOVI (cedazuridine and decitabine).	Revised to list decitabine before cedazuridine because decitabine is the anticancer drug.
Highlights	...	Modified based on changes made to the full prescribing information.
Full Prescribing Information		
Indications and Usage	Included all French-American-British subtypes.	Revised indication to omit refractory anemia with excess blasts in transformation, because this subtype is now considered AML.
Dosage and Administration	...	Added a new subsection "important administration information" to include information about substitution and premedications, because this dosing-related information was considered sufficiently important for practitioners that it should precede the basic dosing information; this proposal is supported by the recommendations found in the Dosage and Administration guidance.
	Included baseline testing and monitoring with recommended dosage.	Included this information with dosage modifications for adverse reactions to house all information regarding safety monitoring and adverse reactions together.
	(b) (4)	Increased the maximum time to 4 weeks for consistency with intravenous decitabine.

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	(b) (4)	Added instructions regarding to use the same or reduced dose following adequate resolution of these adverse reactions. Added instructions to withhold for active or uncontrolled infection for consistency with intravenous decitabine.
Warnings and Precautions (W&P)	Included a W&P for myelosuppression.	Revised to describe the percentage of patients who needed a dose interruption and reduction or who permanently discontinued for myelosuppression to describe the tolerability of INQOVI.
	Included W&P for embryo-fetal toxicity.	Removed (b) (4)
Adverse Reactions	(b) (4)	Presented a pooled safety population for these 2 trials, because these trials included a similar study population. Included serious adverse reactions, fatal adverse reactions, permanent discontinuation, dose interruptions and dose reductions to describe the tolerability of INQOVI. Added a table to describe the laboratory abnormalities as reported in the lab dataset that worsened from baseline, because laboratory abnormalities are included in the definition of an adverse reaction as found in the

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		Adverse Reaction guidance.
Use in Specific Populations	(b) (4)	Omitted because no actionable recommendations.
Clinical Studies	(b) (4)	Limited outcome measures to complete response and median duration of response, because lesser responses than CR/PR do not convey clear clinical benefit to patients.

12 Risk Evaluation and Mitigation Strategies (REMS)

The Regulatory Authorities' Assessment:

No Risk Evaluation and Mitigation Strategy (REMS) is needed for the safe use of INQOVI for the proposed indication. The risks of INQOVI can be adequately managed in the post-market setting through product presentation and labeling.

13 Postmarketing Requirements and Commitment

The Regulatory Authorities' Assessment:

The following clinical pharmacology trials will be required:

PMR

1. Submit the final report and datasets from a clinical pharmacokinetic trial to determine an appropriate starting dose of INQOVI in patients with moderate and severe hepatic impairment that may inform product labeling. Design and conduct the trial in accordance with the FDA Guidance for Industry titled; *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*.
2. Submit the final report and datasets from a clinical pharmacokinetic trial to determine an appropriate starting dose of INQOVI in patients with severe renal impairment and/or end-stage renal disease that may inform product labeling. Design and conduct the trial in accordance with the FDA Guidance for Industry titled; *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*.
3. Submit the final report with datasets from a thorough QT/QTc study to evaluate the effect of cedazuridine on QT interval prolongation that may further inform labelling. Design and conduct the trial in accordance with the ICH E14 Guidances for Industry titled; *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*, and *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs - Questions and Answers (R3)*.

PMC:

1. Submit the final report and datasets from a clinical pharmacokinetic trial to determine the effect of food on decitabine and cedazuridine exposure when administered with INQOVI that may inform product labeling. Design and conduct the trial in accordance with the FDA Guidance for Industry titled; *Food-Effect Bioavailability and Fed Bioequivalence Studies*.

14 Division Director (DHOT) (NME ONLY)

X

Haleh Saber, PhD, MS
Deputy Division Director
OOD/DHOT

15 Division Director (OCP)

X

Brian Booth, PhD
Division Director
OCP/DCPI

16 Division Director (OB)

X

Thomas Gwise, PhD
Division Director
OB/DBIX

17 Division Director (Clinical)

X

R. Angelo de Claro, MD
Acting Division Director
OOD/DHM1

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18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Marc Theoret, MD
Acting Office Deputy Director
OOD

19 Appendices

19.1. References

The Applicant's References:

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The Regulatory Authorities' References:

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19.2. Financial Disclosure

The Applicant's Position:

Astex has adequately disclosed financial interests/arrangements with clinical investigators participating in Studies ASTX727-01 and ASTX727-02, as recommended in the Guidance for Industry Financial Disclosure by Clinical Investigators.

With the exception of Dr. (b) (6) (Study ASTX727-01) and Dr. (b) (6) (Studies ASTX727-01 and ASTX727-02), who received "significant payments of other sorts", Astex certifies that we have not entered into any financial arrangement with any other clinical investigators participating in Studies ASTX727-01 and ASTX727-02.

With the two exceptions noted above, Astex certifies that: 1) the company has not entered into any financial arrangement whereby the value of compensation to the investigator could be affected by the outcome of the study; 2) no listed investigator disclosed a proprietary interest in the product or a significant equity holding in Astex; and 3) no listed investigator was the recipient of significant payments of other sorts.

The financial arrangements made with both Dr. (b) (6) and Dr. (b) (6) do not raise any concerns with data integrity.

The Regulatory Authorities' Assessment:

We agree with the Applicant's assessment.

Covered Clinical Study (Name and/or Number):* ASTX727-01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>16 Principal Investigators; 228 Subinvestigators</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2**</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the Applicant, and confirmed/edited by the FDA.

** Form FDA 3455 was provided for both Dr. ^{(b) (6)} and Dr. ^{(b) (6)}. Dr. ^{(b) (6)} is listed for Study ASTX727-01 and ASTX727-02.

Covered Clinical Study (Name and/or Number):* ASTX727-02 (Phase 3)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>46 Principal Investigators and 434 Subinvestigators</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1**</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the Applicant, and confirmed/edited by the FDA.

** Form FDA 3455 was provided for Dr. (b) (6), who is also listed for Study ASTX727-01.

19.3. Nonclinical Pharmacology/Toxicology

Data:

None

The Applicant's Position:

Not applicable

The Regulatory Authorities' Assessment:

We agree with the Applicant's assessment.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The Regulatory Authorities' Assessment:

Table J: Listing of clinical pharmacology studies

Study Type	Study Number	Population	Study Description
Single Dose Studies	E7727-01	HV	ADME of cedazuridine (refer to Section 19.4.2)
	ASTX727-04	MDS/CMML/A	Food effect (refer to Section 6.3.2.4)
Multiple-dose	ASTX727-01-A	MDS/CMML	Dose escalation, PK (refer to Section 19.4.1)
	ASTX727-01-B		Dose confirmation (refer to Section 6.3.2.1 and 6.3.2.2)
	ASTX727-02	MDS/CMML	Relative BA, Safety, Efficacy (refer to Section 6.3.2.1 and 6.3.2.2)

19.4.1. General Information

A Phase 1, PK-guided 3+3 dose escalation study (ASTX727-01-A) was conducted in patients with intermediate- or high-risk MDS. The starting oral dose was 20 mg decitabine and 40 mg cedazuridine cohort (see Table K). Dosing was administered in each course as shown in Figure J. Cedazuridine and decitabine were administered as separate capsules.

Figure J: Schedule of Pharmacokinetics Assessments

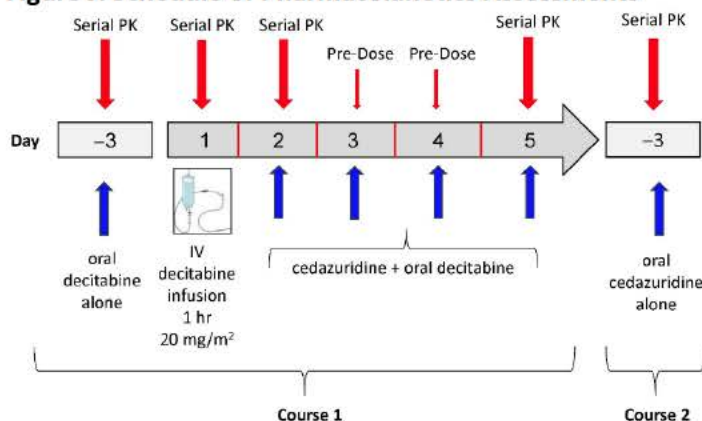
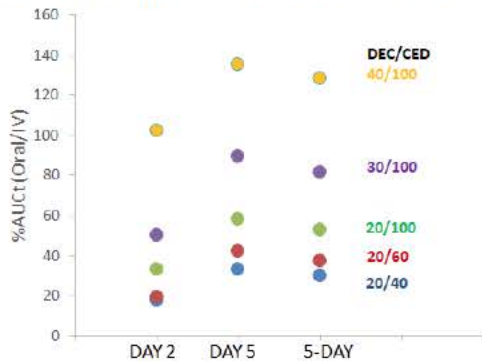


Table K: Dose Escalation

Cohort	Decitabine	Cedazuridine
1	20 mg	40 mg
2	20 mg	60 mg
3	20 mg	100 mg
4	40 mg	100 mg
5	30 mg	100 mg

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Figure K: Comparison of Oral to IV Exposures for Daily and Cumulative Decitabine AUC



Source: Reviewer's Analysis. DEC=decitabine, CED=cedazuridine

The decitabine AUC parameters are listed in Table 10 and Table 11 in Section 6.3.2.2. The dose proportionality of decitabine are listed in Figure K, and Table L. The cedazuridine PK parameters are listed in Table M, and dose proportionality of cedazuridine are listed in Tables N and O.

Table L: Dose Proportionality of 20 to 40 mg Oral Decitabine in presence of 100 mg Oral Cedazuridine

Course Day	Parameter	Slope Estimate	95% Confidence Interval
Day 5	C _{max}	1.04	0.24, 1.84
	AUC _{tau}	1.40	0.59, 2.22
Cumulative	5-d AUC	1.27	0.45, 2.09

Source: Tables 19 and 20, PK Report, ASTX727-01-A

Table M: Summary of Pharmacokinetic Parameters of Oral Cedazuridine

CED Dose (mg)	DEC Dose (mg)	Day	N	Parameter					
				AUC ₀₋₈ (hr*ng/mL)	AUC _{0-t} (hr*ng/mL)	Cave (ng/mL)	C _{max} (ng/mL)	t _{1/2} (hr)	T _{max} (hr)
40	20	2	6	1210 (30)	2020 (28)	--	246 (39)	6.1 (10)	3.0 (36)
	20	5	6	1650 (44)	1640 (43)	206 (43)	309 (50)	7.8 (190)	2.9 (32)
	0	-3	5	1600 (40)	1930 (57)	--	338 (32)	5.9 (9)	2.8 (35)
60	20	2	6	1370 (48)	2540 (48)	--	249 (50)	7.2 (17)	3.1 (26)
	20	5	6	1990 (64)	1940 (69)	251 (64)	376 (67)	--	3.0 (25)
	0	-3	5	1750 (40)	2880 (68)	--	344 (30)	5.4 (61)	3.1 (30)
100	20-40	2	27-31	2620 (49)	4830 (47)	--	486 (49)	6.9 (20)	3.4 (26)
	20-40	5	24-31	3610 (48)	3120 (82)	443 (50)	605 (54)	--	3.3 (27)
	0	-3	18-23	2570 (49)	4300 (62)	--	494 (45)	6.6 (16)	3.0 (30)

Source: Table 39, PK Report, ASTX727-01-A

Table N: Dose Proportionality of 40 to 100 mg Oral Cedazuridine in the presence of Oral Decitabine

Course Day	Cedazuridine	Decitabine	Parameter	Slope Estimate	95% Confidence Interval
Day 5	40-100 mg	20 mg	C _{max}	0.80	0.12, 1.48
			AUC _{tau}	0.72	0.08, 1.55

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	20-40 mg	C _{max}	0.78	0.30, 1.30
		AUC _{tau}	0.85	0.31, 1.40

Source: Reviewer's analysis

Table O: Effect of Decitabine on Pharmacokinetic Parameters of 100 mg Cedazuridine

Cedazuridine Parameter	Cedazuridine Ratio with and without Decitabine (90% CI)		
	20 mg Decitabine	30 mg Decitabine	40 mg Decitabine
AUC _{0-t}	0.92 (0.72, 1.18)	1.17 (0.94, 1.45)	1.04 (0.78, 1.39)
C _{max}	0.72 (0.62, 0.84)	1.02 (0.84, 1.23)	0.97 (0.68, 1.38)

Source: Table 36, PK Report, ASTX727-01-A

19.4.2. Metabolism and Excretion

A Phase 1 open-label, non-randomized, 2-treatment period, fixed-sequence, mass balance study (E7727-01) of single doses of cedazuridine (E7727) was conducted in healthy subjects. During Period 1, subjects were administered 100 mg unlabeled E7727 orally and a microtracer dose of 100 µg ¹⁴C-E7727 IV. During Period 2, subjects were administered 100 mg ¹⁴C-E7727 orally. Blood and urine samples were collected up to 72 hours, and feces were collected in 24 hour intervals in Periods 1 and 2.

After a micro IV dose of E7727, 99% of total radioactivity was found in urine and <1% in feces. Following oral dose of E7727, about 46% of total radioactivity (21% unchanged) was found in urine, and 51% (27%) in the feces. Table P provides PK parameters of E7727 in plasma.

