Official Title:	A Phase 2 Study of Oral Decitabine/Cedazuridine in Combination With Magrolimab for Previously Untreated Subjects With Intermediate- to Very High-Risk Myelodysplastic Syndromes (MDS)
NCT Number:	NCT05835011
Document Dates:	Protocol and SAP Version 2.0: 19 December 2022

16.1.1 Protocol and Protocol Amendments

Protocol Amendment 1.0 (19 December 2022)

- Summary of Changes from Original

Clinical Study Protocol — ASTX727-10

A Phase 2 Study of Oral Decitabine/Cedazuridine in Combination With Magrolimab for Previously Untreated Subjects With Intermediate- to Very High-Risk Myelodysplastic Syndromes (MDS)

Protocol Number:	ASTX727-10
Amendment Number:	1.0
Compound:	Oral Decitabine/Cedazuridine + Magrolimab
Short Title:	A Study of Oral Decitabine/Cedazuridine in Combination With Magrolimab in Subjects With Intermediate- to Very High-Risk MDS
Study Phase:	Phase 2
Sponsor Name:	Astex Pharmaceuticals, Inc.
Legal Registered Address:	4420 Rosewood Drive, Suite 200 Pleasanton, CA 94588
Medical Monitor Name and Contact Information:	[redacted], MD PhD Office: [redacted]
IND Number:	116145
EU CTR Number:	2022-501548-14-00
Version (Date):	Original (28 September 2022) Amendment 1.0 (19 December 2022)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ABO	any of the 4 blood groups (A, B, AB, and O)
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
anti-HBc	antibody against hepatitis B core antigen
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BM	bone marrow
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CMML	chronic myelomonocytic leukemia
CNS	central nervous system
CR	complete response
CS&RM	Clinical Safety and Risk Management
CTCAE	Common Terminology Criteria for Adverse Events
DAT	direct antiglobulin test
DLT	dose-limiting toxicity
DOR	duration of response
DSRC	Data and Safety Review Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
Fc	fragment crystallizable
FDC	fixed-dose combination
GCP	Good Clinical Practice
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HBsAg	hepatitis B surface antigen
HI	hematologic improvement
HIV	human immunodeficiency virus
HMA	hypomethylating agent
HRT	hormonal replacement therapy
HSCT	hematopoietic stem cell transplant
IB	Investigator Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IEC	Independent Ethics Committee
IMP	investigational medicinal product (the specific Astex drug product under study)
IND	investigational new drug
INR	international normalized ratio
IPSS-M	Molecular International Prognostic Scoring System for myelodysplastic syndromes
IPSS-R	Revised International Prognostic Scoring System for myelodysplastic syndromes
IRB	Institutional Review Board
IV	intravenous
IWG	International Working Group
LDH	lactate dehydrogenase
LFS	leukemia-free survival
LTFU	Long-term follow-up
M	Magrolimab
mAb(s)	monoclonal antibody(ies)
mCR	marrow complete response
MDS	myelodysplastic syndromes
MPN	myeloproliferative neoplasm
MRD	minimal residual disease
MTD	maximum tolerated dose
NA	not applicable
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
No.	number
ORR	overall response rate
OS	overall survival
PB	peripheral blood
PE	physical examination
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	by mouth
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
RBC	red blood cell
Rh	rhesus factor
RO	receptor occupancy
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplant
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIRPα	signal regulatory protein alpha
SoA	schedule of activities
SOC	standard of care

Abbreviation	Definition
ULN	upper limit of normal
WBC	white blood cell
w/v	weight by volume

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Study Number and Title: ASTX727-10: A Phase 2 Study of Oral Decitabine/Cedazuridine in Combination With Magrolimab for Previously Untreated Subjects With Intermediate- to Very High-Risk Myelodysplastic Syndromes (MDS)

Short Title: A Study of Oral Decitabine/Cedazuridine in Combination With Magrolimab in Subjects With Intermediate- to Very High-Risk MDS

Clinical Phase: 2

Study Centers Planned/Country: Multicenter; countries in North America, Europe, and Asia Pacific

Rationale: The current study will aim to evaluate oral decitabine/cedazuridine in combination with magrolimab for previously untreated subjects with intermediate- to very high-risk MDS, as determined by the Revised International Prognostic Scoring System for myelodysplastic syndromes (IPSS-R).

Oral decitabine/cedazuridine is a hypomethylating agent (HMA) that is approved for use in subjects with intermediate- to high-risk MDS, as well as in subjects with chronic myelomonocytic leukemia (CMML), in the US, Canada, and Australia. Oral decitabine/cedazuridine was approved based on clinical studies that determined its pharmacokinetic (PK) area under the concentration-time curve (AUC) equivalence to intravenous (IV) decitabine administration. Results from Phase 2 and 3 studies have demonstrated a positive treatment effect of oral decitabine/cedazuridine and that the clinical efficacy of oral decitabine/cedazuridine is consistent with efficacy described for intravenously administered decitabine in subjects with MDS. At the therapeutic dose of 35 mg decitabine and 100 mg cedazuridine (administered concomitantly as separate capsules or as a fixed-dose combination [FDC] tablet), overall results from a Phase 2 study of oral decitabine/cedazuridine (ASTX727-01) showed complete response (CR) rate of 18%, with hematologic improvement (HI) in an additional 16.3% of subjects with MDS or CMML. Among the 41 subjects who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 20 subjects (49%) became independent of RBC and platelet transfusions during any consecutive 56-day post-baseline period. Of the 39 subjects who were independent of both RBC and platelet transfusions at baseline, 25 subjects (64%) remained transfusion independent during any consecutive 56-day post-baseline period.

Results from a Phase 3, multicenter, randomized, crossover study in subjects with MDS/CMML or acute myeloid leukemia (AML) (ASTX727-02) established AUC equivalence of the FDC tablet (35 mg decitabine and 100 mg cedazuridine) with IV administered decitabine (20 mg/m^2). Assessment of efficacy indicated that the best response of CR was observed in 21.8% of all treated subjects and in 24.8% of subjects evaluable for response. Marrow CR was achieved in 32.3% of all treated subjects and in 36.8% of subjects evaluable for response. The overall response rate

(ORR; complete response [CR] + partial response [PR] + marrow CR [mCR] + HI) was 61.7% in all treated subjects and 70.1% in subjects evaluable for response. In addition, mCR with HI was reported in 16.5% of all treated subjects and in 18.8% of subjects evaluable for response. Sixteen subjects (12%) were not evaluable for response. With respect to the rate of subjects who were transfusion independent for ≥56, ≥84, and ≥112 consecutive days at any time post-baseline for subjects who were transfusion dependent at baseline, more than half (51.9%) of the 54 subjects who were RBC transfusion dependent at baseline were RBC transfusion independent for any consecutive ≥56-day period post-baseline. A similar overall rate of platelet TI (50%) for any consecutive ≥56-day period post-baseline was observed for subjects with platelet transfusion dependence at baseline. Rates of RBC and platelet TI were 40.7% and 33.3%, respectively, for ≥84 consecutive days and leveled at 33.3% for ≥112 consecutive days. The overall incidence of common adverse events (AEs) of thrombocytopenia, neutropenia, anemia, and febrile neutropenia observed in Phase 2 and Phase 3 was generally similar between oral decitabine/cedazuridine and IV decitabine.

The anti CD47 monoclonal antibody (mAb) magrolimab has demonstrated encouraging data in the MDS population in combination with the HMA azacitidine (Vidaza®). Clinical studies have demonstrated that this combination has meaningful clinical activity that appears to be enhanced compared with azacitidine monotherapy in subjects with MDS. In a study investigating the clinical activity of magrolimab in combination with azacitidine in subjects with treatment-naïve intermediate- to higher-risk MDS (by IPSS-R), 24 subjects were evaluable for efficacy. The ORR was 92%, with 50% achieving a CR. Complete cytogenetic response was observed in 26% of subjects who had abnormal cytogenetics at baseline. Minimal residual disease negativity was achieved in 23% of subjects, as assessed by flow cytometry. With a median follow-up of 6.4 months, no median duration of response (DOR) had been reached, with several subjects in response over 14 months on therapy. In addition, putative CD34+CD48− leukemia stem cell progenitors were substantially reduced or eradicated by magrolimab in combination with azacitidine in responding subjects who were evaluated. Magrolimab in combination with azacitidine is currently being evaluated for survival and CR (co primary objectives) in a large, randomized Phase 3 study (ENHANCE, NCT04313881) comparing the efficacy and safety of magrolimab plus azacitidine with that of azacitidine + placebo (PBO) in previously untreated subjects with high-risk MDS. Despite its clinical benefit, treatment with azacitidine requires chronic parenteral treatment for 5 to 7 days each month for responding subjects; this number of clinic/hospital visits is a significant burden for what is primarily an elderly population. Furthermore, an online survey that assessed treatment challenges in subjects with MDS determined that IV/subcutaneous HMA administration resulted in pain and impacted daily activities, suggesting that an oral HMA might reduce treatment challenges for this population.

This study will assess the safety and efficacy of combining oral decitabine/cedazuridine (oral HMA) with magrolimab in subjects with intermediate- to very high-risk MDS. This combination with an oral HMA could provide an effective treatment option for this population while minimizing the burden of treatment for subjects and caregivers (ie, number of required clinic visits, transportation time, and complications of parenteral therapy).

Objectives	Endpoints
Primary	
• To evaluate preliminary safety and efficacy of oral decitabine/cedazuridine in combination with magrolimab.	• Adverse events graded according to NCI CTCAE, Version 5.0 (Section 10.5), DLTs, and CR rate.
Secondary	
• To evaluate the PK profile of oral decitabine/cedazuridine and magrolimab.	• Concentration versus time and PK parameters.
• To evaluate other clinical efficacy of oral decitabine/cedazuridine and magrolimab.	• ORR, rate of HI, duration of PFS, LFS, undetectable disease assessed by MRD, DOR, and OS.
• To evaluate efficacy and safety by prespecified subgroups (eg, IPSS-M, p53 status).	• Safety and efficacy based on molecular features (eg, IPSS-M score, p53 status).

CR=complete response; DLT=dose-limiting toxicity; DOR=duration of response; HI=hematologic improvement; IPSS-M=Molecular International Prognostic Scoring System for myelodysplastic syndromes; LFS=leukemia-free survival; MRD=minimal residual disease; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic(s)

Study Design and Investigational Plan: This is a Phase 2, open-label, multicenter, non-randomized interventional study to evaluate the safety, efficacy, and PK of oral decitabine/cedazuridine when given in combination with magrolimab for the treatment of previously untreated intermediate- to very high-risk MDS subjects. The goal of this study is to assess the safety and efficacy of combining oral decitabine/cedazuridine (oral HMA) with magrolimab in subjects with intermediate- to very high-risk MDS. This combination with an oral HMA may provide a safe and efficacious alternative to azacitidine in combination with magrolimab, while minimizing the burden of treatment for subjects and caregivers (ie, number of required clinic visits, transportation time, and complications of parenteral therapy).

Study Duration: Approximately 44 months. The study length may be adjusted based on enrollment rate as well as DOR.

Number of Subjects: Approximately 135 subjects will be screened to achieve approximately 100 evaluable subjects (ie, subjects who received one or more dose of study treatment).