Table P: Summary of Plasma Pharmacokinetic Parameters of E7727

	100 mg Oral E7727		100 mg Oral ¹⁴ C E7727	IV 100 µg Microdose	
	E7727	Epimer	Total Radioactivity	E7727	Epimer
C _{max} (ng [eq]/mL)	349	388	821	6053	1451
	259-470	289-527	529-1254	4601 - 7577	976 - 2810
T _{max} (h)	5.00	4.50	4.00	0.17	0.17
	2.92-6.00	2.92-6.00	2.00-6.00	0.17-0.17	0.17-0.33
AUC _{0-t} (h.ng [eq]/mL)	3532	3915	9826	17165	5009
	2042-4435	2305-4943	4160-16059	11926 - 23456	2933 - 11151
AUC _{0-inf} (h.ng [eq]/mL)	3572	3957	10241	17640	5511
	2070-4465	2335-4976	4755-16484	12794 - 23655	3173 - 12470
t _{1/2} (h)	8.39	8.33	10.9	6.57	7.93
	6.54-15.5	6.51-15.9	8.03-16.7	4.78 - 7.67	5.73 - 14.3
CL _[F] (L/h) ^b	28.0	-	-	5.67	-
	22.4-48.3			4.23 - 7.82	
V _z [F] (L) ^b	339	-	-	53.7	-
	213-599			42.2-68.3	

Source: Table 6, CSR, E7727-01

In addition to parent cedazuridine (59% of total drug-related material), the cedazuridine-epimer (31%) and M266/1 metabolite (exchange of -OH by =O, ie, dehydrogenation, at 10%) were the other 2 major

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entities present in plasma. As indicated in Table P, the systemic exposure to the epimer after oral administration in this study was approximately equal to the systemic exposure to cedazuridine. However, the exposure to the cedazuridine-epimer after IV administration was about 30% of that of cedazuridine.

19.4.3. **Summary of Bioanalytical Method Validation and In-Study Performance**

The validated assay quantitation ranges were 0.5 to 200 ng/mL for decitabine, and 6 to 2310 ng/mL for cedazuridine (E7727), and 4 to 1460 ng/mL for cedazuridine epimer, with acceptable precision and accuracy. The validated stability assessments covered the sample handling and stability conditions during the analysis of clinical study samples. Refer to the Table Q for assay parameters during method validation.

Table Q: Assay Validation (R3385)

Analyte	Decitabine	E7727	Epimer
Assay	Protein precipitation extraction followed by LC/MS/MS detection		
Matrix	THU-stabilized K2EDTA Human Plasma		
Reference Standard	Lot P51702A, 150 mg/vial Lot P51715A, 1.07 mg/vial	Lot H4259B01, 150 mg/vial Lot H4792H01, 1.03 mg/ vial	Lot 554761, 440 mg/vial Lot 3202692, 0.97 mg/vial
Selectivity	6 lots of blank and blank+IS: No interference (Table 4-6: R2)		
Carryover	Blank injected after high calibrator: No carryover (Tables 7-10: R2)		
Matrix effect	Matrix factor 1.06 (5%) to 1.1 (7%) in 6 lots of plasma (Tables 11-18: R2)		
Hemolysis	A: 1.2 to 4.7%, P=0.7 to 4% (Tables 19-21: R2)		
Standard Curve	0.5 to 200 ng/mL: 8 calibrators	5.78 to 2310 ng/mL: 8 calibrators	3.66 to 1460 ng/mL: 8 calibrators
Standard performance	Accuracy 0.1 to 1.8%, and Precision 3.1 to 5.2 % CV		
QC levels	0.5, 1.5, 15, 150 ng/mL	5.78, 17.3, 173, 1730 ng/mL	3.66, 11, 110, 1100 ng/mL
QC performance:			
Intra-assay accuracy	-5.3 % to 5.4%	-3.6% to 2.4%	-4.5% to 9.6%
Intra-assay (%CV)	0.8% to 4.7%	1.2% to 5.5%	1.6% to 8.7%
Inter-assay accuracy	-1.2% to 0%	-1% to 0.6%	-2.7% to 4.6%
Inter-assay (%CV)	2.7% to 3.1%	2% to 5%	3.7% to 7%
Stock soln	129 days at -20C: -0.1 to -1.2%, and 6 hours at room temperature (WL):-0.1 to 0.3%		
Dilution linearity	10x : -2.7 to -4.6% and 1.4 to 2.4% (R2), 200x:-6.7 to 1.7%, 400x: -5.7% to 2.7% (A2)		
Matrix Stability:			
Analyte Room Temperature	6.5 hours at room temperature		
Accuracy	-4.7 to -6.7	0 to -2.3	-3.6 to -2.6
Freeze/Thaw Stability	Up to 3 cycles at ≤ -20° & -70C		
Accuracy	-6.7% to -2.7%	-1.7% to 1.2%	-7.3% to 3.6%
Processed sample	At 4C for 106 hours		
	-1.3% to 0.7%	-1.7% to 1.2%	-6.4% to -1.8%
Reinjection Reproducibility	4C for 108 hours		
	-3.3% to 1.3%	-2.3% to 0.6%	-3.6% to 0.9%
Whole blood (% Time 0)	1 hour at room temperature		

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	-3.1% to -10.4%	-8.4% to 2.9%	-9.9% to 7.3%	
	1 hour at 0-4C			
	-2.3% to -4.6%	-10.4% to 3.9%	-9.3% to 0.7%	
Interconversion	From E7727 (matrix) to Decitabine =0%. From E7727 (matrix) to epimer = 27%*			
	From E7727 (solution) to Decitabine =0%. From E7727 (solution) to epimer = 34%			
Long-term Stability	At -20°C: up to 231 days			
	Accuracy	-63% to -54%	-9% to -4%	-8% to -6%
	At -70°C: up to 706 days			
	Accuracy	-4% to -2.7%	-5.2% to -0.6%	-1.8% to 0%

*No interconversion from E7727 to its epimer in plasma (b) (4)
 Further, stock solution stability indicated no interconversion.

The in-study performance was within acceptable limits in Studies ASTX727-02 and -01-B. Refer to Tables R and S for in-study assay performance in Studies ASTX727-02 and -01-B.

Table R: Assay Performance in Study ASTX727-02

Analyte	Decitabine	E7727	Epimer
Analytical runs	94 runs, 4 failed	94	94, 5 failed
Internal Standard (IS)	Decitabine-d3	Deutero-E7727	
Matrix	Human K2EDTA plasma		
Reference standard (purity)	BRS16-369 (98%)	BRS17-614 (98%)	
		BRS13-434 (95%: 55:45), BRS17-613 (99%: 47% vs. 53%)	
Standard curve concentrations (ng/mL)	0.5 to 200: 8 calibrators	5 to 2000: 8 calibrators	3.2 to 1270: 8 calibrators
QCs	1.5, 15, & 150 ng/mL,	15, 150, 1500 ng/mL	9.53, 95.3, 953 ng/mL
QC Performance:			
Inter-assay accuracy	1.5 ng/ml: 100% 15 ng/ml: 100% 150 ng/ml: 96%	15: 97% 150: 97% 1500: 93%	9.53: 103% 95.3: 103% 953: 98%
Inter-assay precision (%CV)	1.5 ng/ml: 10% 15 ng/ml: 8% 150 ng/ml: 9%	15: 6% 150: 6% 1500: 6%	9.53: 7% 95.3: 8% 953: 8%
Dilution QCs			
Inter-assay accuracy	1500 ng/mL: 95% 15000 ng/mL: 90%	15000: 99%	9530: 108%
Inter-assay precision (%CV)	1500 ng/mL: 7% 15000 ng/mL: 8%	15000: 2%	9530: 4%
ISR (total samples)	91% (443)	93% (289)	93% (288)

Table S: Assay Performance in Study ASTX727-01-B

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 INQOVI (decitabine and cedazuridine)

Analyte	Decitabine	E7727	Epimer
Analytical runs	55 runs	41	42
IS	Decitabine-d3	Deutero-E7727 (IS)	
Matrix	Human K2EDTA plasma		
Reference standard (purity)	BRS13-433 (98%)	BRS13-398 (98.6%)	
		BRS14-036 (4.6% vs 2.9%), BRS16-217 (98%: 46% vs 52%)	
Standard curve concentrations (ng/mL)	0.5 to 200: 8 calibrators	5 to 2000: 8 calibrators	3.2 to 1270: 8 calibrators
QCs	1.5, 15, & 150 ng/mL,	15, 150, 1500 ng/mL 17.3, 173, 1730 ng/mL	9.53, 95.3, 953 ng/mL 11, 110, 1100 ng/mL
QC Performance:			
Inter-assay accuracy	1.5 ng/ml: 95% - 99% 15 ng/ml: 93% - 99% 150 ng/ml: 94% - 95%	15: 93% 17.3: 97% 150: 97% - 99% 173: 100% 1500: 93% - 95% 1730: 95%	9.53: 99% - 102% 11: 101% 95.3: 105% 110: 104% 953: 99% 1100: 92%
Inter-assay precision (%CV)	1.5 ng/ml: 7% - 8% 15 ng/ml: 7% - 8% 150 ng/ml: 6%	15: 5% - 6% 17.3: 7% 150: 3% - 4% 173: 4% 1500: 3% - 5% 1730: 4%	9.53: 5% - 11% 11: 8% 95.3: 7% 110: 6% 953: 7% - 8% 1100: 7%
Dilution QCs			
Inter-assay accuracy	1500 ng/mL: 95% - 97% 15000 ng/mL: 106%	15000: 87% 17300: 102%	9530: 94% 11000: 106%
Inter-assay precision (%CV)	1500 ng/mL: 8% - 9% 15000 ng/mL: 10%	15000: 2% 17300: N/A	9530: 1% 11000: 1%
ISR (total samples)	94% (329)	100% (280)	81% (280)

Study ASTX727-02 and ASTX727-01-B: Majority of the reassays for decitabine were for values above the limit of quantitation (ALQ), predose not less than the limit of quantitation (LOQ), and out of range IS response or no IS response. There were client requested reassays, which are discouraged. Nonetheless, the original values were reported for majority of the client requested reassays and/or many original values were ALQ.

Few samples were reanalyzed for E7727. Majority of reassays were for poor chromatography, and some for IS out of range and per client request. Nonetheless, the original values were reported for majority of the client requested reassays.

19.4.4. Pharmacometrics review report

19.4.4.1. SUMMARY OF FINDINGS

19.4.4.1.1. Key Review Questions

ASTX727 is a fixed dose combination of 100 mg of cedazuridine and 35 mg of decitabine. Decitabine is the active component that is thought to act through 1) incorporation into DNA causing apoptosis of proliferating cells and 2) inhibition of DNA methyltransferase which causes hypomethylation and consequently promotes cellular differentiation of future cancer cells. When taken orally, decitabine is rapidly metabolized by the liver's cytidine deaminase resulting in very low oral bioavailability. Cedazuridine is a potent inhibitor of cytidine deaminase and therefore increases decitabine oral bioavailability. Renal elimination is the major route of cedazuridine excretion. In the stomach, cedazuridine undergoes PH dependent conversion to its epimer (a less potent cytidine deaminase inhibitor) thus decreasing bioavailability of the potent epimer. Based on these disposition pathways, decitabine exposure is therefore dependent on factors influencing hepatic function, renal function and stomach PH. The Applicant evaluated potential covariates and developed population PK models that accounted for the effect of renal impairment and sex on cedazuridine clearance and rate of absorption respectively. In turn, cedazuridine affected decitabine hepatic clearance. The model also accounted for the effect of body size (height) on decitabine hepatic clearance (through empirical model of body size dependent hepatic and portal vein blood flow and volume) and sex on intravenous (IV) decitabine hepatic clearance and central volume. However, none of these covariates had a sufficiently large effect on clearance to justify dose adjustments. On the other hand, it is interesting that sex was identified as a covariate on clearance and absorption parameters while concomitant use of proton pump inhibitors (PPI) was not identified as a covariate to decitabine exposure. Based on this observation, the key pharmacometric review questions were:

1. Do pharmacokinetic and exposure-vs-safety data support dose adjustment based on measures of body size (e.g body surface area or weight)?
2. Do pharmacokinetic and exposure-vs-safety data support dose adjustment based on measures of renal impairment (e.g. creatinine clearance[CLCR])?
3. Do pharmacokinetic data support concomitant use with proton pump inhibitors?
4. Do pharmacokinetic and exposure-vs-safety data support dose adjustment based on biological sex?

19.4.4.1.1.1. *Do pharmacokinetic and exposure-vs-safety data support dose adjustment based on measures of body size (e.g body surface area or weight)?*

No, dose adjustment is not needed based on body surface area (BSA) or weight (WT) for ASTX727. Although measures of body size (BSA and WT) were associated with decitabine exposure and with proportions of patients with any grade neutropenia, prediction from logistic regression model indicated only 5% difference in probability of any grade neutropenia between

lowest and highest BSA quartiles. This effect was not large enough to warrant dose adjustments.

19.4.4.1.1.2. Do pharmacokinetic and exposure-vs-safety data support dose adjustment based on measures of renal impairment (e.g. creatinine clearance[CLCR])?

No, dose adjustment is not needed for patients with mild and moderate renal impairment. Although renal function has a trend for association with decitabine exposure (p-value = 0.063) and with any grade thrombocytopenia (p-value = 0.06), the effects were not statistically significant (alpha = 0.05) to warrant dose adjustments. Furthermore, CLCR was not associated with any grade neutropenia. ASTX727 is not recommended for use in patients with severe renal impairment, end stage renal disease and patients on dialysis since it was not studied in these patients.