Intervention Groups and Duration:

Participation will include screening, treatment, and follow-up.

- The following magrolimab dosing regimen is proposed for this study (Figure 1): The dose of magrolimab is increased over time in a series called priming doses. Priming doses of magrolimab: 1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11, 15, 22, 29, 36, 43, and 50.
- Maintenance doses of magrolimab will be 30 mg/kg on Day 57 and every 14 days thereafter.

  If magrolimab is not administered within 28 days or more and then restarted, the resulting doses, called repriming doses, follow the same schedule and dose level as the first 22 days of the priming doses, then maintenance dosing can start 7 days later. For subjects who have not received at least one 30 mg/kg dose of magrolimab (ie, for subjects who have either not received their first dose of 30 mg/kg or subjects who have received doses <30 mg/kg), a dose delay of only 14 days is allowed until repriming is required.

Oral decitabine/cedazuridine study treatment will be administered according to the following schedule (Figure 1):

- Oral decitabine/cedazuridine will be administered on Days 1-5 of a cycle. In this protocol, a cycle is defined as a cycle of oral decitabine/cedazuridine, which is normally 28 days.
- Days 1-5: oral decitabine/cedazuridine by mouth daily on an empty stomach (morning before breakfast) with no food for 2 hours before and 2 hours after administration. When taking oral decitabine/cedazuridine, subjects may have clear liquids such as water, black coffee, or tea. The dosing regimen for this study may be modified during the assessment of dose-limiting toxicities (DLTs) in the DLT cohort.

Note: DLTs are defined in Section 8.5.6.

Alternative options for oral decitabine/cedazuridine administration on Days 1-5 are outlined in Section 4.5.

Systematic dosing reductions of oral decitabine/cedazuridine may be necessary, as detailed in Section 4.1.1 and Section 6.6.1. Dose reductions of magrolimab may be considered in rare circumstances, as outlined in Section 6.6.2.

Treatment will continue until disease progression, death, or unacceptable treatment related toxicity, the subject withdraws or is withdrawn from the study, the treatment becomes commercially available, or the sponsor stops the study.

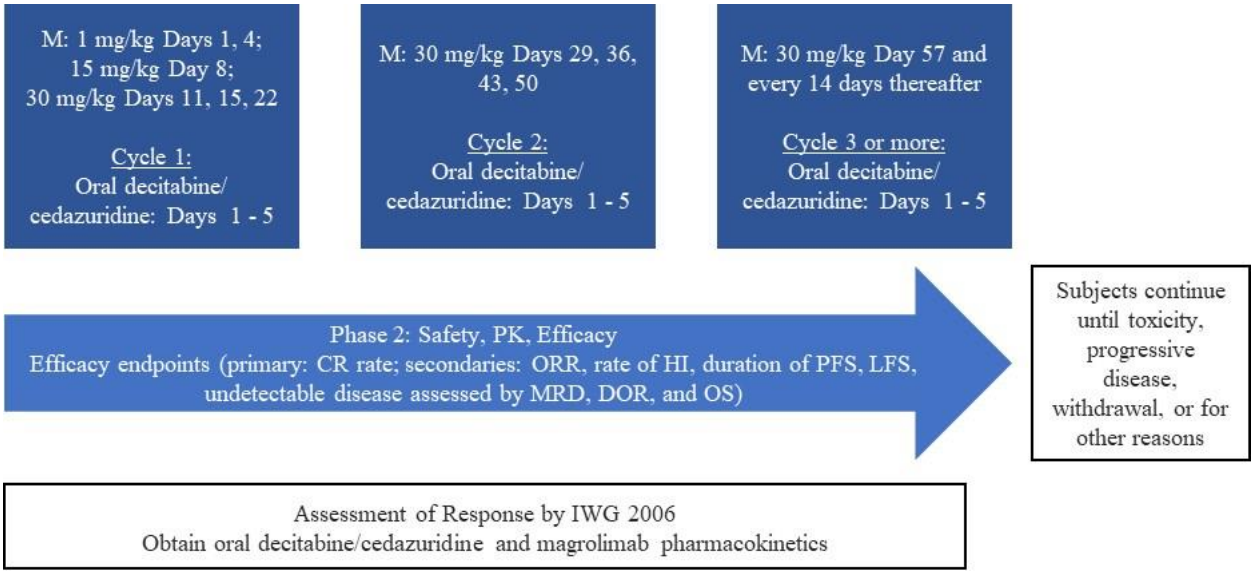
Data Safety Review Committee and Safety Monitoring Plan:

The Data and Safety Review Committee (DSRC) will comprise the principal investigators (or designees), and the Astex medical monitor, clinical pharmacologist, lead statistician, and other study team members as appropriate.

The DSRC will review emerging safety data after the first 6 subjects are enrolled. The first 6 to approximately 18 subjects enrolled will be evaluated for DLTs during the first 2 cycles; if present (following standard 3+3 design), there will be dosing reductions of oral decitabine/cedazuridine which will be applied to all subsequent subjects. In addition, the DSRC will continue to review safety data after approximately 20 subjects are enrolled and receive at least 2 cycles of treatment. Ad hoc meetings may occur throughout the study.

1.2 Schema

Figure 1: Schema



CR=complete response; DOR=duration of response; HI=hematologic improvement; IWG=International Working Group; LFS=leukemia-free survival; M=magrolimab; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic(s).

Note: Each cycle of oral decitabine/cedazuridine will normally be 28 days.

1.3 Schedules of Activities (SoA)

Table 1: Schedule of Activities for Oral Decitabine/Cedazuridine

Treatment Cycles (28 Days)		In-Clinic Visits													
		Cycle 1					Cycle 2				Cycle ≥3[b]				
Cycle Day (Window)	Screening[a]	1	4	5	8 (±1)	15 (±3)	1	4	8 (±1)	15 (±3)	1	15 (±3)	Tx Disc[c]	30-day Safety follow-up (±5)[d]	LTFU (±14)[e]
Study Treatment[f]															
Oral decitabine/cedazuridine dispensation		×					×				×				
Distribute dosing diary[g]		×					×				×				
Dosing compliance[g]							×				×				
Clinical and Safety Assessments/Procedures															
Informed consent	×														
Medical and surgical history	×														
Serum or urine pregnancy test[h]	×	×					×				×		×	×	
Investigator's confirmation of eligibility	×	×													
PE[i]	×	×											×		
Symptom-directed PE[j]							×				×			×	
Height	×														
Weight[k]	×	×					×				×		×		
Vital Signs[l]	×	×					×				×				
ECOG performance status	×	×					×				×		×	×	
12-lead ECG[m]	×	×					×				×				
Laboratory Assessments															
Collect blood for PK[n]		×	×	×				×							
Hematology (CBC)[o]		×	×	×	×	×	×		×	×	×	×	×		
Chemistries[p]	×	×				×	×			×	×	×	×		
Urinalysis	×	×											×		
Reporting concomitant medications/AEs[q]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
Reporting transfusions[r]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×

Treatment Cycles (28 Days)		In-Clinic Visits													
		Cycle 1					Cycle 2				Cycle ≥3[b]				
Cycle Day (Window)	Screening[a]	1	4	5	8 (±1)	15 (±3)	1	4	8 (±1)	15 (±3)	1	15 (±3)	Tx Disc[c]	30-day Safety follow-up (±5)[d]	LTFU (±14)[e]
Disease Assessments															
BM aspirate/biopsy/MRD[s]	×										×		×		
Survival follow-up															×

AE=adverse event; BM=bone marrow: CBC=complete blood count; CR=complete response; DOR=duration of response; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; LTFU=long-term follow-up; MDS=myelodysplastic syndromes; MRD=minimal residual disease; PB=peripheral blood; PE=physical examination; SCT=stem cell transplant; Tx Disc=treatment discontinuation.

Note: For any given laboratory assessment or clinical/safety assessments/procedures required on a given day for both oral decitabine/cedazuridine and magrolimab, one such activity suffices for both drugs.

[a] Screening: must occur within 21 days before first dose of study drug.

[b] In Cycle ≥3, pregnancy testing on Day 1 of each cycle (or within a 3-day window prior).

[c] Treatment Discontinuation: Treatment discontinuation refers to the discontinuation of both oral decitabine/cedazuridine and magrolimab. The treatment discontinuation visit should occur within 1 week after the last study treatment or within 3 days before starting a new treatment for MDS/leukemia. If a subject discontinues study treatment at a scheduled visit, the assessments at that visit can be used to fulfill the visit requirements. If the subject cannot attend the clinic, the visit may be conducted by telephone to collect, at minimum, AE information.

[d] 30-day Safety Follow-up Visit: Safety follow-up visit may occur at the same time as treatment discontinuation if the decision to permanently discontinue treatment is made at least 30 days after last dose of study treatment or within 3 days before starting a new anticancer therapy.

[e] Long-term Follow-up (LTFU) visits: Beginning 3 months after the 30-day Safety Follow-up visit (for subjects who permanently discontinued treatment), subjects will be followed in LTFU for health status information, which will be gathered every 3 months (±2 weeks) until death, the subject withdraws consent, the subject is lost to follow-up, or the study ends, whichever occurs first. Additionally, disease response assessments, including conversion to acute myeloid leukemia (transfusion, hematology, and/or BM aspirate/biopsy) are done only for subjects who discontinued treatment before documented disease progression, until peripheral blood or BM assessment shows disease progression or relapse, or the subject starts new anti-leukemia/MDS treatment. Visits may be conducted by telephone if appropriate. Women of childbearing potential will be reminded that they should not get pregnant for 250 days after discontinuation of study medication and will be asked if they are pregnant during the LTFU either in person or by telephone. Male subjects should be reminded to continue contraception for a minimum of 160 days after treatment discontinuation.

[f] Study treatment: When both study drugs are given on the same visit day, magrolimab will be administered at least 1 hour after oral decitabine/cedazuridine administration.

[g] Distribute dosing diary and dosing compliance: only for oral decitabine/cedazuridine.

[h] A highly sensitive serum pregnancy test (from whole blood) is required at screening; serum or urine testing may be used at subsequent time points, as required by local regulations.

[i] Physical examination (PE): Complete PE will be performed at screening, predose on Cycle 1 Day 1, and at treatment discontinuation.

[j] Symptom-directed PE is not required if it is performed within 3 days of Day 1. After Cycle 1 Day 1, symptom-directed PE will be done, unless otherwise indicated, at the investigator's discretion.

[k] Weight: Weight should be measured at screening, each visit in which oral decitabine/cedazuridine and/or magrolimab is administered, and at treatment discontinuation.

[l] Vital signs: On dosing days, all vital signs will be measured predose per the institutional standard practice. In addition to the vital signs measured predose on Cycle 1 Day 1, systolic and diastolic blood pressure and heart rate will also be obtained 2 hours (±30 minutes) postdose on Cycle 1 Day 1. Vital signs are resting systolic/diastolic blood pressure, resting respiration rate, resting heart rate, oxygen saturation, and body temperature.

[m] Twelve-lead ECG: Assessments on dosing days will be obtained predose. Postdose ECGs will also be obtained during PK assessment per Section 8.4.

[n] Collect blood for PK (oral decitabine/cedazuridine): Central laboratory assessment. Predose assessments will be obtained at Cycle 1 Day 4, Cycle 1 Day 5, and Cycle 2 Day 4. The blood collection on Cycle 1 Day 5 must be within 24 ± 1 hour after the blood collection on Cycle 1 Day 4. Postdose assessments will be obtained at Cycle 1 Day 1, Cycle 1 Day 4, Cycle 2 Day 4, and ad-hoc throughout the study (if needed). Further details are provided in Table 14.

[o] CBC: Local laboratory assessment. Day 1 CBC does not need to be drawn if drawn 1 day prior, Day 15 CBC does not need to be drawn if drawn within 3 days prior. If there is Grade ≥3 neutropenia or thrombocytopenia present, consider weekly CBCs.

[p] Chemistries: Perform only if not obtained within the previous 7 days.

[q] Reporting of concomitant medications starts from 14 days before treatment and ends 30 days after the last dose of study treatment. Reporting of AEs starts at the signing of the informed consent form and ends 30 days after the last dose of study treatment.

[r] Recording transfusions: Record all blood and platelet transfusions from 56 days before the start of study treatment through 30 days after the last dose of study treatment and in long-term follow up for subjects who discontinue treatment before documented disease progression until disease progression is documented.

[s] BM aspirate/biopsy: Screening BM will be accepted up to 6 weeks prior to first dose; however, cytogenetics is required. If a subject undergoes SCT, they will continue to be followed using BM aspirate/biopsy per SOC for SCT. Cytogenetic data will be collected from the BM aspirate/biopsy sample each time a BM aspirate/biopsy is performed. Postdosing BM is to be performed on Day 1 (or within a 3-day window prior to Day 1) of Cycles 3, 5, and 7, and every 3 cycles thereafter (or within a 7-day window), as well as at the end of treatment or at disease progression, whichever is earlier. If the investigator suspects that the development of Grade 4 neutropenia or thrombocytopenia is drug related and the event continues for 7 days in Cycle 1 or 2, a BM assessment (no later than the 10th day of Grade 4 cytopenia) may be done, at the discretion of the investigator, to assist with determination of DLT. If hematologic recovery is in progress, a repeat CBC may be done no more than 7 days after the BM evaluation for response assessment. BM evaluation may occur as clinically indicated to monitor DOR as appropriately guided by PB counts after achieving a confirmed CR but should occur at least every 3 cycles for the first year, then as clinically indicated at additional time points. MRD will be obtained per local standard of care.

Table 2: Schedule of Activities for Magrolimab

	In-Clinic Visits															
Day (Window)	**Screening**	**1**	**2**	**3**	**4 (±3)**	**5 (±3)**	**8 (±3)**	**11 (±3)**	**15 (±3)**	**22 (±3)**	**29 (±3)**	**36 (±3)**	**43 (±3)**	**50 (±3)**	**57 (±3)**	**Every 14 days thereafter (±3)**
Study Treatment[a]																
Magrolimab infusion[b]		×			×		×	×	×	×	×	×	×	×	×	×
Laboratory Assessments																
Blood type and screen (ABO, Rh) DAT, and extended RBC phenotyping or genotyping[c]	×															
Hematology (CBC)[c,d]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Coagulation[c]	×															
Chemistry[c]	×	×					×		×		×		×		×	×
Urinalysis[c]	×	×														
Collect blood for PK and ADA[e]		×												×	×	
Collect blood for molecular analysis[f]	×															
Clinical and Safety Assessments/Procedures																
Vital signs[g]	×	×			×		×	×	×	×	×	×	×	×	×	×
Weight[h]	×	×			×		×	×	×	×	×	×	×	×	×	×
Reporting concomitant medications/AEs[i]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Reporting transfusions[j]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Premedication[k]		×			×		×	×	×	×	×	×	×	×	×	×
Compete PE and Symptom-directed PE[l]	×															

ABO=any of the 4 blood groups (A, B, AB, and O); ADA=antidrug antibody; AE=adverse event; CBC=complete blood count; eCRF=electronic case report form; MDS=myelodysplastic syndromes; PK=pharmacokinetic(s); Rh=Rhesus factor; Tx Disc=treatment discontinuation.

Note: For any given laboratory assessment or clinical/safety assessments/procedures required on a given day for both oral decitabine/cedazuridine and magrolimab, one such activity suffices for both drugs.

[a] Study treatment: When both study drugs are given on the same visit day, magrolimab will be administered at least 1 hour after oral decitabine/cedazuridine administration. Subjects should be monitored (including measurement of vital signs, as clinically appropriate) for signs and symptoms of infusion-related reactions, which have been observed in previous magrolimab studies.

[b] Magrolimab infusion: If magrolimab is not administered for 28 days or more and restarted, the resulting doses, called repriming doses, follow the same schedule and dose level as the first 22 days of the priming doses, then maintenance dosing can start 7 days later. For subjects who have not received at least one 30 mg/kg dose of magrolimab, a dose delay of only 14 days is allowed until repriming is required. During the first 2 doses of priming and repriming, blood testing of hemoglobin will be required 3 to 6 hours after a magrolimab dose, and the results must be reviewed prior to discharging the subject from clinic. The duration of each magrolimab infusion including flush will be 3 hours (±30 minutes) for the first 3 doses of treatment. After the third dose of treatment, the magrolimab infusion including flush will be 2 hours (±30 minutes).

[c] Lab assessment done at a local laboratory.

[d] No safety window will be permitted for assessments made for the first 2 doses of magrolimab (priming or repriming), otherwise CBC does not need to be drawn if done one day prior. CBC for Days 4 and 5 must be on consecutive days.

[e] Collect blood for PK and ADA (magrolimab): Assessment done at a central lab, and will take place predose at all time points shown, plus on Day 141 and at the end of treatment. A sample at the end of infusion for PK only will be collected on Day 57 only. No safety window will be permitted for assessments made on the day of the first magrolimab dose (priming or repriming). A time window of ±3 day will be permitted for subsequent assessments starting on Day 8 (or Day 8 of repriming).

[f] Collect peripheral blood to be sent to central lab for molecular analysis.

[g] Vital signs: Vital signs will be measured with each magrolimab dosing. Vital signs to be measured are heart rate, respiratory rate, oxygen saturation, blood pressure, and temperature. Height is recorded only at screening. Vital signs are to be recorded prior to the infusion of magrolimab. All subjects should be monitored hourly during infusion and for 1 hour after infusion for doses during the first 28 days and the repriming doses

[h] Weight: Weight should be measured at screening, each visit in which oral decitabine/cedazuridine and/or magrolimab is administered, and at treatment discontinuation.

[i] Concomitant medications/AE: Concomitant medication can be used throughout study. Concomitant medications/AEs should be reported on the eCRF and reviewed at each visit. Reporting of concomitant medications starts from 14 days before treatment and ends 30 days after the last dose of study treatment. Reporting of AEs starts at the signing of the informed consent form and ends 30 days after the last dose of study treatment.

[j] Recording transfusions: Record all blood and platelet transfusions from 56 days before the start of study treatment through 30 days after the last study treatment and in long-term follow-up for subjects who discontinue treatment before documented disease progression until disease progression is documented.

[k] Premedication is required prior to the administration of magrolimab through the Day 22 infusion of priming or repriming. Premedications may be continued based on the treating physician's clinical judgment and the presence/severity of prior infusion-related reactions.

[l] Compete PE at screening and treatment discontinuation; symptom-directed PE at the discretion of the investigator.

Table 3: Dosing Schedule for Oral Decitabine/Cedazuridine

Day for Dosing Oral Decitabine/Cedazuridine					
1	**2**	**3**	**4**	**5**	**6-28**
×	×	×	×	×	—

DLT=dose-limiting toxicity; FDC=fixed-dose combination; "×"= dosing day; "—"= non-dosing day.
Note: Oral decitabine/cedazuridine will be administered as a single agent or in combination with magrolimab and will follow the same dosing schedule for each cycle. Each dose of oral decitabine/cedazuridine is an FDC tablet (35 mg decitabine/100 mg cedazuridine) administered on Days 1-5 of each 28-day cycle. The dosing schedule may be altered if DLTs are observed in the DLT cohort; see Section 4.1.1 for further information.

Table 4: Dosing Schedule for Magrolimab

Day for Dosing Magrolimab During Priming, Maintenance, and Repriming																				
Priming Days 1-28[a]																				
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13-14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23-28**
×	—	—	×	—	—	—	×	—	—	×	—	—	×	—	—	—	—	—	—	×	—
Priming Days 29-56[b]																				
29	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41-42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51-56**
×	—	—	—	—	—	—	×	—	—	—	—	—	×	—	—	—	—	—	—	×	—
Maintenance Days 57-84[c]																				
57	**58**	**59**	**60**	**61**	**62**	**63**	**64**	**65**	**66**	**67**	**68**	**69-70**	**71**	**72**	**73**	**74**	**75**	**76**	**77**	**78**	**79-84**
×	—	—	—	—	—	—	—	—	—	—	—	—	×	—	—	—	—	—	—	—	—
Repriming Days 1-28[d]																				
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13-14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23-28**
×	—	—	×	—	—	—	×	—	—	×	—	—	×	—	—	—	—	—	—	×	—

CBC=complete blood count; DLT=dose-limiting toxicity; FDC=fixed-dose combination; Hgb=hemoglobin; "×"= dosing day; "—"= non-dosing day.
Note: The dosing schedule may be altered if DLTs are observed in the DLT cohort; see Section 4.1.1 for further information. Magrolimab should not be given on consecutive days.

[a] Priming doses of magrolimab: 1 mg/kg on Days 1 and 4; 15 mg/kg Day 8; 30 mg/kg Days 11, 15, and 22. All subjects should be monitored for 1 hour after infusion for doses during the first 28 days. Within 24 hours prior to each of the first 2 priming doses of magrolimab, all subjects must have a documented Hgb ≥9 g/dL. Subjects who do not meet these criteria must be transfused and have their Hgb rechecked to meet the minimum Hgb threshold prior to each of the first 2 doses of magrolimab. During the first 2 doses of priming, blood testing of Hgb will be required 3 to 6 hours after a magrolimab dose and the results must be reviewed prior to discharging the subject from the clinic. The subject should be transfused as clinically appropriate. Investigators should consider additional Hgb monitoring during the first week of treatment in subjects with symptoms of anemia or increased risk for complications of anemia.

[b] Dosing of magrolimab: 30 mg/kg on Days 29, 36, 43, and 50.

[c] Maintenance days are the days on which the magrolimab dose remains the same from dose to dose. Dosing of magrolimab: 30 mg/kg on Days 57 and 71. Maintenance dosing beyond Day 71 should repeatedly use the dose schedule of Days 57-84. Maintenance days can continue repeatedly after Day 84 following the same interval of dosing as seen in Maintenance Days 57-84.

[d] If magrolimab is not administered for 28 days or more and then restarted, the resulting doses, called repriming doses, follow the same schedule and dose level as the first 22 days of the priming doses, then maintenance dosing can start 7 days later. For subjects who have not received at least one 30 mg/kg dose of magrolimab, a dose delay of only 14 days is allowed until repriming is required. Within 24 hours prior to each of the repriming doses of magrolimab, all subjects must have a documented Hgb ≥9 g/dL. Subjects who do not meet these criteria must be transfused and have their Hgb rechecked to meet the minimum Hgb threshold prior to each of the first 2 doses of magrolimab. During the first 2 doses of repriming, blood testing of Hgb will be required 3 to 6 hours after a magrolimab dose and the results must be reviewed prior to discharging the subject from clinic.