19.4.4.1.1.3. Do pharmacokinetic data support concomitant use with proton pump inhibitors?

Yes, ASTX727 can be used concomitantly with PPI. Although decitabine exposure was higher in patients on concomitant PPI compared to other patients, the difference (less than 25%) does not support avoiding concomitant use of PPI with ASTX727.

19.4.4.1.1.4. Do pharmacokinetic and exposure-vs-safety data support dose adjustment based on biological sex?

No, there is no need for dose adjustments based on sex. Although male subjects had about 30% lower 5-days cumulative AUC compared to female subjects, no differences were observed when day 1, 2, and 5 AUCs were compared between the sexes separately. Furthermore, the association between sex and adverse events of any grade neutropenia (p-value = 0.1724 at treatment-cycle 2) and thrombocytopenia (p-value = 0.12) were not statistically significant. In totality, the difference between male and female AUCs and incidences of adverse events do not warrant dose adjustment given that ASTX727 dosing will be down-titrated in subjects experiencing intolerable toxicity.

19.4.4.1.2. Recommendations

No dose adjustment is recommended for ASTX727 based on sex, BSA, WT or CLCR. However, female and patients with low BSA (<1.97) and impaired renal function (CLCR < 60 ml/minor category) should be monitored for cytopenia adverse events and dosing reduced as studied in phase 3 clinical trial.

19.4.4.1.3. Label Statements

[\(12.2. Pharmacodynamics\)](#)

[Based on the exposure-response analyses, a relationship between an increase in 5-day cumulative daily decitabine exposure and a greater likelihood of some adverse reactions \(e.g., any grade neutropenia, thrombocytopenia\) was observed in clinical studies.](#)

[\(12.3. Pharmacokinetics/special populations\)](#)

Decitabine exposure (AUC) increased with decreasing body surface area or body weight.

19.4.4.2. Results of Applicant's Analysis

19.4.4.2.1. Applicants' population pharmacokinetics results.

Data for PK analyses were obtained from phase 1 (ASTX727-01) and phase 2 (ASTX727-02) studies that were designed to compare the pharmacokinetics of ASTX727 to that of intravenous decitabine. In the phase 1 study, combinations of different doses of cedazuridine and decitabine were tested to identify optimal combination with comparable exposure to 20mg/Kg of IV decitabine. The optimal dose was compared to 20mg/Kg of IV decitabine in part-2 of the phase 1 study (ASTX727-01) to confirm dose-comparability and treatment outcomes. The phase 2 study was a bioequivalence and treatment-outcome study comparing optimal dose tested in phase 1B to 20mg/Kg of IV decitabine. Intensive PK sampling for characterization cedazuridine and decitabine PK were collected. The final dataset for PK analyses consisted of 18940 PK observations from 243 individuals. The patient population across all studies consisted of 168 males and 75 females, with a mean age of 70.3 years (with a range of 32.0-90.0 years), a mean weight of 83.1 kg (with a range of 41.0-158 kg), a mean height of 171 cm (with a range of 144-193 cm), a mean BSA of 1.97 m² (with a range of 1.30-2.90 m²), a mean CrCL of 65.5 mL/min/1.73m² (with a range of 27.7-156 mL/min/1.73m²), and a mean bilirubin of 13.2 umol/L (with a range of 3.0-51.3 umol/L)

The Applicant developed cedazuridine and decitabine population pharmacokinetics models sequentially. A cedazuridine semi-physiologic pharmacokinetic model was developed first (**Figure 29**); the estimated population PK parameters are given in Table 73. In brief, the model

(b) (4)



(b) (4)



2.3. Reviewer's comments

The Applicant followed appropriate pharmaco-statistical principles for model development. However, the Applicant's final semi-physiologic PK model for IV decitabine under-predicts C_{max} and AUCs. (b) (4)

. Based on this, the reviewer performed additional model evaluation to look for any model misspecification (Figure 28).

After comparing observed versus model predicted AUC the reviewer found that the Applicant's model unacceptably underpredicted decitabine AUC (See Figure 28). An information request was sent to the Applicant to explain the identified underprediction of decitabine AUC. The Applicant acknowledges the underprediction and attributed it to (b) (4)

Due to this misspecification, the reviewer concludes that the Applicant's IV decitabine model failed to identify PK covariates. The Applicant did not assess impacts of covariates on oral decitabine clearance and distributions. Estimates obtained during IV decitabine model development were fixed when oral decitabine data were included for modeling. Based on this, results from the Applicant's model do not support labelling statements on dose adjustment in renal and hepatic impaired patient nor based on body surface area. Furthermore, predictions from the model cannot be used in exposure-vs-response or safety modeling.

19.4.4.3. Reviewer's Analysis

19.4.4.3.1. Introduction

The Applicant's semi-physiologic PK model underpredicted observed decitabine AUC. This can be attributed to structural model misspecifications particularly the un-estimated physiological parameters. This misspecification may cause inaccurate identification and characterization of effects covariates of PK parameters. Fortunately, due to intensive PK sampling, 5-day-AUC can be calculated from observed data and used to assess PK covariates.

Furthermore, identification of factors associated with treatment related adverse events can be extended by performing additional analyses e.g. assess factors associated with adverse events in cycle 1 and cycle 2 separately; and to use a sequential approach to building a GLM model for adverse events where by only potential predictors identified through univariate logistic regression analysis are included in the final multivariate model.

19.4.4.3.2. Objectives

The reviewer performed additional PK and exposure-safety analyses to:

Identify intrinsic and extrinsic factors associated with decitabine AUC using intensively collected PK data

Identify predictors of neutropenia and thrombocytopenia in each treatment cycle separately.

19.4.4.3.3. Methods

19.4.4.3.3.1. Data Sets

Datasets for PK and exposure-safety analyses were constructed from ADAM datasets supplied by the Applicant i.e. adsl.xpt, lb.xpt, pc.xpt, and adae.xpt. For preparation of PK datasets, records on intensive PK sampling on day 1, 2 and 5 from both phase 1B (ASTX727-01-B) and phase 2 (ASTX727-02) studies were identified and used to calculate AUC between 0 – 8 hours (AUC₀₋₈) for each day. AUCs were calculated using the linear trapezoidal method. For the decitabine PK dataset, cumulative five-day AUC was calculated by multiplying average of day 2 and day 5 AUC by 5 (5-day-AUC = (day2-AUC+day5-AUC)/2) while for IV decitabine 5-day-AUC was calculated by multiplying average of day 1 and day 5 AUC by 5 (5-day-AUC = (day1-AUC+day5-AUC)/2). Individuals with less than 5 PK observation in a day were removed from the dataset due to potentially unreliable AUC. Covariate information were obtained from adsl.xpt and lb.xpt datasets. Creatine clearance (CLCR) and estimated glomerular filtration rates (eGFR) were calculated using Cockcroft-Gault and MDRD equations respectively.

For exposure-safety datasets, dependent variables were identified from the AEHLT variable in the adae.xpt datasets. The NCYCSTD variable was used to identify treatment cycles, and 3 separate adverse events datasets were prepared for each treatment cycle. The pc.xpt datasets provided PK data for calculation of 5-day-AUC. The exposure and covariate datasets were joined to adverse events datasets to complete construction of analysis datasets.

19.4.4.3.3.2. *Software*

The R software for statistical computing (Version 3.5.3) was used for preparation of the analysis datasets, for graphical analyses and for linear and generalize linear modeling

19.4.4.3.3.3. *Models*

Univariate and multivariate linear and logistic regression models were used in the analyses. Before such analyses, collinearities among independent variables were assessed. In univariate analyses one independent variable was assessed for association with a dependent variable. For PK analysis, 5-day-AUC was log transformed to create a dependent variable. Independent variables with univariate p-values of < 0.05 were included in the multivariate analysis regardless of collinearity among them to control for possible confounding effect. For exposure-safety analyses, variables which were collinear with AUC were not included in the multivariate analyses.

19.4.4.3.4. Results

19.4.4.3.4.1. Extrinsic and intrinsic factors associated with decitabine AUC

Figure 30 shows results from collinearity analyses among independent variables.

Graphical exploration and univariate analyses indicated that age, sex, weight, height, CLCR, and BSA were associated with oral decitabine 5-day-AUCs at p-values < 0.05. A multivariate analysis identified both sex (p-value = 0.000082) and BSA (p-value = 0.020) to be the independent predictors of 5-day-AUC for oral decitabine (See **Table 77**). **Table 77** indicates that male subjects (represented by intercept parameter) with age of 70 years, BSA of 1.73 m² and CLCR of 90 ml/min would have about 30% lower 5-days-AUC compared to female patients of the same age, BSA, and CLCR.

Table 77. Intrinsic factors associated with cumulative 5-days-AUC in a multivariate linear model analysis of log-transformed 5-days-AUC

Predictors	Estimate	P-value	Adjusted R square
(Intercept)	6.79	0.000000	0.27
log (AGE/70)	0.23	0.398345	
FEMALE	0.33	0.000082	
log (BSABL/1.73)	-0.82	0.020	
log (CLCR/90)	-0.25	0.063	

Linear model for log transformed 5-day-AUC:
 $\ln(\text{LOGD5AUC}) \sim \log(\text{AGE}/70) + \text{FEMALE} + \log(\text{BSABL}/1.73) + \log(\text{CLCR}/90)$

The model is equivalent to:

$$5 - \text{day} - \text{AUC} = \text{Intercept} \times \left(\frac{\text{AGE}}{70}\right)^{0.23} \times \left(\frac{\text{CLCR}}{90}\right)^{-0.25} \times \left(\frac{\text{BSA}}{1.73}\right)^{-0.82} \times e^{0.33}$$

In addition to 5-day-AUC, the reviewer assessed the impact of BSA, sex, weight and height on decitabine AUC observed on day 1, day 2, and day 5 separately. The results from multivariate linear regression analyses are given in **Table 78**. These results indicate that only BSA is strongly associated with decitabine daily AUC after adjusting for sex, weight and height.

Table 78. Intrinsic factors associated with daily AUC in a multivariate linear model analysis of log-transformed daily AUC

Multivariate models	Coefficients	Estimates	P-value	Adjusted R square
DAY 1	(Intercept)	7.673	0.000	0.287
	BSA	-2.674	0.001	

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	SEX	0.090	0.367	
	WT	0.022	0.023	
	HT	0.002	0.743	
DAY 2	(Intercept)	8.862	0.000	0.295
	BSA	-1.563	0.064	
	SEX	0.101	0.334	
	WT	0.012	0.216	
	HT	-0.009	0.200	
DAY 3	(Intercept)	6.228	0.000	0.101
	BSA	-1.720	0.088	
	SEX	0.166	0.173	
	WT	0.013	0.279	
	HT	0.007	0.421	

Concomitant use of proton pump inhibitors was assessed as a potential extrinsic factor impacting decitabine exposure. Data for concomitant drug use was obtained from *cm.xpt* dataset. The CMENRTPT variable was used to identify patients who were on ongoing PPI use and those who were not. Graphical and linear model analysis was used to determine if ongoing PPI used has impact on decitabine exposure. Figure 31 and **Table 79** shows that subjects on ongoing PPI use in the phase 2 study had 23.3% higher decitabine 5-day-AUC (P-value=0.009) compared to subjects not on PPI. Despite this significant trend the effect is considered small and is not consistent with results from the phase 1 study

Table 79. Impact of ongoing PPI use on oral decitabine cumulative 5-day-AUC estimated in phase 1 and phase 2 studies separately.

	Parameters	Estimates	P-value	Adjusted R square
Phase 1	Intercept	895	0.00	-0.01
	ONGOING PPI USE	156	0.42	-0.01
Phase 2	Intercept	901.5	0.000	0.041
	ONGOING PPI USE	210.5	0.009	0.041

Linear model for 5-day-AUC: $\text{lm}(\text{D5AUC} \sim \text{factor}(\text{ONGOINGPPIUSE}))$

The model is equivalent to: 5-day-AUC = Intercept + coefficient for ONGOINGPPIUSE (0, or 1)

19.4.4.3.4.2. Factors associated with any grade neutropenias in phase 1B and 2 studies

Graphical analyses for the relationship between any grade neutropenias in treatment-cycle 1 and different patient characteristics are given in Figure 32 and **Figure 33**. In univariate General Linear Model (GLM) analyses, none of the patient characteristics were associated with likelihood of any grade neutropenias.

Figure 34 and **Figure 35**, show results from graphical analyses for the relationship between any grade neutropenias in treatment-cycle 2 with different patient characteristics. Female subjects appear to higher proportions of any grade neutropenias compared to male subjects. However, in univariate GLM, sex was not a predictor of any grade neutropenias (p-value = 0.172), only day-5-AUC was associated with likelihood of any grade neutropenias (p-value = 0.0187). Nevertheless, in a multivariate GLM, independent variables included log-transformed 5-days-AUC, sex, and study (phase 1 or 2), treatment-sequence (Oral->IV or IV->oral) and interaction term between study and sequence. **Table 80** shows results from the multivariate logistic regression analysis. The multivariate analysis indicate that the likelihood of any grade neutropenia increased with increasing 5-days-AUC. Furthermore, subjects in phase 2 study had more likelihood of any grade neutropenias than in phase 1. Similarly, in treatment-cycle 2, subjects in phase 2 and in oral->IV sequence (i.e. receiving IV decitabine in cycle 2) had less likelihood of neutropenias compared to other study/sequence interactions.