A CBC is needed before each dose during the repriming cycle. Within 24 hours prior to each of the first 2 repriming doses of magrolimab, all subjects must have a documented Hgb ≥9 g/dL. Subjects who do not meet these criteria must be transfused and have their Hgb rechecked to meet the minimum Hgb threshold prior to each of the first 2 repriming doses of magrolimab. Magrolimab should be infused over 3 hours (±30 minutes) following the repriming dose schedule (1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; and 30 mg/kg on Days 11, 15, 22.). Days are adjusted depending on when repriming occurs. During the first 2 doses of repriming, blood testing of Hgb will be required 3 to 6 hours after a magrolimab dose and the results must be reviewed prior to discharging the subject from the clinic. The subject should be transfused as clinically appropriate. Vital signs, weight, reporting of concomitant medications/transfusions/AEs, premedications, chemistries, and urinalysis follow the same schedule as given for priming in Table 2.

2.0 INTRODUCTION

2.1 Background

Myelodysplastic syndromes (MDS) are premalignant clonal hematopoietic disorders characterized by bone marrow (BM) failure due to the production of dysfunctional, dysplastic BM cells. Primarily, these disorders affect individuals ≥60 years of age (Ma 2012). Low- and very low- risk subjects, as defined by the Revised International Prognostic Scoring System for myelodysplastic syndromes (IPSS-R; Greenberg et al 2012), are often treated with erythroid and myeloid growth factor support and carry a low risk of leukemic progression. In contrast, intermediate- to high-risk subjects with MDS have up to a 25% chance of leukemic transformation (NCCN 2022).

Intermediate- to high-risk subjects with MDS and are generally treated with hypomethylating agents (HMAs). The HMAs azacitidine (Vidaza®) and decitabine (DACOGEN®) are given as standard of care (SOC) for newly diagnosed MDS subjects with specific high-risk subtypes, and the approved schedules comprise consecutive daily dosing for 5 or 7 days in 28-day cycles. Treatment, which may continue for several months or even years, may engender significant hardship due to the 5 to 7 daily visits required each month, and the 1-hour intravenous (IV) infusion or large-volume subcutaneous injections. A possible consequence is noncompliance or premature discontinuation. In addition, the overall response rate (ORR; complete response [CR] + partial response [PR]) is approximately 16%, and overall survival (OS) is approximately 18 months (Silverman et al 2002). Thus, novel therapies that replace or augment the efficacy of HMAs or that can be formulated as a more convenient oral administration are needed to improve outcomes and extend survival for subjects with MDS.

Many of the steps in cancer progression subvert the multiple mechanisms of programmed cell death and the expression of the dominant antiphagocytic signal, CD47, may represent an important checkpoint (Chao et al 2011). Increased CD47 expression was identified first on leukemic stem cells in human acute myeloid leukemia (AML) (Majeti et al 2009), and since then, it has been found that CD47 expression is increased on the surface of cancer cells from a large number of diverse human tumor types. The binding of CD47 on cancer cells to its ligand signal regulatory protein alpha (SIRPα) expressed on phagocytes leads to inhibition of tumor phagocytosis. Thus, blockade of the CD47 SIRPα-signaling pathway by an anti-CD47 antibody leads to phagocytosis and elimination of tumor cells. CD47-blocking monoclonal antibodies (mAbs) have shown synergistic efficacious activity with cancer-specific targeting antibodies, including anti-CD20 antibody rituximab in a nonclinical model of non-Hodgkin lymphoma (NHL; Chao et al 2010).

Astex Pharmaceuticals, Inc. (Astex) has developed oral decitabine/cedazuridine, composed of the HMA decitabine in combination with cedazuridine. Cedazuridine (Ferraris et al 2014) is a new potent cytidine deaminase inhibitor that is pharmaceutically stable. Concomitant administration of oral decitabine with cedazuridine has been shown to markedly enhance the bioavailability of decitabine in nonclinical animal models (monkeys; Ricerca 031253). In addition, the safety profile of oral decitabine/cedazuridine has been evaluated in multiple clinical trials with MDS subjects and has been shown to be similar to the established safety profile of IV decitabine (current

DACOGEN® US prescribing information) supporting the approval of oral decitabine/cedazuridine in patients with MDS/chronic myelomonocytic leukemia (CMML) in the US, Canada, and Australia.

The anti-CD47 mAb magrolimab is a first in class oral investigational anticancer therapeutic agent targeting the CD47-SIRPα axis. The activity of magrolimab is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of fragment crystallizable (Fc)-dependent effector functions, although the presence of the immunoglobulin 4 Fc domain is required for its full activity. For this reason, magrolimab was engineered with a human immunoglobulin 4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47-expressing cells (Liu et al 2015). Binding of magrolimab to human CD47 on-target malignant cells blocks the "don't eat me" signal to macrophages and enhances tumor cell phagocytosis. In addition, magrolimab has the potential to elicit an antitumor T-cell response. Extensive nonclinical studies have demonstrated activity against both human solid tumors (breast, ovarian, pancreas, colon, leiomyosarcoma, bladder, prostate, and others) and hematologic malignancies (AML, acute lymphoblastic leukemia, NHL, myeloma, MDS, and others). This represents a novel strategy for the treatment of cancer. Magrolimab has demonstrated encouraging safety and efficacy in the treatment of previously untreated subjects with intermediate- to very high-risk MDS when used in combination with parenteral azacitidine, an HMA (Sallman et al 2022).

2.2 Study Rationale

The current study will aim to evaluate oral decitabine/cedazuridine in combination with magrolimab for previously untreated subjects with intermediate- to very high-risk MDS, as determined by IPSS-R.

Oral decitabine/cedazuridine is an HMA that is approved for use in subjects with intermediate- to high-risk MDS, as well as in subjects with CMML, in the US, Canada, and Australia. Oral decitabine/cedazuridine was approved based on clinical studies that determined its pharmacokinetic (PK) area under the concentration-time curve (AUC) equivalence to IV decitabine administration. Results from Phase 2 and 3 studies have demonstrated a positive treatment effect of oral decitabine/cedazuridine and that the clinical efficacy of oral decitabine/cedazuridine is consistent with efficacy described for intravenously administered decitabine in subjects with MDS; further details on the clinical development of oral decitabine/cedazuridine can be found in the Investigator Brochure (IB). At the therapeutic dose of 35 mg decitabine and 100 mg cedazuridine (administered concomitantly as separate capsules or as a fixed-dose combination [FDC] tablet), overall results from a Phase 2 study of oral decitabine/cedazuridine (ASTX727-01) showed a CR rate of 18%, with hematologic improvement (HI) in an additional 16.3% of subjects with MDS or CMML. Among the 41 subjects who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 20 subjects (49%) became independent of RBC and platelet transfusions during any consecutive 56-day post-baseline period. Of the 39 subjects who were independent of both RBC and platelet transfusions at baseline,

25 subjects (64%) remained transfusion-independent during any consecutive 56-day post-baseline period.

Results from a Phase 3, multicenter, randomized, crossover study in subjects with MDS/CMML or AML (ASTX727-02) established AUC equivalence of the FDC tablet (35 mg decitabine and 100 mg cedazuridine) with IV administered decitabine (20 mg/m^2). Assessment of efficacy indicated that the best response of CR was observed in 21.8% of all treated subjects and in 24.8% of subjects evaluable for response. Marrow CR was achieved in 32.3% of all treated subjects and in 36.8% of subjects evaluable for response. The ORR (CR + PR + mCR + HI) was 61.7% in all treated subjects and 70.1% in subjects evaluable for response. In addition, mCR with HI was reported in 16.5% of all treated subjects and in 18.8% of subjects evaluable for response. Sixteen subjects (12%) were not evaluable for response. With respect to the rate of subjects who were transfusion independent for ≥56, ≥84, and ≥112 consecutive days at any time post-baseline for subjects who were transfusion dependent at baseline, more than half (51.9%) of the 54 subjects who were RBC transfusion dependent at baseline were RBC transfusion independent for any consecutive ≥56-day period post-baseline. A similar overall rate of platelet TI (50%) for any consecutive ≥56-day period post-baseline was observed for subjects with platelet transfusion dependence at baseline. Rates of RBC and platelet TI were 40.7% and 33.3%, respectively, for ≥84 consecutive days and leveled at 33.3% for ≥112 consecutive days. The overall incidence of common adverse events (AEs) of thrombocytopenia, neutropenia, anemia, and febrile neutropenia observed in Phase 2 and Phase 3 was generally similar between oral decitabine/cedazuridine and IV decitabine. Further details can be found in the oral decitabine/cedazuridine IB.

The anti-CD47 mAb magrolimab has demonstrated encouraging data in the MDS population in combination with the HMA azacitidine (Vidaza®). Clinical studies have demonstrated that this combination has meaningful clinical activity that appears to be enhanced compared with azacitidine monotherapy in subjects with MDS. In a study investigating the clinical activity of magrolimab in combination with azacitidine in subjects with treatment-naïve intermediate- to higher-risk MDS (by IPSS-R) (Study 5F9005; Sallman et al 2019), 24 subjects were evaluable for efficacy. The ORR was 92%, with 50% achieving a CR. Complete cytogenetic response was observed in 26% of subjects who had abnormal cytogenetics at baseline. Minimal residual disease (MRD) negativity was achieved in 23% of subjects, as assessed by flow cytometry. With a median follow-up of 6.4 months, no median duration of response (DOR) had been reached, with several subjects in response over 14 months on therapy. In addition, putative CD34+CD48− leukemia stem cell progenitors were substantially reduced or eradicated by magrolimab in combination with azacitidine in responding subjects who were evaluated. Magrolimab in combination with azacitidine is currently being evaluated for survival and CR (co-primary objectives) in a large, randomized Phase 3 study (ENHANCE, NCT04313881) comparing the efficacy and safety of magrolimab plus azacitidine with that of azacitidine plus placebo (PBO) in previously untreated subjects with high-risk MDS; further details can be found in the magrolimab IB. Despite its clinical benefit, treatment with azacitidine requires chronic parenteral treatment for 5 to 7 days each month for responding subjects; this number of clinic/hospital visits is a significant burden for what is primarily an elderly population. Furthermore, an online survey that assessed treatment challenges

in subjects with MDS determined that IV/subcutaneous HMA administration resulted in pain and impacted daily activities, suggesting that an oral HMA might reduce treatment challenges for this population (Zeidan et al 2022).

This study will assess the safety and efficacy of combining oral decitabine/cedazuridine (oral HMA) with magrolimab in subjects with intermediate- to very high-risk MDS. This combination with an oral HMA may provide a safe and efficacious alternative to azacitidine in combination with magrolimab, while minimizing the burden of treatment for subjects and caregivers (ie, number of required clinic visits, transportation time, and complications of parenteral therapy).

2.3 Benefit/Risk Assessment

2.3.1 Oral Decitabine/Cedazuridine

It is difficult to separate risks associated with oral decitabine/cedazuridine from those of MDS itself, as the AEs that occur with MDS are similar to those that occur with oral decitabine/cedazuridine. The safety of oral decitabine/cedazuridine mimics the safety of decitabine, which is mainly the risk of myelosuppression and its consequences (pneumonia, sepsis, or hemorrhage) with potential gastrointestinal (GI) effects due to oral administration. All safety issues that have been identified with oral decitabine/cedazuridine to date are consistent with the safety profile of IV decitabine at oral doses/cycle of up to 200 mg decitabine and 500 mg of cedazuridine. Blood levels of decitabine (at 35 mg decitabine and 100 mg cedazuridine and) in study ASTX727-01 have been shown to be similar to levels seen after 1-hour IV infusion with 20 mg/m^2 decitabine. For more detailed information, please refer to the oral decitabine/cedazuridine IB.

In addition, most cancer subjects prefer oral to injectable drug formulations (Liu et al 1997); benefits of an oral HMA (oral decitabine/cedazuridine) include alleviating the inconvenience of potential long-duration parenteral therapy as well as minimizing the hardship involved with the frequent hospital/clinic visits associated with a drug that must be administered intravenously. This is of particular importance considering the prevalence of this disease in the elderly and the need for continued monthly treatment potentially for years, particularly for those subjects who respond to treatment and benefit the most. An oral drug may also improve compliance with 5 days/month treatment.

2.3.2 Magrolimab

As of 24 July 2021, over 700 participants have been treated with magrolimab monotherapy or magrolimab in combination with other agents. Overall, nonclinical and clinical data to date on magrolimab in combination with azacitidine show evidence of efficacy in untreated higher-risk MDS and also demonstrate the acceptable safety profile of the combination therapy in this patient population, with no maximum tolerated dose (MTD) reached and a treatment discontinuation rate due to AEs of 1.6%. No significant exacerbation of azacitidine related AEs by magrolimab has been observed, as evidenced by the minimally observed myelosuppression from the combination. Therefore, based on the available safety data, magrolimab has an acceptable safety profile both as

a monotherapy and a combination therapy across multiple hematologic and advanced solid tumor malignancies; the clinical study findings are consistent with nonclinical toxicology studies and there are no additional expected risks expected in the present study. In addition, while magrolimab requires frequent IV dosing in the first 56 days of treatment, subsequent administration is every 14 days Combining this with an oral HMA (decitabine/cedazuridine) will significantly reduce overall requirement for subjects to attend in-person clinic visits.

3.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate preliminary safety and efficacy of oral decitabine/cedazuridine in combination with magrolimab.	• Adverse events graded according to NCI CTCAE, Version 5.0 (Section 10.5), DLTs, and CR rate.
Secondary	
• To evaluate the PK profile of oral decitabine/cedazuridine and magrolimab.	• Concentration versus time and PK parameters.
• To evaluate other clinical efficacy of oral decitabine/cedazuridine and magrolimab.	• ORR, rate of HI, duration of PFS, LFS, undetectable disease assessed by MRD, DOR, and OS.
• To evaluate efficacy and safety by prespecified subgroups (eg, IPSS-M, p53 status).	• Safety and efficacy based on molecular features (eg, IPSS-M score, p53 status).

CR=complete response; DLT=dose-limiting toxicity; DOR=duration of response; HI=hematologic improvement; IPSS-M=Molecular International Prognostic Scoring System for myelodysplastic syndromes; LFS=leukemia-free survival; MRD=minimal residual disease; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic(s)

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, open-label, multicenter, non-randomized interventional study to evaluate the safety, efficacy, and PK of oral decitabine/cedazuridine when given in combination with magrolimab for the treatment of subjects with previously untreated intermediate- to very high-risk MDS. Subjects with higher-risk MDS (IPSS-R ≥3.5) will be screened for participation with the goal of obtaining approximately 100 subjects who are evaluable, those subjects receiving one or more dose of study treatment, for the primary study endpoint. The first 6 to approximately 18 subjects enrolled will be evaluated for dose-limiting toxicities (DLTs) during the first 2 cycles of oral decitabine/cedazuridine and will be used to confirm the dosing for oral decitabine/cedazuridine in combination with magrolimab. In this protocol, a cycle is defined as a

cycle of oral decitabine/cedazuridine, which is normally 28 days. Dose-limiting toxicities are defined in Section 8.5.6.

The primary analysis of the CR rate will be conducted approximately 8 months after enrollment of approximately 100 subjects has occurred. Participation will include screening, treatment, and follow-up. The screening period will last up to 21 days before the first dose of study treatment, during which time the participant's eligibility and baseline characteristics will be determined. Subjects will receive study treatment per the dosing schedule in Table 3 and Table 4. Study treatment may be continued until disease progression (including treatment failure by the International Working Group [IWG] 2006 criteria or relapse after PR/CR), or unacceptable toxicities occur, the subject is withdrawn from study treatment, or the sponsor stops the study. In case subjects choose to discontinue the study treatment due to reasons other than disease progression, eg, voluntary withdrawal, subjects will be followed up for response assessments until documented disease progression occurs. For subjects who stop receiving the study treatment to receive a stem cell transplant (SCT), follow-up for response assessment and collection of SOC BM biopsy/aspirate results will continue until documented disease progression occurs or start of new anticancer therapy, whichever occurs first. Then subjects will be observed for survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

The study duration will be approximately 44 months. This may be adjusted based on enrollment rate as well as DOR.

The Schedules of Activities (SoAs) are detailed in Table 1 and Table 2.

The COVID-19 pandemic may continue to affect the way clinical studies need to be conducted such that alternative measures may need to be implemented to ensure the safety of subjects and maintain the integrity of clinical trial data. Section 10.7 details information regarding potential modifications to the conduct of the study in the event of a COVID-19 health emergency.

4.1.1 Dose-Limiting Toxicity Cohort

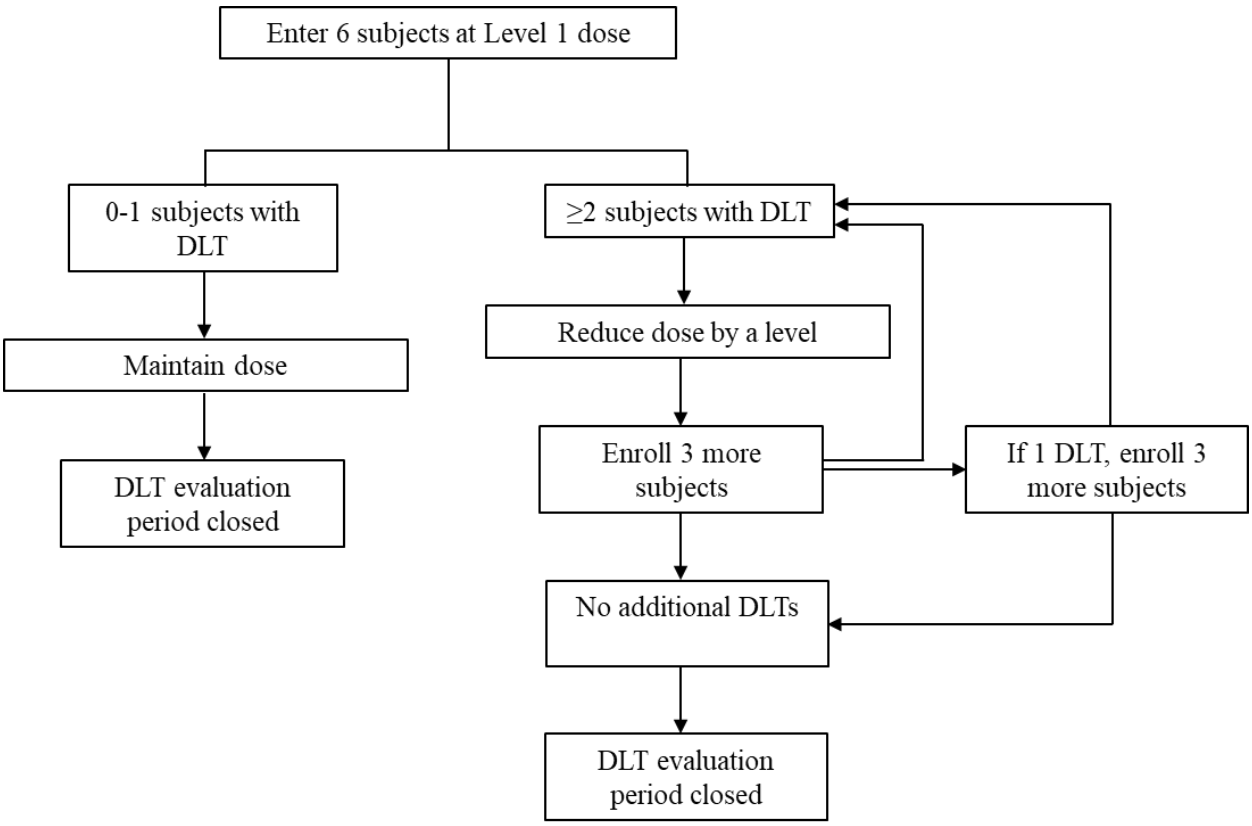
The first 6 to approximately 18 subjects enrolled, the DLT cohort, will be evaluated to confirm that the dosing of oral decitabine/cedazuridine in combination with magrolimab is well tolerated (Section 8.5.6). Due to the low incidence of magrolimab DLTs (please reference Investigational New Drug [IND] 147229 for the magrolimab Investigator Brochure), it is expected that most DLTs will be related to oral decitabine/cedazuridine, especially those related to neutropenia, thrombocytopenia, GI toxicity, and infection. Thus, a DLT should generally be considered related to oral decitabine/cedazuridine unless the investigator feels that a DLT is related to magrolimab. The DLT period will last the first 2 cycles of oral decitabine/cedazuridine treatment as defined in Section 4.1. Evaluation of the cohort will end when a tolerated dosing is identified, or the study is stopped due to toxicity. Oral decitabine/cedazuridine and magrolimab dosing will initiate as outlined in Section 4.5. If there are DLTs associated with magrolimab that occur in the DLT cohort, the investigator in consultation with the Astex medical monitor and the Data and Safety

Review Committee (DSRC) will determine if a dose modification of magrolimab is appropriate (see Section 6.6.2 for magrolimab dose modification recommendations).

The dosing reduction process for oral decitabine/cedazuridine-associated DLTs will follow a 3+3 design (Figure 2), as follows:

- The first 6 subjects will be evaluated for myelosuppression and other DLTs (Section 8.5.6).
- If fewer than 2 subjects among the first 6 (<33%) experience a DLT (Section 8.5.6), the current dosing level will be maintained, and no further DLT cohort evaluation will be conducted.
- If a DLT occurs in 2 or more of the initial 6 subjects, then oral decitabine/cedazuridine dosing will be reduced 1 level (Table 9) and 3 more subjects will be enrolled at that dosing level.
- If no additional DLTs occur, the dosing will be maintained, and no further DLT cohort evaluation will be conducted. If any DLT occurs, another 3 subjects will be enrolled. If fewer than 2 subjects (<33%) have a DLT out of the 6 subjects, then the dosing will be maintained, and no further DLT cohort evaluation will be conducted. If oral decitabine/cedazuridine associated DLTs occur in 2 or more out of 6 subjects, dosing of oral decitabine/cedazuridine will be reduced one dose level as per Table 9, and 3 more subjects will be enrolled.
- This process is repeated until a tolerated oral decitabine/cedazuridine dosing is identified and the dosing will be maintained with no further DLT cohort evaluation OR the dosing levels falls to Level 5 (Table 9) and in consultation with the DSRC, the study will be closed or the protocol amended to modify the dosing of oral decitabine/cedazuridine.
- During the study, a stopping rule for observation of excess toxicity will be implemented, as described in Section 9.5.