Figure 36 shows the proportions of patients with any grade neutropenias in treatment-cycle 3 for different categories of subject characteristics. The figure shows decreasing proportion of neutropenia with increasing body-surface area, and lower proportion with neutropenia in male subjects compared to female. In contrast, proportions of neutropenias seem to increase with higher 5-days-AUC and higher baseline neutrophil counts. However, in univariate analyses, none of the covariates are associated with neutropenia in treatment-cycle3 (p-values of 0.125, 0.449, 0.229, 0.165, for 5-days-AUC, BSA, baseline neutrophils, and sex). A multivariate analysis with 5-days-AUC, baseline neutrophils, study (phase 1 or 2), treatment-sequence (Oral->IV or IV->oral) and interaction term between study and sequence had a better fit than any other combination of independent variables. **Table 81** shows parameters of the multivariate model while **Figure 37** shows good agreement between observed and predicted proportions of neutropenia in different quantiles of 5-days-AUC and BSA for treatment cycle 3.

In conclusion, the results from these additional analyses do not warrant dose reduction based on the assessed patient factors.

Table 80. Parameter estimates and odds ratio for multivariate logistic regression model of any grade neutropenias in treatment cycle 2.

Predictors	Estimate (95%CI)	P-value	Odds Ratio
(Intercept)	-5.27 (99.63 - -0.91)	0.02	-
log(D5AUC)	0.57 (-0.04 – 1.18)	0.07	1.77 (0.96 – 3.26)
Male	-0.25 (-0.92 – 0.42)	0.46	0.78 (0.40 – 1.52)
Phase 2	1.27 (0.25 – 2.28)	0.01	3.54 (1.28 – 9.81)
Oral -> IV	0.90 (-24 – 2.04)	0.12	2.46 (0.78 – 7.71)
Phase2: Oral -> IV	-1.44 (-2.80 – -0.08)	0.04	0.24 (0.06 – 0.92)

Table 81. Parameter estimates and odds ratio for multivariate logistic regression model of any grade neutropenias in treatment cycle 3

Predictors	Estimate (95%CI)	P-value	Odds Ratio (95%CI)
(Intercept)	-5.18 (-9.63 - -0.73)	0.02	-
LOGD5AUC	0.62 (-0.03 – 1.28)	0.06	1.87 (0.97 – 3.59)
LOGNEUT	0.19 (-0.07 – 0.45)	0.14	1.21 (0.94 – 1.58)
Phase 2	-0.65 (-.64 – 0.33)	0.19	0.52 (0.19 – 1.40)
Oral -> IV	-0.32 (-1.37 – 0.73)	0.55	0.73 (0.25 – 2.07)
Phase2: Oral -> IV	0.54 (-0.83 – 1.92)	0.44	1.72 (0.44 – 6.80)

19.4.4.3.4.3. Factors associated with any grade thrombocytopenias in phase 1 and 2 studies

Graphical and univariate GLM identified some covariates with trend for association with any grade thrombocytopenias in treatment cycles 1 and 2 (p-value > 0.05 and p-value ≤0.20). **Table 82** and **Figure 38** show results from univariate GLM and graphical analyses respectively for treatment-cycle 1, while **Table 83** and **Figure 39** shows similar results for treatment cycle 2. In conclusion, despite differences in 5-days-AUC based on BSA and sex, incidences of thrombocytopenia was not associated with these covariates. Therefore, dose adjustment is not necessary based on these factors.

Table 82. Parameter estimates and odds ratio for univariate logistic regression model of any grade thrombocytopenias in treatment-cycle 1

Univariate models	Predictors	Estimate (95%CI)	P-value	Odds Ratio (95%CI)
5-day-AUC	Intercept	-2.08(-5.34-1.17)	0.21	-
	LOGD5AUC	0.27(-0.2-0.75)	0.26	1.31(0.81-2.11)
eGFR	Intercept	0.66(-0.3-1.63)	0.18	-
	EGFR	-0.01(-0.02-0)	0.06	0.99(0.98-1)

Body surface area	Intercept	1.35(-0.84-3.54)	0.23	-
	BSABL	-0.8(-1.9-0.31)	0.16	0.45(0.15-1.36)
Body weight	Intercept	-0.71(-0.6-2.02)	0.29	-
	WGTBL	-0.01(-0.03-0)	0.15	0.99(0.97-1)
Baseline platelet count	Intercept	-0.26(-0.63-0.11)	0.17	-
	PLAT	0.00024(-0.00216-0.00263)	0.85	1(1-1)
Sex	Intercept	-0.09(-0.58-0.39)	0.71	-
	Male	-0.21(-0.79-0.38)	0.49	0.81(0.45-1.46)

Table 83. Parameter estimates and odds ratio for univariate logistic regression model of any grade thrombocytopenias in treatment-cycle 2

Univariate models	Predictors	Estimate (95%CI)	P-value	Odds Ratio (95%CI)
5-day-AUC	Intercept	-4.61(-8.62 - -0.61)	0.02	-
	LOGD5AUC	0.55(-0.03 - 1.14)	0.06	1.74(0.97 - 3.12)
eGFR	Intercept	-0.35(-1.42 - 0.72)	0.52	-
	EGFR	-0.01(-0.02 - 0.01)	0.35	0.99(0.98 - 1.01)
Body surface area	Intercept	1.02(-1.44 - 3.47)	0.42	-
	BSABL	-0.95(-2.2 - 0.3)	0.14	0.39(0.11 - 1.35)
Body weight	Intercept	0.4(-1.09 - 1.9)	0.60	-
	WGTBL	-0.02(-0.03 - 0.0027)	0.10	0.98(0.97 - 1)
Baseline platelet count	Intercept	-1.09(-1.51 - -0.66)	0.00	-
	PLAT	0.00212(-0.0004 - 0.00464)	0.10	1.002(0.999 - 1.004)
Sex	Intercept	-0.5(-1.02 - 0.02)	0.06	-
	Male	-0.51(-1.15 - 0.13)	0.12	0.6(0.32 - 1.14)

19.4.4.3.5. Tables and Figures

19.4.4.3.5.1. *Figures*

(b) (4)



Figure 29. Semi-physiologic Pharmacokinetic models for cedazuridine and decitabine

Source: Applicant's population PK Report No. ASTX727-Report-PopPK, page 44

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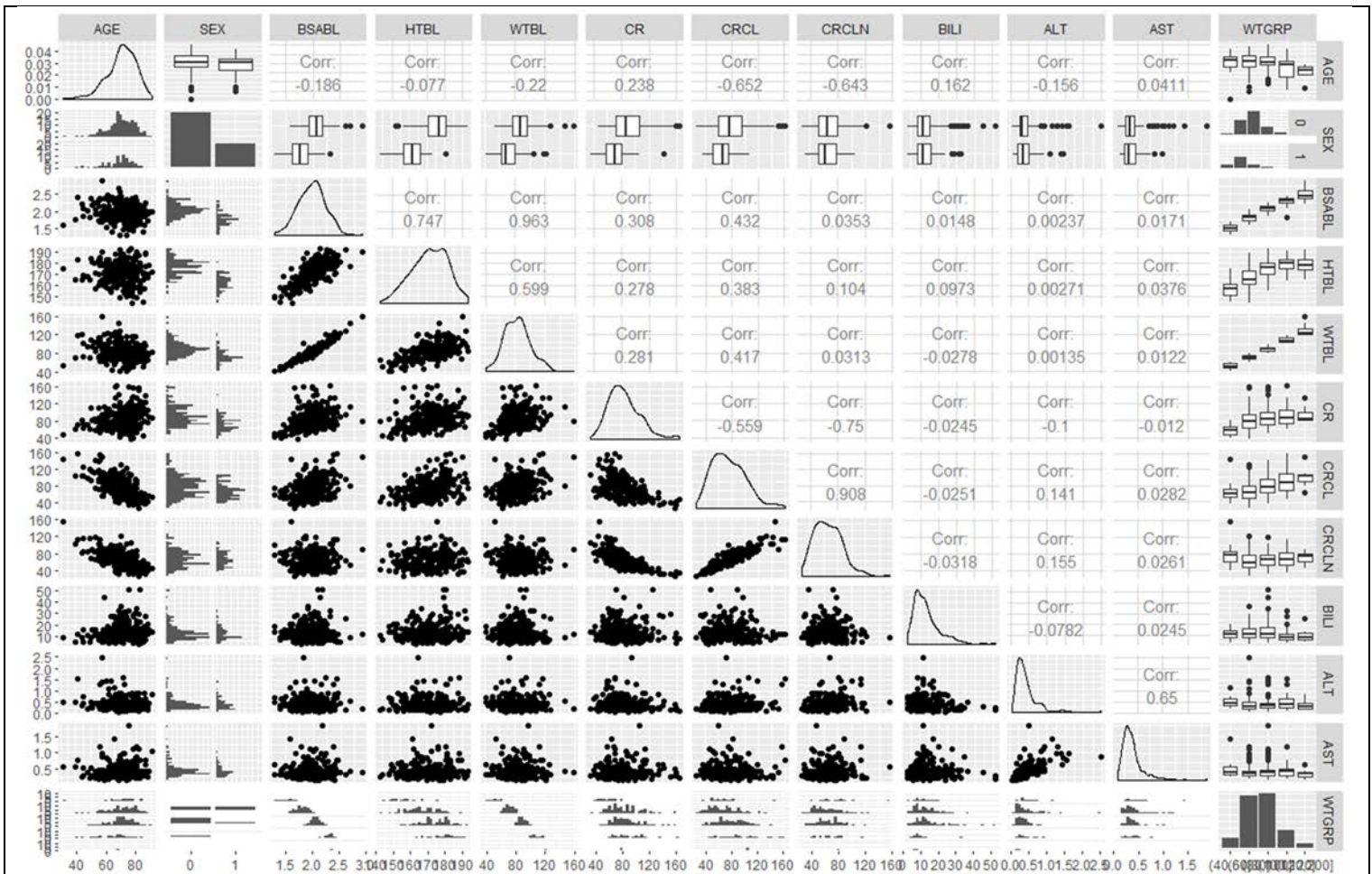


Figure 30. Results from collinearity analyses among independent variables

Source: Reviewer’s independent analysis of PK data from studies ASTX727-01-B and ASTX727-02

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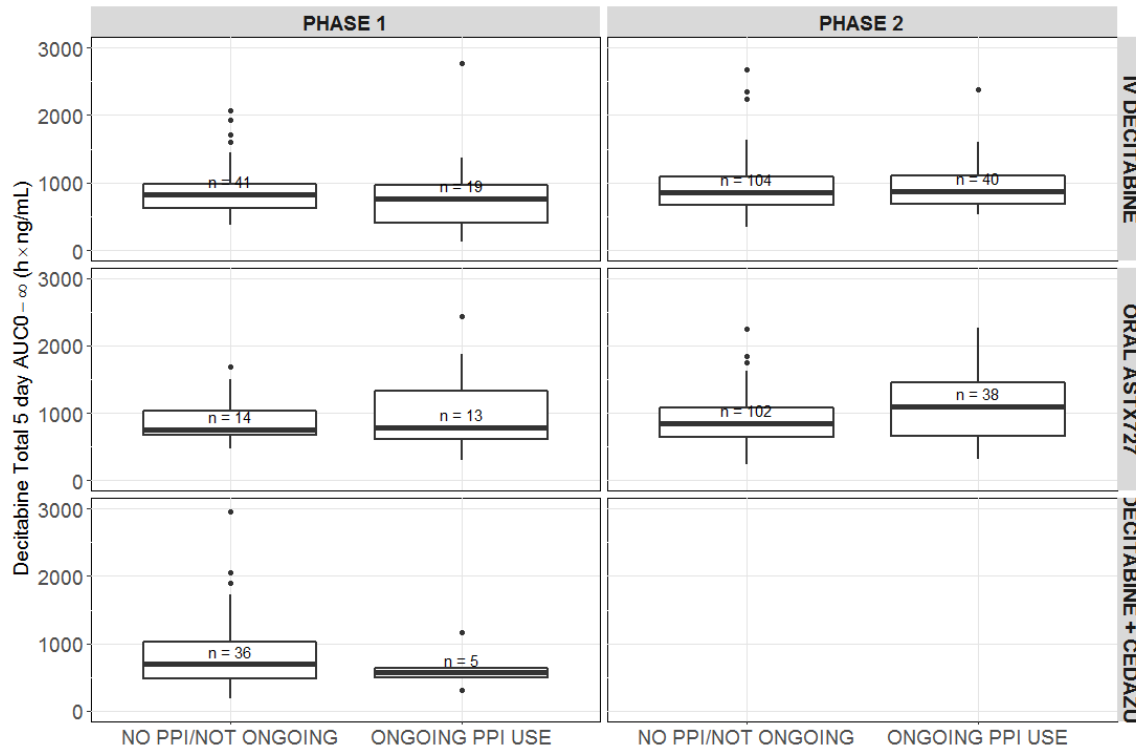


Figure 31. Boxplots showing distributions of 5-day-AUC stratified by study, route of administration and PPI use status