Figure 2: Dosing Reduction Process for Oral Decitabine/Cedazuridine-Associated Dose-Limiting Toxicities



DLT=dose-limiting toxicity

4.2 Scientific Rationale for Study Design

Oral decitabine/cedazuridine has been developed by Astex and is an HMA approved for use in subjects with intermediate to high-risk MDS, as well as in subjects with CMML. As discussed in Section 2.2, results from Phase 2 and 3 studies have demonstrated a positive treatment effect of oral decitabine/cedazuridine. This is a Phase 2, open-label, multicenter, non-randomized interventional study with no active comparator or control. The goal of this study is to assess the safety and efficacy of combining oral decitabine/cedazuridine with magrolimab in subjects with intermediate- to very high-risk MDS. This combination with an oral HMA may provide a safe and efficacious alternative to azacitidine in combination with magrolimab for this population while minimizing the burden of treatment for subjects and caregivers (ie, number of required clinic visits, transportation time, and complications of parenteral therapy).

Complete response was the efficacy endpoint in several Phase 1 studies with magrolimab and it is the co-primary endpoint in two Phase 3 studies (ENHANCE [ClinicalTrials.gov Identifier: NCT04313881] and VERONA [ClinicalTrials.gov Identifier: NCT04401748]); therefore, measurement of CR will form part of the primary endpoint in the proposed study (alongside measurement of AEs and DLTs). Other efficacy endpoints, including ORR (including CR, mCR,

and any HI), rate of HI, duration of progression-free survival (PFS), leukemia-free survival (LFS), undetectable disease assessed by minimal residual disease (MRD), DOR, and OS will also be evaluated to better characterize the clinical efficacy of oral decitabine/cedazuridine in combination with magrolimab.

4.3 Data and Safety Review Committee

The DSRC will comprise the principal investigators (or designees), and the Astex medical monitor, clinical pharmacologist, and lead statistician, and other study team members as appropriate.

The DSRC will review emerging safety data after the first 6 subjects are enrolled. The first 6 to approximately 18 subjects enrolled will be evaluated for DLTs during the first 2 cycles; if present (following standard 3+3 design), there will be dosing reductions of oral decitabine/cedazuridine which will be applied to all subsequent subjects.

Further details of the DLT cohort are provided in Section 4.1.1.

4.4 Recruitment

Approximately 58 sites in North America, Europe, and Asia Pacific will be included in this study. Approximately 135 subjects will be screened to achieve 100 evaluable subjects.

All subjects must be provided with an informed consent form (ICF) describing the study with sufficient information for subjects to make an informed decision regarding their participation. Subjects must sign the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved ICF prior to participation in any study-specific procedure. Data from assessments performed as part of SOC prior to ICF signature may be used if they are within the required timeframe. The participant must receive a copy of the signed and dated consent documents. A signed copy of the consent documents must be retained in the site file.

Once subjects sign the ICF, they will enter the screening period for the study and receive a unique subject identification number before any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject, including if a subject is rescreened.

Screening assessments do not need to be repeated if they were previously performed during screening and were within 21 days of Cycle 1 Day 1. Blood samples for determination of Molecular International Prognostic Scoring System for myelodysplastic syndromes (IPSS-M) score and p53 status do not need to be repeated if they were obtained within 6 weeks (42 days) of Cycle 1 Day 1. Subjects who fail screening may undergo up to 2 repeated screenings.

All subjects who provide informed consent must be registered in the electronic data capture (EDC) system and interactive voice/web/mobile response system (IXRS), including screen failures.

4.5 Dosing Administration

The treatment administration schedule for oral decitabine/cedazuridine and magrolimab is presented in Table 5 and Table 6. The detailed PK assessment schedule is presented in Table 13 and Table 14.

The following magrolimab dosing regimen is proposed for this study:

- The dose of magrolimab is increased over time in a series called priming doses. Priming doses of magrolimab: 1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11, 15, 22, 29, 36, 43, and 50.
- Maintenance doses of magrolimab: 30 mg/kg on Day 57 and every 14 days thereafter.
- If magrolimab is not administered for 28 days or more and then restarted, the resulting doses, called repriming doses, follow the same schedule and dose level as the first 22 days of the priming doses, then maintenance dosing can start 7 days later. For subjects who have not received at least one 30 mg/kg dose of magrolimab (ie, for subjects who have either not received their first dose of 30 mg/kg or subjects who have received doses <30 mg/kg), a dose delay of only 14 days is allowed until repriming is required.

  The duration of each magrolimab infusion including flush will be 3 hours (±30 minutes) for the first 3 doses of priming and repriming. Recommended premedications are listed in Section 6.5. After the third dose of treatment, the magrolimab infusion including flush will be 2 hours (±30 minutes). The reduced infusion time to 2 hours is based on prior data demonstrating the majority CD47 receptor occupancy (RO) on peripheral blood cells, thus mitigating anticipated RBC toxicities from magrolimab.

Oral decitabine/cedazuridine study treatment is to be administered according to the following schedule:

- Days 1-5: oral decitabine/cedazuridine by mouth daily on an empty stomach (morning before breakfast) with no food for 2 hours before and at least 2 hours after administration. When taking oral decitabine/cedazuridine, subjects may have clear liquids such as water, black coffee, or tea. The dosing regimen may be modified during assessment of DLTs in the DLT cohort (Section 4.1.1).

Table 5: Treatment Administration Schedule for Oral Decitabine/Cedazuridine

Day →	1	2	3	4	5	6-28
All Cycles	×	×	×	×	×	—

DLT=dose-limiting toxicity; FDC=fixed-dose combination; "×"= dosing day; "—"= non-dosing day
Note: All treatments are one FDC tablet (35 mg decitabine/100 mg cedazuridine). After evaluation of the DLT cohort, the dosing regimen for subsequent subjects may be altered.

Table 6: Treatment Administration Schedule for Magrolimab

Day →	**1**	**2-3**	**4**	**5-7**	**8**	**9-10**	**11**	**12-14**	**15**	**16-21**	**22**	**23-28**
Dose (mg/kg)	1	—	1	—	15	—	30	—	30	—	30	—
Day →	**29**	**30-35**	**36**	**37-42**	**43**	**44-49**	**50**	**51-56**	**57**	**58-70**	**71**	**72-84**
Dose (mg/kg)	30	—	30	—	30	—	30	—	30	—	30	—

Note: The dose of magrolimab is increased from 1 mg/kg to 30 mg/kg during priming on Days 1-56. Maintenance doses continue after priming at 30 mg/kg, starting at Day 57 and every 14 days thereafter. If magrolimab is not administered for 28 days or more and then restarted, the resulting doses, called repriming doses, follow the same schedule and dose level as the first 22 days of the priming doses, then maintenance dosing can start 7 days later. For subjects who have not received at least one 30 mg/kg dose of magrolimab, a dose delay of only 14 days is allowed until repriming is required.

Alternative options for oral decitabine/cedazuridine administration on Days 1-5 are detailed in Table 7.

Table 7: Alternative Options for Oral Decitabine/Cedazuridine Administration on Days 1-5

Oral decitabine/cedazuridine	**Last meal (≥2 hours before taking oral decitabine/cedazuridine)**	**Next meal (≥2 hours after taking oral decitabine/cedazuridine)**
Between breakfast and lunch	Breakfast	Lunch
Between lunch and dinner	Lunch	Dinner
At bedtime	Dinner	Breakfast (next day)

Systematic dosing reductions of oral decitabine/cedazuridine may be necessary, as detailed in Section 4.1.1 and Section 6.6.1. Dose reductions of magrolimab may be considered in rare circumstances, as outlined in Section 6.6.2.

Treatment will continue until disease progression, death, or unacceptable treatment-related toxicity, the subject withdraws or is withdrawn from the study, the treatment becomes commercially available, or the sponsor stops the study.

Initially, magrolimab will be administered according to the current magrolimab IB and Table 6, and oral decitabine/cedazuridine will be administered according to the approved dosing regimen (Daily×5); please refer to the latest oral decitabine/cedazuridine IB and magrolimab IB for further information.

This study will follow the dosing schedule as determined in the DLT cohort. The primary objective of the study is to evaluate preliminary safety and efficacy of oral decitabine/cedazuridine in combination with magrolimab. Efficacy will be determined by CR, which is based on the

2006 IWG criteria (Cheson et al 2006), described in Section 10.6. Subjects should be premedicated in accordance with Section 6.5. Oral decitabine/cedazuridine and magrolimab should be prepared as outlined in the Pharmacy Manual for the study.

There is no dose modification for oral decitabine/cedazuridine based on weight.

The dose of each magrolimab study treatment will be calculated based on actual weight at enrollment (using weight obtained either at screening or on Day 1) and remains constant throughout the study unless there is a >10% change in weight from baseline. Modifications to the magrolimab study treatment doses administered should be made for a >10% change in body weight from baseline and according to local and regional prescribing standards. Dose modifications for changes in body weight ≤10% may be made according to local institutional guidelines. In the event that a dose is modified due to a >10% weight change, the weight on which the new dose is based will become the new baseline weight.

When both study drugs are given on the same visit day, magrolimab will be administered at least 1 hour after oral decitabine/cedazuridine administration.

Magrolimab doses will be given twice weekly during priming and escalation (2 weeks), with a window of ±3 days for each dose; however, magrolimab doses are not to be given on consecutive days. If additional delay is needed to ensure a white blood cell (WBC) of $\leq 20\times10^3/\mu L$, please contact the sponsor's medical monitor.

During the first 28 days of treatment (Days 1, 4, 8, 11, and 22), WBC count must be $\leq 20\times10^3/\mu L$ prior to each magrolimab dose. Subjects with WBC $>20\times10^3/\mu L$ can be treated with hydroxyurea (up to 4 g/day) during the first 56 days to reduce the WBC to $\leq 20\times10^3/\mu L$.

Within 24 hours prior to each of the first 2 priming or repriming doses of magrolimab, all subjects must have a documented hemoglobin (Hgb) ≥9 g/dL. Subjects who do not meet these criteria must be transfused and have their Hgb rechecked to meet the minimum Hgb threshold prior to each of the first 2 doses of magrolimab. During the first 2 doses of priming and repriming, blood testing of Hgb will be required 3 to 6 hours after a magrolimab dose and the results must be reviewed prior to discharging the subject from the clinic. The subject should be transfused as clinically appropriate. Investigators should consider additional Hgb monitoring during the first week of treatment in subjects with symptoms of anemia or increased risk for complications of anemia.

All subjects should be monitored hourly during infusion and for 1 hour after infusion for doses during the first 28 days and the repriming doses. Subjects should be monitored (including measurement of vital signs, as clinically appropriate) for signs and symptoms of infusion-related reactions, which have been observed in previous magrolimab studies.