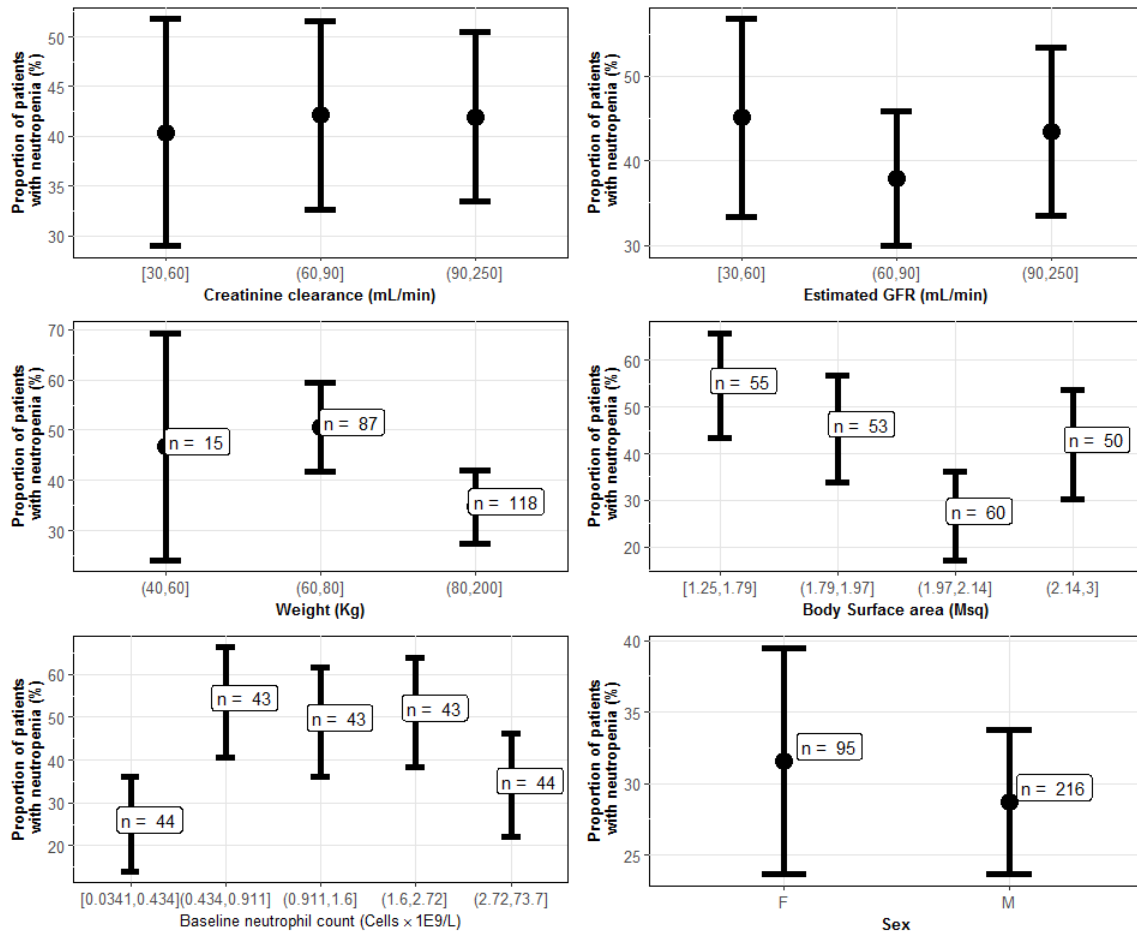


Figure 32. Proportions of patients with any grade neutropenias in treatment-cycle 1 for different categories of patient characteristics.

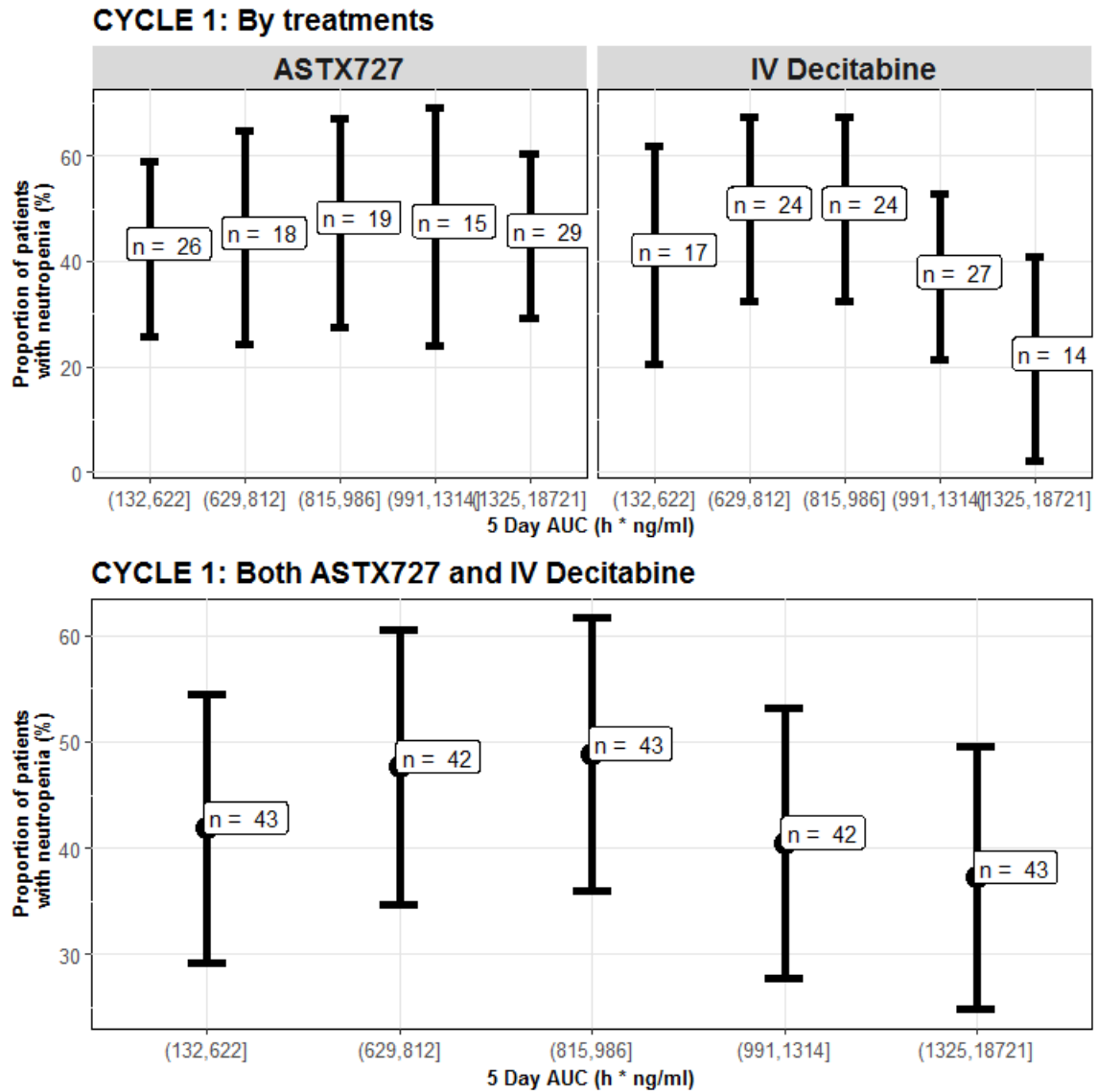


Figure 33. Proportions of patients with any grade neutropenias in treatment-cycle 1 for different quantiles of decitabine 5-days-AUC.

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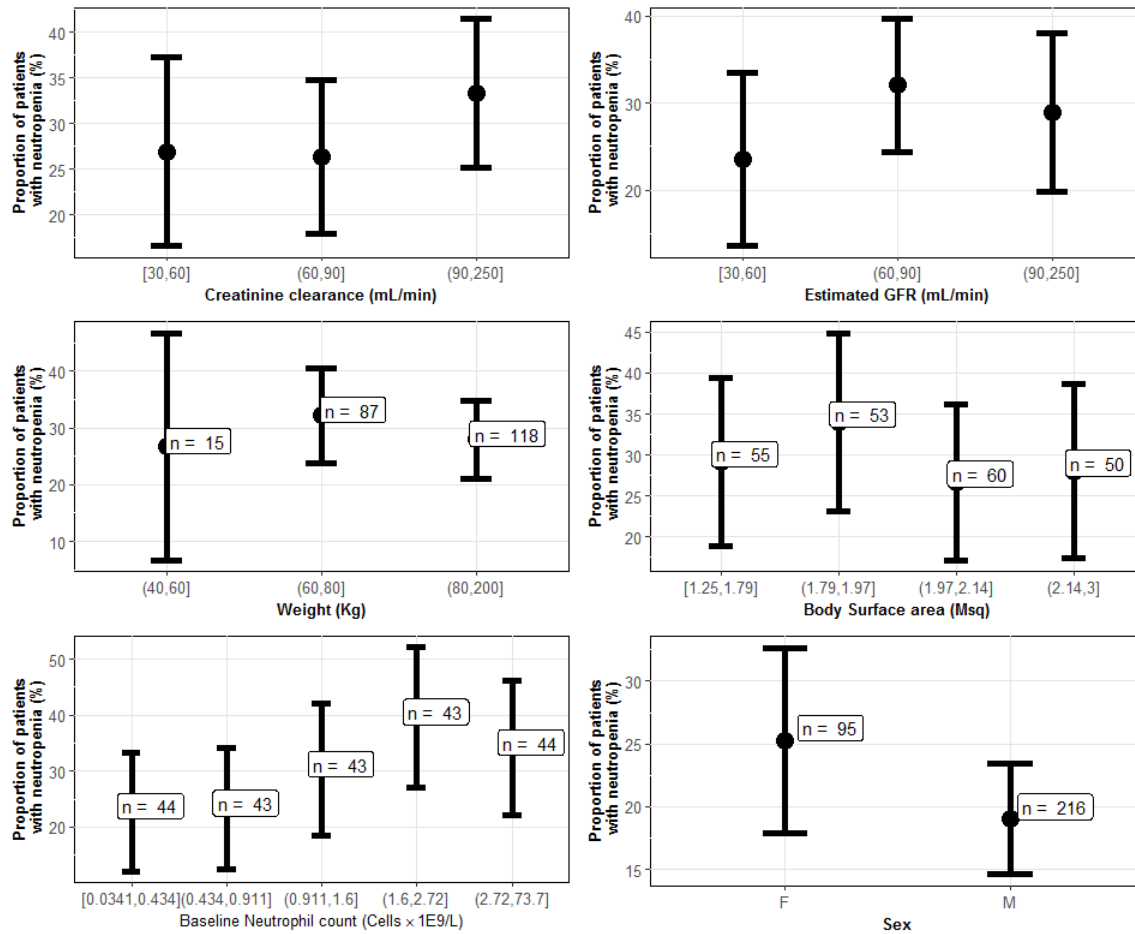


Figure 34. Proportions of patients with any grade neutropenias in treatment-cycle 2 for different categories of patient characteristics.

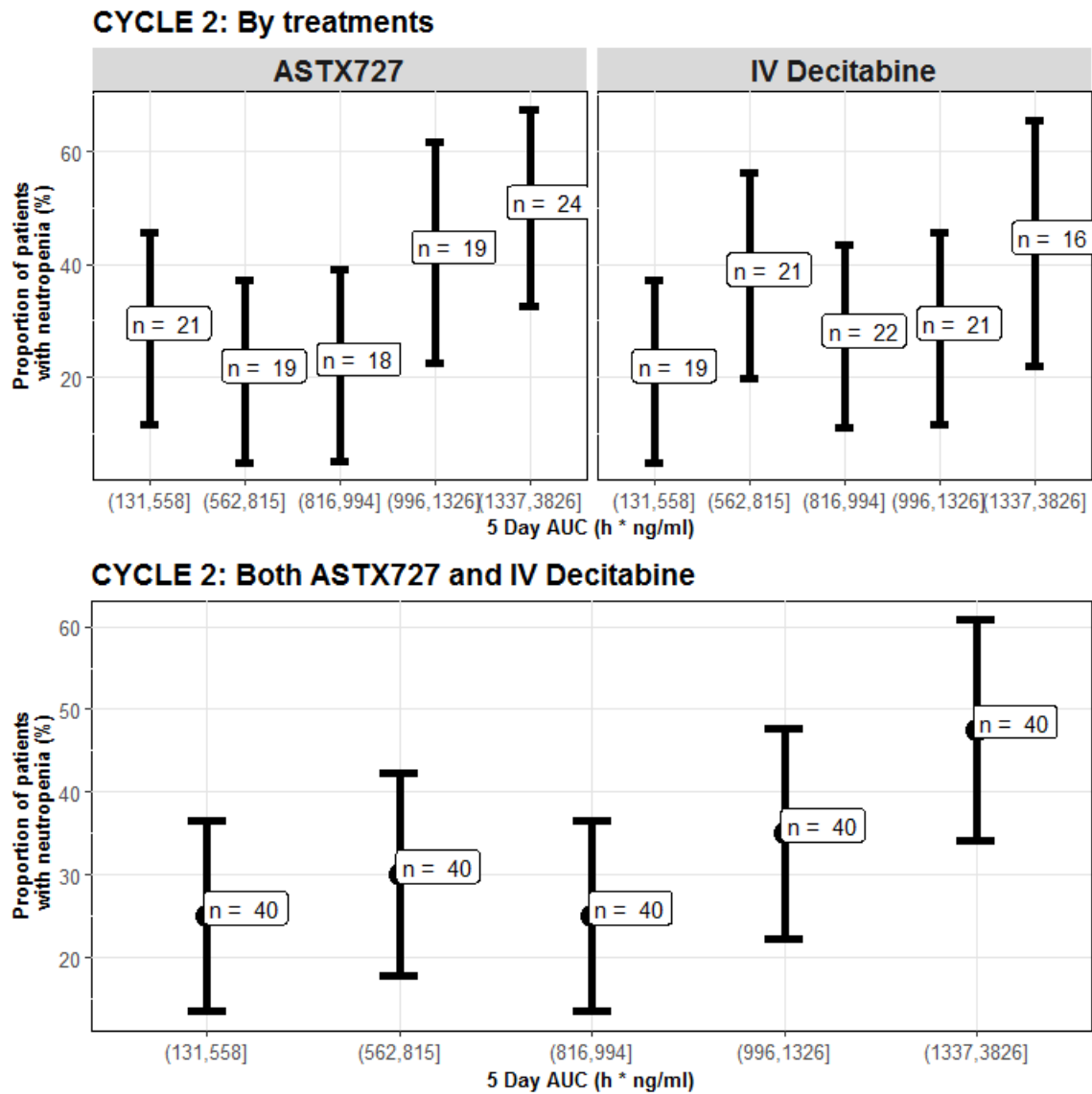


Figure 35. Proportions of patients with any grade neutropenias in treatment-cycle 2 for different quantiles of decitabine 5-days-AUC

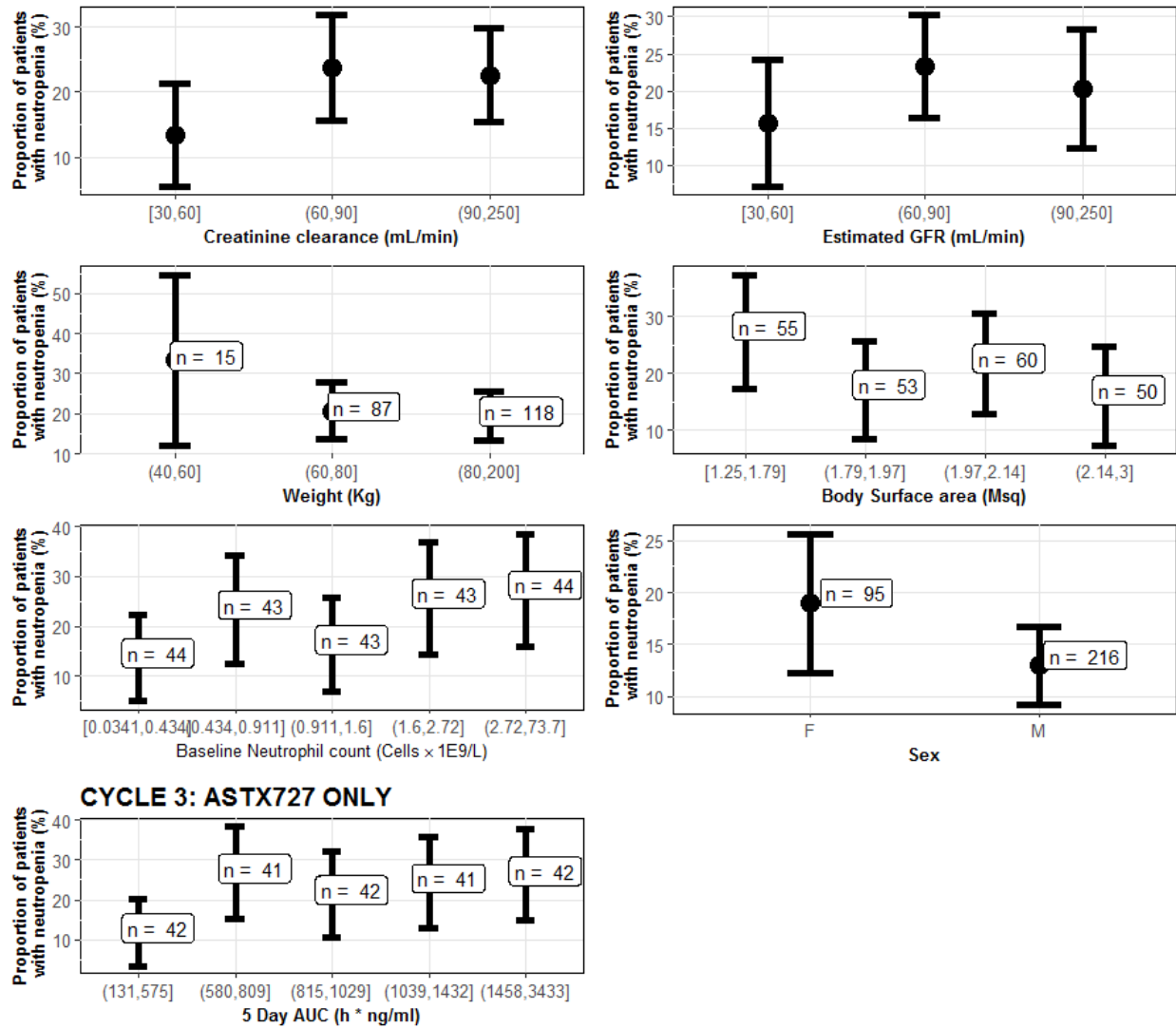


Figure 36. Proportions of patients with any grade neutropenias in treatment-cycle 3 for different categories of patient characteristics.

CYCLE 3: ASTX727 ONLY

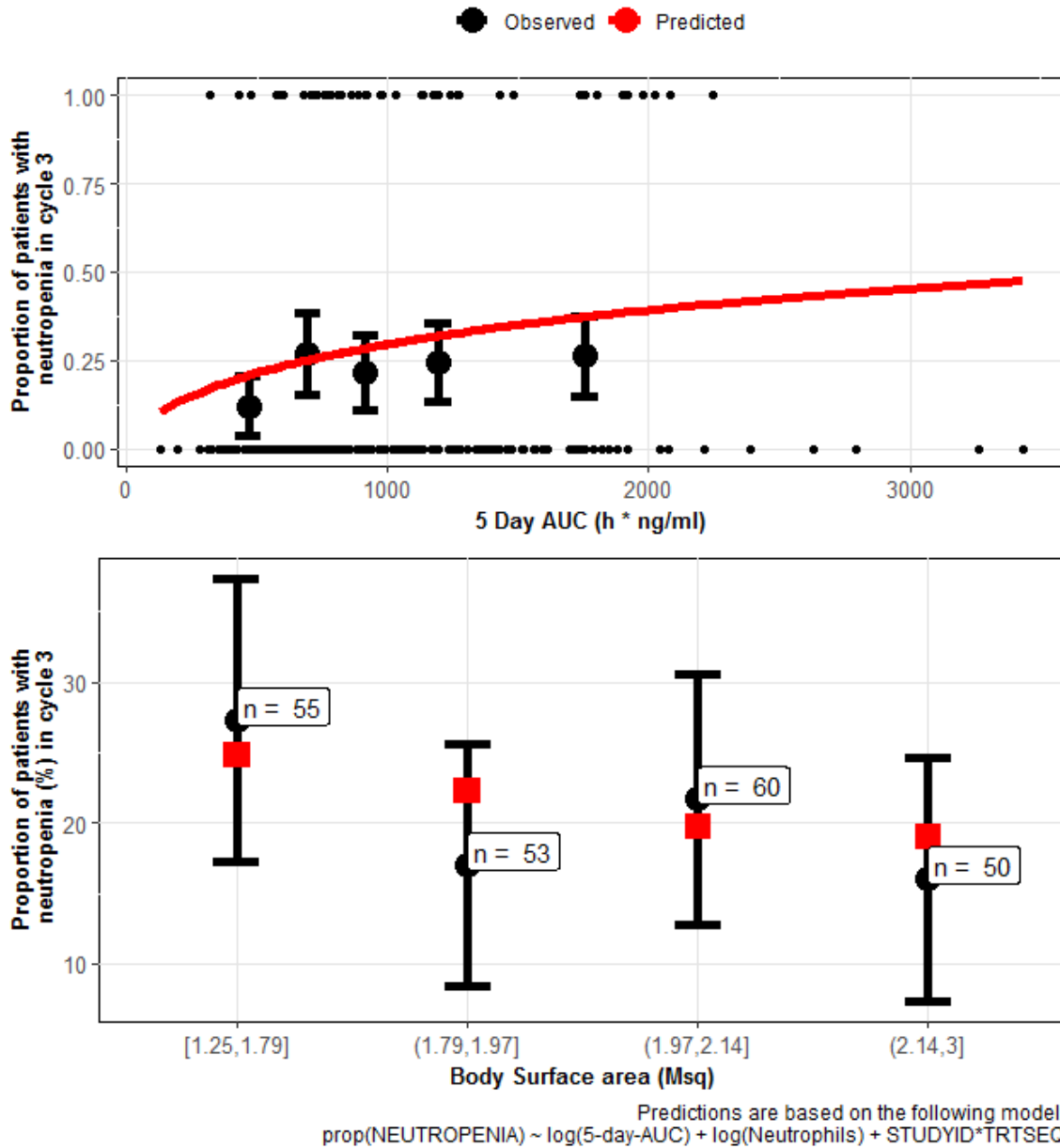


Figure 37. VPC showing agreement between model predicted and observed proportion of neutropenias in treatment-cycle 3.

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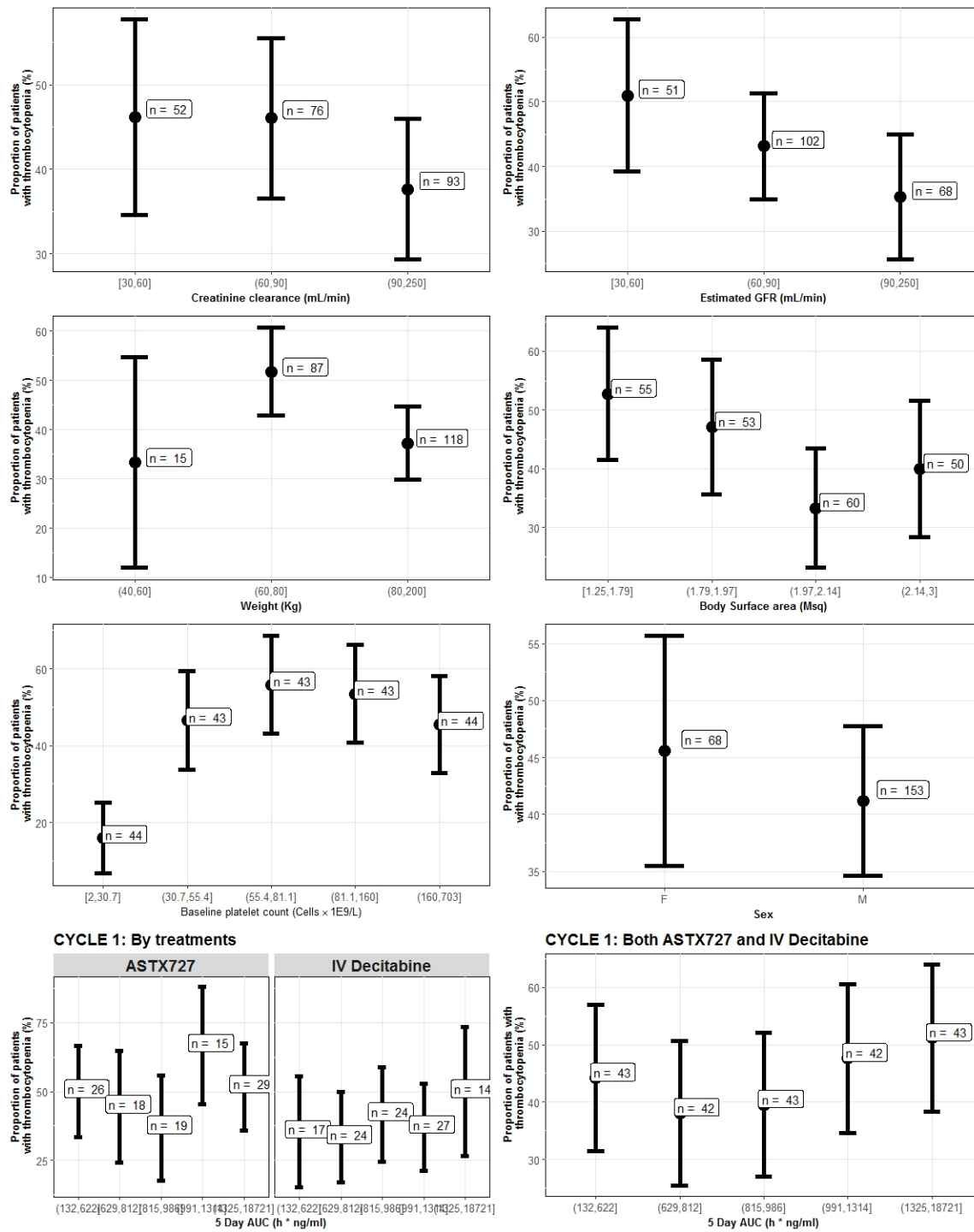


Figure 38. Proportions of patients with any grade thrombocytopenias in treatment-cycle 1 for different categories of patient characteristics

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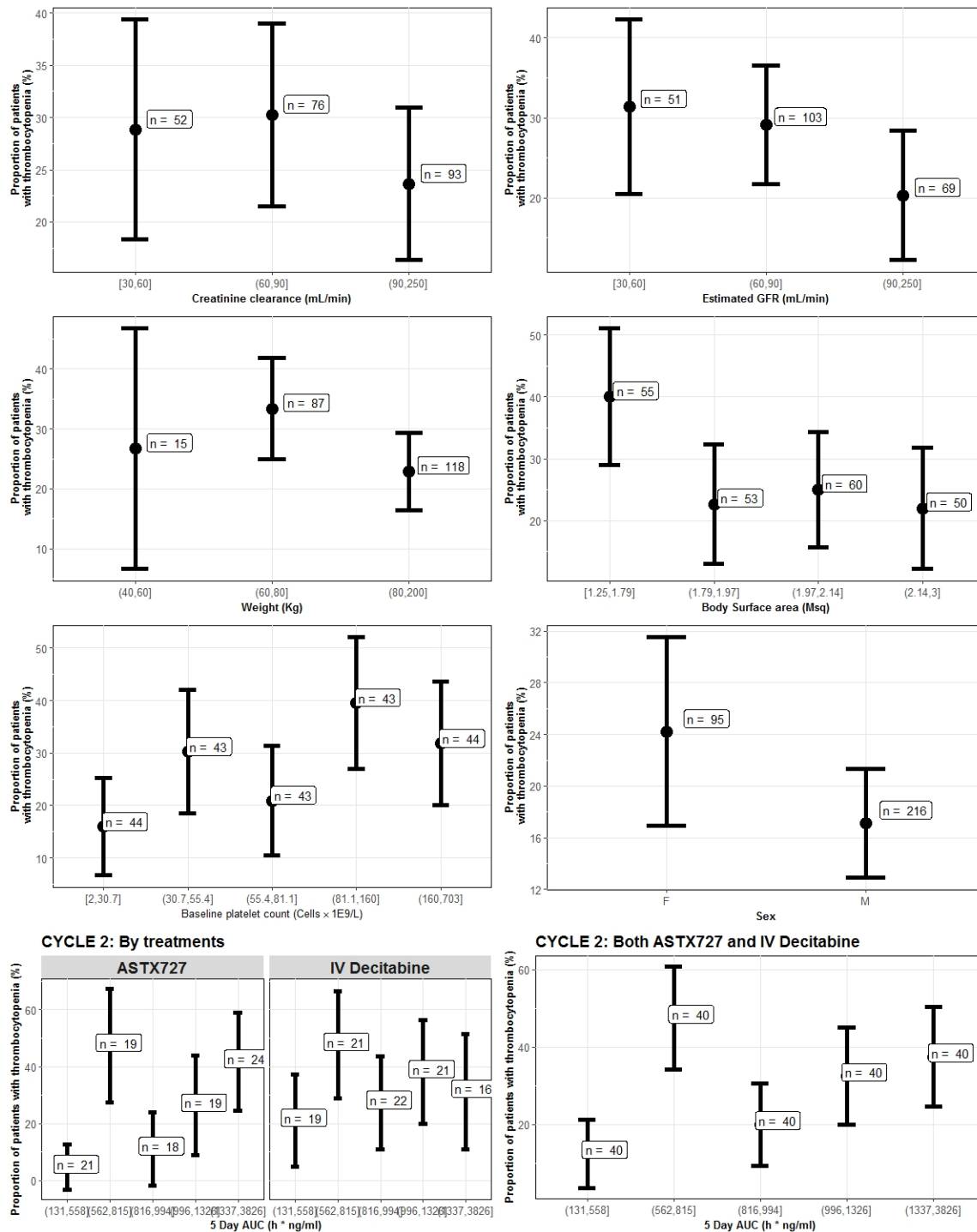


Figure 39. Proportions of patients with any grade thrombocytopenias in treatment-cycle 2 for different categories of patient characteristics

19.5. Additional Safety Analyses Conducted by Regulatory Authority

The Regulatory Authorities' Assessment:

Grouped preferred terms are displayed in the Table below.

Grouped Term	Preferred Terms
abdominal pain	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort, gastrointestinal pain
abscess	abscess oral, anal abscess, colonic abscess, furuncle, liver abscess, perirectal abscess, subcutaneous abscess, tooth abscess
altered mental status	confusional state, delirium, disturbance in attention, memory impairment, somnolence
anemia	Anaemia, haemoglobin decreased
arrhythmia	atrial fibrillation, atrial flutter, bradycardia, conduction disorder, sinus bradycardia, sinus tachycardia, tachycardia
arthralgia	arthralgia, back pain, bursitis, joint injury, joint range of motion decreased, joint stiffness, joint swelling, ligament sprain, neck pain, pain in jaw
cardiac failure	brain natriuretic peptide increased, cardiac failure, cardiac failure congestive, cardiomyopathy, ejection fraction decreased
cellulitis	catheter site cellulitis, cellulitis, infected bite
chest pain	angina pectoris, chest discomfort, chest pain
constipation	constipation, faeces hard
cough	cough, productive cough
cytopenia	bone marrow failure, pancytopenia
diarrhea	diarrhea, faeces soft
dizziness	dizziness, dizziness postural, vertigo, vertigo positional
dysgeusia	ageusia, dysgeusia, taste disorder
dyspepsia	dyspepsia, gastrooesophageal reflux disease, reflux laryngitis
dyspnea	chronic obstructive pulmonary disease, dyspnoea, dyspnoea exertional, hypoxia, tachypnoea, wheezing
edema	eye swelling, eyelid oedema, face oedema, fluid overload, fluid retention, generalized oedema, localized oedema, oedema, oedema peripheral, periorbital swelling, peripheral swelling, scrotal oedema, scrotal swelling, swelling, swelling face
eye disorders	cataract, choroidal neovascularization, eye discharge, eye disorder, eye irritation, eye pain, lacrimation increased, neovascularization age-related macular degeneration, ocular hyperaemia, retinal detachment, vitreous floaters
fatigue	asthenia, fatigue, lethargy
fracture	cervical vertebral fracture, facial bones fracture, hip fracture, lumbar vertebral fracture, rib fracture, spinal compression fracture, spinal fracture, upper limb fracture, wrist fracture

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Grouped Term	Preferred Terms
fungal infection	abscess fungal, Aspergillus infection, bronchopulmonary aspergillosis, candida infection, fungal infection, fungal oesophagitis, fungal skin infection, hepatosplenic candidiasis, oesophageal candidiasis, oral candidiasis, pulmonary mycosis, sinusitis fungal, skin candida, tinea cruris, tinea versicolour, vulvovaginal mycotic infection
gastrointestinal hemorrhage	gastric haemorrhage, gastrointestinal haemorrhage, haematochezia, haemorrhoidal haemorrhage, lower gastrointestinal haemorrhage, melaena, rectal haemorrhage, upper gastrointestinal haemorrhage
headache	headache, migraine, sinus headache, sinus pain
hemorrhage intracranial	cerebral haemorrhage, subdural haematoma, subdural haemorrhage
herpesvirus infection	herpes simplex, herpes zoster, oral herpes
hyperbilirubinemia	blood bilirubin abnormal, blood bilirubin increased, hyperbilirubinaemia, jaundice, ocular icterus
hypercapnia	carbon dioxide increased, hypercapnia
hypersensitivity	drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis
hypotension	blood pressure decreased, cardiogenic shock, hypotension
infectious diarrhea	clostridium difficile colitis, clostridium difficile infection, gastroenteritis, gastroenteritis Escherichia coli, gastroenteritis viral
mucositis	aphthous ulcer, colitis, duodenitis, enteritis, gingival discomfort, gingival pain, gingival swelling, gingivitis, glossodynia, lip disorder, lip ulceration, mouth swelling, mouth ulceration, mucosal ulceration, nasal ulcer, noninfective gingivitis, oesophagitis, oral disorder, oral mucosal blistering, oral mucosal erythema, oral pain, oropharyngeal pain, pharyngeal erythema, pharyngeal ulceration, pharyngitis, proctalgia, proctitis, stomatitis, tongue ulceration, vulvitis
myalgia	flank pain, iliotibial band syndrome, muscle spasms, muscle strain, muscle tightness, muscular weakness, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, non-cardiac chest pain, pain, pain in extremity
myocardial ischemia	acute coronary syndrome, acute myocardial infarction, myocardial infarction, troponin I increased, troponin increased, troponin T increased
neuropathy	ataxia, balance disorder, brachial plexopathy, carpal tunnel syndrome, gait disturbance, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, radicular pain
pneumonia	atypical pneumonia, lung infection, pneumonia, pneumonitis
pruritus	pruritus, pruritus allergic, pruritus generalized
rash	dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis contact, eczema, eczema nummular, erythema, erythema multiforme, folliculitis, genital erythema, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, seborrheic dermatitis, seborrheic keratosis, skin exfoliation, skin irritation, skin lesion, skin ulcer, stasis dermatitis, ulcerative keratitis

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Grouped Term	Preferred Terms
renal impairment	acute kidney injury, azotaemia, blood creatine increased, blood creatinine increased, blood urea increased, renal failure
respiratory failure	acute respiratory distress syndrome, respiratory failure
seizure	epilepsy, seizure, seizure like phenomena
sepsis	bacteremia, endocarditis, Escherichia bacteraemia, Pseudomonal bacteraemia, sepsis, septic shock, Staphylococcal bacteraemia
thrombosis	deep vein thrombosis, device related thrombosis, embolism, embolism arterial, pulmonary embolism
transaminase increased	alanine aminotransferase increased, ascites, aspartate aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, liver function test increased, transaminases increased
upper respiratory tract infection	nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection
visual impairment	diplopia, dyschromatopsia, vision blurred, visual field defect, visual impairment

19.6. Additional Safety Data

Table 84. ASTX727-02 Phase 2: Serious Adverse Events in Cycle 1 and Cycle 2 by SOC of Interest (Safety Analysis Set)

Preferred Term ^a	Number (%) of Subjects			
	Cycle 1		Cycle 2	
	ASTX727 (N=39)	IV Decitabine (N=41)	IV Decitabine (N=36)	ASTX727 (N=37)
Number of subjects reporting at least 1 SAE	14 (35.9)	15 (36.6)	7 (19.4)	13 (35.1)
Acute febrile neutrophilic dermatosis	0	0	0	1 (2.7)
Anal abscess	0	0	1 (2.8)	0
Anal fissure	1 (2.6)	0	0	0
Arthralgia	0	1 (2.4)	0	0
Atypical pneumonia	1 (2.6)	0	0	0
Bacteraemia	0	0	0	2 (5.4)
Cellulitis	0	1 (2.4)	0	1 (2.7)
Dehydration	1 (2.6)	0	0	0
Dyspnoea	1 (2.6)	0	0	1 (2.7)
Failure to thrive	0	1 (2.4)	0	1 (2.7)
Febrile neutropenia	8 (20.5)	3 (7.3)	1 (2.8)	5 (13.5)
Gastrointestinal haemorrhage	0	1 (2.4)	1 (2.8)	0
Gout	0	1 (2.4)	0	0
Hypertension	1 (2.6)	0	0	0
Influenza	0	0	0	1 (2.7)
Joint stiffness	0	1 (2.4)	0	0
Large intestinal obstruction	0	0	1 (2.8)	0
Musculoskeletal stiffness	0	1 (2.4)	0	0
Neck pain	0	1 (2.4)	0	0
Pharyngitis	0	0	0	1 (2.7)
Pneumonia	2 (5.1)	3 (7.3)	3 (8.3)	2 (5.4)
Pyomyositis	1 (2.6)	0	0	0
Respiratory failure	0	2 (4.9)	0	0
Sepsis	1 (2.6)	3 (7.3)	1 (2.8)	1 (2.7)
Septic shock	0	1 (2.4)	0	0
Soft tissue infection	1 (2.6)	0	0	0
Subdural haematoma	1 (2.6)	0	0	0
Subdural haemorrhage	1 (2.6)	0	0	0
Syncope	0	1 (2.4)	0	0
Urinary tract infection	1 (2.6)	0	0	1 (2.7)

Source: Supplemental table

Table 85. ASTX727-02 Phase 3: Serious Adverse Events in Cycle 1 and Cycle 2 by SOC of Interest (Safety Analysis Set)

MedDRA System Organ Class and Preferred Term ^a	Number (%) of Subjects			
	Cycle 1		Cycle 2	
	ASTX727 (N=66)	IV Decitabine (N=67)	IV Decitabine (N=65)	ASTX727 (N=64)
Total Number of AEs	21	17	21	30
Number of subjects reporting at least 1 AE	17 (25.8)	11 (16.4)	13 (20.0)	23 (35.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	7 (10.6)	5 (7.5)	5 (7.7)	11 (17.2)
Febrile neutropenia	6 (9.1)	4 (6.0)	3 (4.6)	10 (15.6)
Anaemia	1 (1.5)	0	0	0
Thrombocytopenia	0	0	1 (1.5)	1 (1.6)
Neutropenia	0	0	1 (1.5)	0
Pancytopenia	0	1 (1.5)	0	0
GASTROINTESTINAL DISORDERS	0	0	1 (1.5)	1 (1.6)
Small intestinal obstruction	0	0	0	1 (1.6)
Nausea	0	0	1 (1.5)	0
INFECTIONS AND INFESTATIONS	7 (10.6)	2 (3.0)	5 (7.7)	10 (15.6)
Pneumonia	3 (4.5)	2 (3.0)	3 (4.6)	4 (6.3)
Sepsis	2 (3.0)	0	0	2 (3.1)
Cellulitis	1 (1.5)	1 (1.5)	1 (1.5)	1 (1.6)
Device related infection	0	0	0	1 (1.6)
Diverticulitis	0	0	0	1 (1.6)
Enterobacter infection	0	0	0	1 (1.6)
Gastroenteritis Escherichia coli	0	0	0	1 (1.6)
Pharyngitis	1 (1.5)	0	0	0
Septic shock	0	1 (1.5)	0	1 (1.6)
Infection	0	0	1 (1.5)	0

Denominators are numbers of subjects who received at least one dose of study treatment. Subjects are counted once for each AE SOC and PT.

^a PTs are coded using MedDRA v22.0.

Source: ASTX727-02 CSR, Table 14.4.1.23

Table 86. Subjects with Treatment-Emergent AEs of Sepsis or Septic Shock (Phase 2 and 3)

Subject/ Demog	Preferred Term/ Reported Term	Onset (Cycle/Day)	Most Recent Treatment	Related?	SAE?	Other Clinically Relevant Information ^a
Cycle 1						
(b) (6) 75/M/W	Sepsis/ Septic febrile neutropenia	C1D11	ASTX727	Related to ASTX727	Yes	In the context of active disease at baseline (Grade 3 neutropenia present at baseline) and worsening to Grade 4 neutropenia from C1D8.
(b) (6) 76/F/W	Sepsis/ Sepsis	C1D15	ASTX727	No	Yes	In the context of active disease at baseline (Grade 4 neutropenia present at baseline).
(b) (6) 69/M/W	Sepsis/ Sepsis	C1D16	ASTX727	No	Yes	Grade 0 neutropenia at baseline, Grade 3 neutropenia from C1D8, Grade 4 neutropenia from C1D22. AE of leukopenia C1D16.
(b) (6) 67/F/A	Sepsis/ Sepsis	C1D21	ASTX727	Related to ASTX727	Yes	Grade 0 neutropenia at baseline, Grade 3 neutropenia from C1D8, and Grade 4 from C1D15. AE of febrile neutropenia C1D21.
(b) (6) 50/M/W	Sepsis/ Sepsis	C1D22	ASTX727	No	Yes	Grade 0 neutropenia at baseline, Grade 2 from C1D15 and Grade 4 from C1D22.
(b) (6) 70/M/W	Sepsis/ <i>P.</i> <i>aeruginosa</i> sepsis	C1D23	IV decitabine	No	Yes	Grade 0 neutropenia from baseline, Grade 4 from C1D15.
(b) (6) 68/M/W	Septic shock/ Septic shock	C1D28	IV decitabine	Related to IV decitabine	Yes Fatal	Grade 2 neutropenia at baseline, Grade 4 from C1D15. Febrile neutropenia C1D27. AE of pneumonia C1D27.
(b) (6) 72/F/W	Septic shock/ Septic shock	C1D30	ASTX727	No	Yes Fatal	In the context of active disease at baseline (Grade 3 neutropenia present at baseline) and worsening to Grade 4 from C1D4. AE of pneumonia C1D30.
Cycle 2						
(b) (6) 61/M/W ^b	Sepsis/ Gram negative rod sepsis	C2D3	IV decitabine	No	Yes	In the context of active disease at baseline (Grade 4 neutropenia from baseline). AE of febrile neutropenia C2D3.
(b) (6) 88/M/W	Sepsis/ Sepsis	C2D14	ASTX727	No	No	Grade 0 neutropenia at baseline, Grade 2 neutropenia from C2D8, Grade 4 from C2D15.
(b) (6) 77/M/W	Sepsis/ Sepsis	C2D23	ASTX727	Related to ASTX727	Yes	Grade 0 neutropenia at baseline, Grade 3 or 4 neutropenia from C1D15. AE of febrile neutropenia C2D23.
(b) (6) 67/M/W	Septic shock/ Septic shock	C2D28	ASTX727	Related to IV decitabine	Yes Fatal	Grade 0 neutropenia at baseline, Grade 4 neutropenia from C2D3.

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Subject/ Demog	Preferred Term/ Reported Term	Onset (Cycle/Day)	Most Recent Treatment	Related?	SAE?	Other Clinically Relevant Information ^a
(b) (6) 73/F/W	Sepsis/ Neutropenic sepsis	C2D32	ASTX727	No	Yes	Grade 0 neutropenia at baseline, Grade 4 neutropenia from C1D15. AE of diverticulitis C2D29.
(b) (6) 72/F/W	Sepsis/ Pneumosepsis	C2D33	ASTX727	No	Yes Fatal	In the context of active disease at baseline (Grade 3 neutropenia present at baseline) and worsening to Grade 4 from C2D8.
Cycles ≥3						
(b) (6) 75/F/W	Sepsis/ Sepsis	C3D18	ASTX727	No	Yes Fatal	Grade 2 neutropenia from baseline, Grade 3 or 4 neutropenia from C1D8. AE of pneumonia C3D18.
(b) (6) 65/M/W	Sepsis/ Sepsis, <i>Candida albicans</i>	C3D20	ASTX727	No	Yes	Grade 0 neutropenia at baseline, Grade 4 neutropenia from C3D17. AE of drug hypersensitivity C3D15. AE of myocarditis C3D15 (fatal).
(b) (6) 79/M/W	Sepsis/ Sepsis	C4D1	ASTX727	No	Yes	In the context of active disease at baseline (Grade 3 neutropenia present at baseline) and worsening to Grade 4 neutropenia from C1D8. AE of febrile neutropenia C4D1.
(b) (6) 61/M/W ^b	Septic shock/ Septic shock	C4D20	ASTX727	No	Yes Fatal	In the context of active disease at baseline (Grade 4 neutropenia from baseline). AE of febrile neutropenia C2D3.
(b) (6) 77/F/W	Sepsis/ Urosepsis	C4D21	ASTX727	No	Yes	In the context of active disease at baseline (Grade 3 neutropenia present at baseline) and worsening to consistent Grade 4 neutropenia from C2D8. AE of pneumonia C4D50.
(b) (6) 53/F/W	Sepsis/ Sepsis	C5D15	ASTX727	No	Yes	Grade 0 neutropenia at baseline, Grade 2 to 4 neutropenia from C1D8, with Grade 4 neutropenia from C5D1.
(b) (6) 70/M/W	Sepsis/ Sepsis	C5D23	ASTX727	No	Yes Fatal	Grade 1 neutropenia at baseline, continuous Grade 4 neutropenia from C2D8.
(b) (6) 78/F/W	Sepsis/ Sepsis (related to pancytopenia)	C6D20	ASTX727	Related to ASTX727	Yes Fatal	Grade 0 neutropenia at baseline, Grade 2 to 4 neutropenia from C2D8, Grade 4 from C6D1. AE of colitis C6D16.
(b) (6) 76/M/W	Sepsis/ Sepsis	C6D28	ASTX727	Related to ASTX727	Yes	In the context of active disease at baseline (Grade 4 neutropenia present from baseline). AE of febrile neutropenia C6D28.

^a Hematological information based on laboratory parameters unless specified as an AE.

^b Subject (b) (6) had 2 events of sepsis (the first at C2D3, the second at C4D20).

Source: ISS Listing 6.2.1, Listing 6.3.1; ASTX727-01-B CSR Listing 16.2.4.1, 16.2.7.1, 16.2.8.1; ASTX727-02 CSR Listing 16.2.7.1, 16.2.8.1

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INQOVI (decitabine and cedazuridine)

Cheson, B. D., J. M. Bennett, H. Kantarjian, A. Pinto, C. A. Schiffer, S. D. Nimer, B. Lowenberg, M. Beran, T. M. de Witte, R. M. Stone, M. Mittelman, G. F. Sanz, P. W. Wijermans, S. Gore, P. L. Greenberg and g. World Health Organization international working (2000). "Report of an international working group to standardize response criteria for myelodysplastic syndromes." Blood **96**(12): 3671-3674.

NCCN. (2020). "NCCN Guidelines - Myelodysplastic Syndromes Version 2.2020." from https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf.

NDA 212576 INQOVI (decitabine and cedazuridine)
Multidisciplinary Review Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/APPROVED
Nonclinical Reviewer	Michael Manning, PhD	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☐ Approved
	Signature: Michael L. Manning -S			Digitally signed by Michael L. Manning -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001207192, cn=Michael L. Manning -S Date: 2020.06.19 13:36:21 -04'00'
Acting Nonclinical Team Leader	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Brenda Gehrke -S			Digitally signed by Brenda Gehrke -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brenda Gehrke -S, 0.9.2342.19200300.100.1.1=0012062023 Date: 2020.06.19 13:41:04 -04'00'
Deputy Division Director (DHOT)	Haleh Saber, PhD, MS	OOD/DHOT	Sections: 5, 14	Select one: ☒ Authored ☒ Approved
	Signature: Haleh Saber -S			Digitally signed by Haleh Saber -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Haleh Saber -S, 0.9.2342.19200300.100.1.1=1300212858 Date: 2020.06.19 13:55:18 -04'00'
Clinical Pharmacology Reviewer	Sriram Subramaniam, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
	Signature: Sriram Subramaniam -S			Digitally signed by Sriram Subramaniam -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300115066, cn=Sriram Subramaniam -S Date: 2020.06.25 15:19:28 -04'00'
Clinical Pharmacology Team Leader	Olanrewaju Okusanya, PharmD, MS	OCP/DCPI	Sections: 6, 19.4	Select one: ☒ Authored ☒ Approved
	Signature: Olanrewaju Okusanya -S			Digitally signed by Olanrewaju Okusanya -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001410838, cn=Olanrewaju Okusanya -S Date: 2020.06.25 14:22:23 -04'00'
Pharmacometrics Reviewer	Eliford Kitabi, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
	Signature: Eliford N. Kitabi -S			Digitally signed by Eliford N. Kitabi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002641767, cn=Eliford N. Kitabi -S Date: 2020.06.25 18:53:53 -04'00'
Pharmacometrics Team Leader	Justin Earp, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
	Signature: Justin C. Earp -S			Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2020.06.25 15:48:18 -04'00'

NDA 212576 INQOVI (decitabine and cedazuridine)
Multidisciplinary Review Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/APPROVED
Division Director (OCP)	Brian Booth, PhD	OCP/DCPI	Sections: 6, 15, 19.4	Select one: ☐ Authored ☒ Approved
				Signature: Brian P. Booth -S Digitally signed by Brian P. Booth -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brian P. Booth -S, 0.9.2342.19200300.100.1.1=1300137436 Date: 2020.06.25 15:29:45 -04'00'
Clinical Reviewer	Kelly Norsworthy, MD	OOD/DHMI	Section : 1, 2, 4, 7, 8, 9, 10, 11, 12, 13, 19	Select one: ☒ Authored ☐ Approved
				Signature: Kelly Norsworthy -S Digitally signed by Kelly Norsworthy -S DN: c=US, o=U.S. Government, ou=HHS, ou=CDA, ou=People, ou=FDA, ou=People, cn=Kelly Norsworthy -S, 0.9.2342.19200300.100.1.1=001151302 Date: 2020.06.24 14:19:12 -04'00'
Statistical Reviewer	Haiyan Chen, PhD	OB/DBIX	Sections: 8	Select one: ☒ Authored ☐ Approved
				Signature: Haiyan Chen -S Digitally signed by Haiyan Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Haiyan Chen -S, 0.9.2342.19200300.100.1.1=2002254462 Date: 2020.06.21 09:08:45 -04'00'
Acting Statistical Team Leader	Jonathon Vallejo, PhD	OB/DBIX	Sections: 8	Select one: ☒ Authored ☒ Approved
				Signature: Jonathon J. Vallejo -S Digitally signed by Jonathon J. Vallejo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002146299 cn=Jonathon J. Vallejo -S Date: 2020.06.19 15:00:28 -04'00'
Division Director (OB)	Thomas Gwise, PhD	OB/DBIX	Sections: 8, 16	Select one: ☒ Authored ☒ Approved
				Signature: Thomas E. Gwise -S Digitally signed by Thomas E. Gwise -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300369224, cn=Thomas E. Gwise -S Date: 2020.06.23 16:11:27 -04'00'
Associate Director for Labeling	Stacy Shord, PharmD	OOD/DHMI	Sections: 11	Select one: ☒ Authored ☐ Approved
				Signature: Stacy Shord -S Digitally signed by Stacy Shord -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, ou=People, 0.9.2342.19200300.100.1.1=2000356537 cn=Stacy Shord -S, 0.9.2342.19200300.100.1.1=2000356537 Date: 2020.07.01 15:38:59 -04'00'
Cross-Disciplinary Team Leader (CDTL)	Lori Ehrlich, MD, PhD	OOD/DHMI	Sections: All	Select one: ☒ Authored ☒ Approved
				Signature: Lori Ehrlich -S Digitally signed by Lori Ehrlich -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lori Ehrlich -S, 0.9.2342.19200300.100.1.1=2001528093 Date: 2020.06.25 17:46:49 -04'00'

NDA 212576 INQOVI (decitabine and cedazuridine)
Multidisciplinary Review Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/APPROVED
Acting Division Director (Clinical)	R. Angelo de Claro, MD	OOD/DHMI	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: Romeo De Claro -S			Digitally signed by Romeo De Claro S DN: c US o U.S. Government ou HHS ou FDA ou People on Romeo De Claro S 0.9.2342.19200300.100.1.1.2000486745 Date: 2020.07.02 13:14:53 -04:00
Acting Office Deputy Director/signatory	Marc Theoret, MD	OOD	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: See DARRTS signature			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ESTHER H PARK
07/06/2020 09:42:14 AM

LORI A EHRLICH
07/06/2020 09:56:42 AM

ROMEO A DE CLARO
07/07/2020 07:14:22 AM

MARC R THEORET
07/07/2020 10:28:11 AM

My signature indicates that I have considered the assessments and FDA recommendations included in this Integrated Review in determining the regulatory action