Postinfusion monitoring is not required for doses after Day 22 of priming or repriming. Subjects who experience any treatment-related AEs prior to this point should be further monitored as

clinically appropriate. Management of infusion-related reactions is further described in Section 8.5.7.2.

Subjects may continue study treatment until they show evidence of disease progression (including treatment failure by IWG criteria or relapse after PR/CR), loss of clinical benefit, or unacceptable toxicity. Further details about treatment discontinuation are described in Section 7.1.

4.6 Justification for Dose

4.6.1 Oral Decitabine/Cedazuridine

The recommended dose and regimen of oral decitabine/cedazuridine for initiating the study is 35 mg decitabine and 100 mg cedazuridine given orally as the FDC tablet once daily (QD) on Days 1-5 of each 28-day cycle (Days 1-5 in all cycles). This is the approved dose of oral decitabine/cedazuridine for MDS per INQOVI prescribing information in Australia, Canada, and the US (Australia, Canada, US) and the selection of this dose and regimen is based on the decitabine 5-day AUC from time 0 to 24 hours equivalence of oral decitabine/cedazuridine with IV decitabine (20 mg/m^2 Daily×5). This dose and regimen were shown in the Phase 2 study (ASTX727-01) and confirmed in the Phase 3 study (ASTX727-02) in subjects with MDS/CMML. In addition, oral decitabine/cedazuridine treatment at the recommended dose and regimen achieved almost identical demethylation to IV decitabine (<1% as measured by percentage of long interspersed nucleotide elements-1 demethylation), with clinical response, transfusion independence, and survival data consistent with previous results for the approved IV decitabine 5-day regimen (current DACOGEN US Prescribing Information; Steensma et al 2009). Likewise, safety data from the Phase 2 and Phase 3 studies (in MDS/CMML) largely mirrored the safety profile of IV decitabine in the same subject population. This dose is expected to yield efficacy similar to that of azacitidine.

4.6.2 Magrolimab

The magrolimab dosing regimen for this study is outlined in Section 4.5.

Rationale for the magrolimab dose proposed in this study originates from safety, efficacy, and PK/pharmacodynamic data and modeling and simulation analyses based on data obtained from all ongoing and completed clinical trials with magrolimab in subjects with solid tumors, NHL, and AML/MDS. In the first-in-human study of magrolimab (SCI-CD47-001) in subjects with solid tumors and lymphomas, after an initial priming dose of 1 mg/kg on the first day, magrolimab was tested as a monotherapy at weekly doses of up to 45 mg/kg. The use of an initial 1 mg/kg priming dose was integrated to the dosing regimen based on mitigation of the on-target anemia induced by CD47 blockade. An initial priming dose leads to elimination of aged RBCs that are sensitive to CD47 blockade and triggers a reticulocytosis of young RBCs that are not affected by CD47 blockade (Chen et al 2018). Utilizing a priming dose leads to an initial, transient, and mild anemia that generally normalizes back to baseline over several weeks even in the presence of repeated therapeutic doses of magrolimab (Advani et al 2018; Liu et al 2015; Sikic et al 2019). The top dose of 45 mg/kg has an acceptable safety profile, and no MTD was identified in this study

(SCI-CD47-001). In Studies SCI-CD47-002 and 5F9005, in subjects with AML/MDS, magrolimab was administered as a monotherapy at doses of up to 30 mg/kg twice weekly and in combination with azacitidine at doses of up to 30 mg/kg weekly. In these studies, no significant DLT was observed, and magrolimab has an acceptable safety profile over the tested dose range up to a maximum of 30 mg/kg twice a week. Furthermore, in these 2 studies, an intrasubject dose escalation approach was followed; after the priming dose, the subjects received doses of 15 mg/kg on Day 8 during Week 2, after which the dose was escalated to 30 mg/kg on Day 11 and then weekly thereafter. This was based on nonclinical data indicating enhanced safety of intrasubject dose escalation. In Studies 5F9003 and 5F9004, magrolimab in combination with rituximab and cetuximab, respectively, was found to have an acceptable safety profile at doses up to 45 mg/kg every other week. Based on the safety data in multiple oncology populations, including the proposed study population, both as a monotherapy and in combination with other tumor targeted antibodies and chemotherapeutics, the proposed dosing regimen of magrolimab is expected to have an acceptable safety profile.

Currently, there are limited data on dose/exposure-response in the treatment-naïve MDS population, but available dose-ranging data in subjects with NHL also support the proposed dosing regimen. After a priming dose of 1 mg/kg in the first week, maintenance doses in the range of 10 to 45 mg/kg every week and 30 to 45 mg/kg every 2 weeks are being tested in an ongoing Phase 1b/2 study of magrolimab in combination with rituximab in subjects with relapsed/refractory NHL (Study 5F9003). Based on data obtained from this study so far, there was no significant difference in efficacy across the dose range tested. For instance, in relapsed/refractory diffuse large B-cell lymphoma, the ORR of subjects in the combined 30 mg/kg dose arm (N=35) and at 45 mg/kg (N=17) was 34% and 38%, respectively (Advani et al 2019). Preliminary PK/PD modeling indicated lack of relationship between exposure and ORR across the dose/concentration range. Also, no relationship was observed between concentrations and DOR in responders across the tested dose range. Together, these results indicated maximal efficacy at 30 mg/kg with no further efficacy benefit at higher doses.

In addition, in Study SCI-CD47-002 and Study 5F9005, CD47 RO was tested at baseline and at multiple time points on treatment for both peripheral blood (PB) and BM cells, including leukemic blasts. A PK/PD model linking dose exposure and blood and BM RO was developed and described these data well. Simulations with the model predicted that >90% RO would be achieved in the BM cells at the magrolimab dosing regimen proposed in this study. This level of RO is typically associated with maximal efficacy for many immune-oncology antibodies. Therefore, the proposed dose regimen is expected to maximize efficacy in the MDS patient population. Exploratory analysis of exposure-objective response data from Study 5F9005 also indicated a lack of relationship between concentration and likelihood of response in this concentration range, indicating that doses in this range are likely to be maximally effective.

Based on results from the Phase 1b study of magrolimab in MDS and AML (Study 5F9005), this study will employ the same intrasubject dose escalation regimen for oral decitabine/cedazuridine in combination with magrolimab in treatment-naïve subjects with MDS to mitigate on-target

toxicities such as anemia and other toxicities observed in nonclinical AML models. The intrasubject dose escalation regimen uses initial twice-weekly dosing at a starting magrolimab dose of 1 mg/kg for Week 1 (Days 1 and 4), with escalation to 15 mg/kg on Day 8 and 30 mg/kg on Days 11 and 15, followed by 30 mg/kg weekly for 5 doses (Day 22, Day 29, Day 36, Day 43, and Day 50). The maintenance dose of magrolimab is 30 mg/kg on Day 57 and every 14 days thereafter. Treatment should be continued until disease progression, loss of clinical benefit, or unacceptable toxicities occur. The strategy of intrasubject dose escalation was found to result in both mitigation of acute toxicities seen in nonclinical models and in expected RBC toxicities that were manageable for this subject population.

In summary, the proposed dose regimen is like the dose regimen being tested in a Phase 3 study in higher risk MDS in combination with azacitidine. The combination has been shown to have an acceptable safety profile in multiple oncology patient populations, including MDS subjects. Based on PK/PD modeling, the proposed dose is predicted to result in optimal efficacy in this population. Further increases in dose beyond 30 mg/kg are not predicted to result in increased efficacy.

4.7 End of Study Definition

The study will be considered complete for data reporting purposes when all subjects have died, withdrawn from study treatment (Section 7.2), or the sponsor terminates the study, whichever occurs first. Astex reserves the right to terminate the study at any time for any reason.

Upon completion or closure of the study, the sponsor will provide the opportunity to continue study drug(s) for those that continue to derive benefit from treatment through expanded access, or the local equivalent, and collect, at a minimum, safety information from subjects until disease progression, death, or unacceptable treatment-related toxicity, the subject is withdrawn from study treatment, or treatment becomes commercially available.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Adherence to study eligibility criteria is essential.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria apply:

Age

1) Aged ≥18 years at the time of signing the ICF.

Type of Participant and Disease Characteristics

2) Histological confirmation of previously untreated MDS (ie, no HMA, chemotherapy, or allogenic SCT) per World Health Organization 2016 classification with <20% BM blasts per marrow biopsy/aspirate at screening.
3) Projected life expectancy of at least 3 months.
4) Overall IPSS-R score ≥3.5 MDS (intermediate risk or higher).
5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2.
6) Hematopoietic stem cell transplant (HSCT) eligible without any pre-arranged HSCT on Cycle 1 Day 1, or HSCT ineligible.
7) Hemoglobin ≥9 g/dL on the first day of drug administration, transfusions allowed.
8) Blood type and screen (ABO/Rh) along with extended red blood cell phenotyping or genotyping completed prior to study drug treatment.
9) Willing to undergo blood transfusions as per parameters of protocol and clinically necessary.
10) White blood cell count $\leq 20 \times 10^3/\mu L$ prior to first dose and throughout study. Hydroxyurea can be used to achieve this goal prior to and during the first 56 days of magrolimab administration.

Sex and Contraceptive/Barrier Requirements

11) Subject can be male or female.
    a) Male subjects:
        i) Male subjects are eligible to participate if they agree to the following during the treatment period and for at least 90 days plus 5 half-lives of magrolimab (70 days), totaling 160 days (approximately 5.5 months), after the last dose of study treatment:
            - Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent;

OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
  - Female partners should be advised of the benefit of using an additional highly effective contraceptive method with a failure rate of <1% per year as described in Section 10.2 as a condom may break or leak.

b) Female subjects:

i) A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a woman of childbearing potential (Section 10.2);

OR

- Is a woman of childbearing potential and using a contraceptive method that is highly effective with a failure rate of <1% per year), preferably with low user dependency, as described in Section 10.2, during the treatment period and for at least 180 days plus 5 half-lives of magrolimab (70 days), totaling 250 days (approximately 8.5 months), after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study treatment.
  - A woman of childbearing potential must have a negative serum pregnancy test within 24 hours before the first dose of study treatment.
  - Additional requirements for pregnancy testing during and after study treatment are located in Section 8.2.5.
  - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

12) Capable of giving signed informed consent (Section 10.1.3), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol, and willing to participate in the study.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Medical Conditions

1) Known active hepatitis B (eg, HBsAg reactive), or hepatitis C (eg, HCV RNA [qualitative] is detected), or chronic hepatitis B or C infection or human immunodeficiency virus (HIV) infection in medical history, with the following exceptions:
   a) Those with a history of hepatitis with a negative polymerase chain reaction (either qualitative or quantitative) OR have documentation of stable disease with aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase <2.0×upper limit of normal (ULN) may be eligible for this study.
   b) Subjects with history of HIV who have an undetectable viral load for the prior 3 months, and who agree to maintain antiviral therapy, may be eligible for the study.
2) Significant medical diseases or conditions, as assessed by the investigators and sponsor, that would substantially increase the risk benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, and congestive heart failure New York Heart Association Class III-IV.
3) Abnormal biochemical indices as listed below:
   a) Aspartate aminotransferase/serum glutamic oxaloacetic transaminase and ALT/serum glutamic pyruvic transaminase >3.0×ULN.
   b) Total or direct bilirubin >1.5×ULN or >3.0×ULN and primarily unconjugated unless the participant has a previously documented history of Gilbert's syndrome or genetic equivalent.
   c) Serum creatinine >1.5×ULN, calculated glomerular filtration rate (GFR) <40 mL/min/1.73 m^2, or calculated creatinine clearance <50 mL/min by Cockcroft Gault formula or other medically acceptable formulas.
4) Known inherited or acquired bleeding disorders that require medication or medical intervention.

5) Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which subjects are not on active anticancer therapies and have had no evidence of active malignancy for at least ≥1 year.

Prior/Concomitant Therapy

6) Immediate eligibility for an allogeneic SCT, as determined by the investigator, with an available donor.
7) Prior therapy for MDS with chemotherapy, allogenic SCT, or ≥1 full cycle of treatment with any HMA.
8) History of therapy-related MDS, MDS evolving from a pre-existing myeloproliferative neoplasm (MPN), MDS/MPN including CMML, atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, and unclassifiable MDS/MPN.
9) Prior anti-CD47 treatment.
10) Previous SCT within 6 months before first dose administration, active graft-versus-host disease, or requiring transplant-related immunosuppression.

Other Exclusions

11) Known or suspected hypersensitivity to decitabine, cedazuridine, magrolimab, or any of their excipients.
12) Known significant mental illness or other condition such as active alcohol or other substance abuse or addiction that, in the opinion of the investigator, predisposes the subject to high-risk of noncompliance with the protocol.
13) Clinical suspicion of active central nervous system (CNS) involvement by MDS.
14) History of psychiatric illness or substance abuse likely to interfere with the ability to comply with protocol requirements or give informed consent.
15) Pregnant or actively breastfeeding.

5.3 Lifestyle Considerations

Subjects are required to adhere to all guidelines in this section.

5.3.1 Meals and Dietary Restrictions

Oral decitabine/cedazuridine tablets should be taken with water on empty stomach (defined as having no food for 2 hours before dosing) with no food for 2 hours after administration (Section 4.5).

5.3.2 Contraceptive Requirements

Lifestyle considerations pertaining to contraceptive requirements while on study are described in Section 10.2 for both men and women. Magrolimab has a longer half-life than oral decitabine/cedazuridine, which forms the basis of the duration of contraceptive requirements for both men and women.

5.3.3 Type and Screen and Direct Antiglobulin Test

Magrolimab may interfere with RBC phenotyping due to expected coating of the RBC membrane. Due to the risk of developing anemia, and because magrolimab may make phenotyping difficult, any of the 4 blood groups (A, B, AB, and O)/Rhesus factor (ABO/Rh) type, antibody screen, extended phenotyping or genotyping, and DAT need to be performed at screening before exposure to magrolimab, as described in Section 8.5.7.

Red blood cell genotyping (instead of an extended RBC phenotyping) must be performed if a subject received any RBC or whole blood transfusion within the previous 3 months (unless the laboratory has availability for special techniques for performing phenotyping for subjects with a recent transfusion). Extended RBC genotyping instead of extended RBC phenotyping is acceptable for any subject. Red blood cell phenotyping/genotyping, ABO type, and DAT need not be repeated if results dated before screening are available. Antibody screen need not be repeated if results dated before screening are available, unless the subject was transfused since that time. Results must be available before the first dose of magrolimab.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study (ie, sign the ICF), but are not subsequently treated. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any screening procedure-related AEs.

Individuals who do not meet the criteria for participation (screen failure) may be rescreened (no minimum time is required before rescreening and the number of times a subject can be rescreened is limited to 2). Rescreened subjects should be assigned the same subject number as for the initial screening.

6.0 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

6.1 Description of Study Interventions Administered

Descriptions of the study treatments to be administered are shown in Table 8. ASTX727 and oral decitabine/cedazuridine are often used interchangeably.

Table 8: Oral Decitabine/Cedazuridine and Magrolimab Products Used in the Study

	Single Arm	
	Oral Decitabine/Cedazuridine (also known as ASTX727)[a,b]	**Magrolimab**
Intervention Name	Oral decitabine/cedazuridine	Magrolimab
Type	Drug	Drug
Dose Formulation	Tablet	IV
Unit Dose Strength(s)	35 mg decitabine and 100 mg cedazuridine	1 mg/kg, 15 mg/kg, and 30 mg/kg
Dosage Level(s)	Cycle 1: • One tablet QD on Days 1-5[a] Cycles ≥2: • One tablet QD on Days 1-5[a]	Priming Dose: • 1 mg/kg on Days 1 and 4 • 15 mg/kg on Day 8 • 30 mg/kg on Days 11, 15, followed by weekly administration for 5 doses (on Day 22, Day 29, Day 36, Day 43, and Day 50) Maintenance Dose: • 30 mg/kg on Day 57 and • 30 mg/kg every 14 days thereafter
Route of Administration	PO	IV
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Provided in 5-count opaque high-density polyethylene bottle with child resistant closure. Each bottle labeled per country requirement.	Single-use, 10 mL vials containing 200 mg of the antibody in a formulation of 10 mM sodium acetate, 5% (w/v) sorbitol, 0.01% (w/v) polysorbate 20, at a pH of 5.0.

DLT=dose-limiting toxicity; IV=intravenous; PO=by mouth; QD=once daily; w/v=weight by volume

a. ASTX727 and oral decitabine/cedazuridine are often used interchangeably.

b. Dosing may be modified if DLTs are observed in the DLT cohort.

6.2 Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained at the study center for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only subjects enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

Store oral decitabine/cedazuridine tablets at room temperature at 20°C to 25°C (68°F to 77°F); excursions from 15°C to 30°C (59°F to 86°F) are permitted. Excursions for ≤7 days at temperatures >30°C (86°F) and ≤40°C (104°F) are not expected to affect the strength or stability; however, excursions at these temperatures for >7 days may impact investigational medicinal product (IMP) quality depending upon severity. Excursion at temperatures <15°C (59°F) or >40°C (104°F) for any amount of time will impact IMP quality. For those temperature excursions that impact IMP quality, the IMP should be quarantined and stored at the recommended temperature, while the Astex staff is contacted for further instructions.

Instructions regarding transport from pharmacy to home and at-home storage instructions should be given to the study subject, as applicable.

Magrolimab is supplied in single-use, 10 mL vials containing 200 mg of the antibody in a formulation of 10 mM sodium acetate, 5% (weight by volume) sorbitol, 0.01% (weight by volume) polysorbate 20, at a pH of 5.0.

The labeling complies with the requirements of the applicable regulatory agencies. Vials containing magrolimab should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) in an appropriate, locked room and/or locked refrigerator, accessible only to pharmacy personnel or a duly designated person. Magrolimab should not be frozen. Protect from light during storage. DO NOT SHAKE.

Additional details about oral decitabine/cedazuridine and magrolimab are provided in the Pharmacy Manual.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

This study is not blinded or randomized; therefore, bias may occur. To minimize bias, response assessments to determine efficacy will be assessed by the investigator and calculated using a pre-specified program based on the 2006 IWG criteria (Section 10.6) and methods to assess CR as described in 2006 (Cheson et al 2006), as defined in Table 21 and Table 22.

6.4 Study Intervention Compliance

Subject compliance with oral decitabine/cedazuridine will be assessed at time points defined in the SoA (Table 1). Compliance will be assessed by direct questioning, counting returned tablets, and reviewing subject's dosing diaries. Deviation(s) from the prescribed dosage regimen should be recorded in the subject's dosing diary.

Treatment start and stop dates, including dates and reasons for treatment interruption and/or dose modifications will also be recorded in the electronic case report form (eCRF).

6.5 Premedication

Premedication is required prior to the administration of magrolimab through the Day 22 infusion of priming and repriming. Premedications may be continued based on the treating physician's clinical judgment and the presence/severity of prior infusion-related reactions. In the case of a Grade 3 infusion-related reaction, a premedication regimen for subsequent infusions is required (Section 8.5.7.2).

Premedications are oral acetaminophen 650 mg to 1000 mg and oral or IV diphenhydramine 25 mg to 50 mg or comparable regimen. If less than 4 hours have elapsed since a prior dose of acetaminophen has been given, the dose of acetaminophen premedication may be omitted.

These premedications are to be entered as concomitant medications.

6.6 Dose Modification

6.6.1 Oral Decitabine/Cedazuridine Dose Modifications

In the event of toxicity that prevents initiation of a subsequent cycle containing oral decitabine/cedazuridine, the first intervention is dosing delay rather than dosing reduction. Subsequent cycles should be delayed in subjects with an absolute neutrophil count ≤500 cells/µL, until recovery to >500 cells/µL. Delays of up to 2 weeks are acceptable without a change in dosing. The planned dosing of oral decitabine/cedazuridine may be reduced for individual subjects in the event of unacceptable treatment-related toxicity or delay in initiating a treatment cycle (eg, an AE that meets the definition of a DLT) as assessed by the investigator (Section 8.5.6), and should be reduced based on the guidelines outlined in Table 9.

When delays are required, the following parameters should be followed:

- If dosing of oral decitabine/cedazuridine is delayed more than 3 days prior to Day 15, then the next dosing of oral decitabine/cedazuridine will be further delayed to align with the next dose of magrolimab.
- If oral decitabine/cedazuridine is delayed to Day 15 of a cycle, then that cycle length will be increased to 42 days. The next cycle will start 28 days after Day 15.

- If oral decitabine/cedazuridine is delayed beyond 15 days into a cycle, then administration of oral decitabine/cedazuridine will be held for that cycle.

Table 9: Dosing Reduction Guidelines for Oral Decitabine/Cedazuridine

Number of Dose Reductions per Individual Subject	Dose per Cycle
Level 1	Oral decitabine/cedazuridine Daily×5 for each 28-day cycle
Level 2	Oral decitabine/cedazuridine Daily×4 for each 28-day cycle
Level 3	Oral decitabine/cedazuridine Daily×3 for each 28-day cycle
Level 4	Oral decitabine/cedazuridine on Days 1, 3, and 5 of each 28-day cycle
Level 5	Discontinue oral decitabine/cedazuridine

DLT=dose-limiting toxicity

Note: For subjects receiving oral decitabine/cedazuridine outside of the period of DLT assessment in the DLT cohort, a maximum of 2 dose reductions are allowed before study treatment must be permanently discontinued.

6.6.2 Magrolimab Dose Modifications

In clinical experience with magrolimab, no significant dose-dependent toxicities have been identified. Therefore, in general, dose modifications or delays to magrolimab should not be made. The dose of magrolimab may be reduced for Grade ≥3 AEs that are deemed clearly related to magrolimab and not oral decitabine/cedazuridine and that do not resolve to Grade ≤2 or baseline value within 14 days of onset. However, dose delay of magrolimab should occur first, and if the AE does not resolve, then a magrolimab dose reduction can be considered (Section 6.6.2.1). If there is a delay of dosing of magrolimab during a cycle of oral decitabine/cedazuridine, the cycle can be extended by up to 14 days to allow for dosing of the study drug(s) on Day 1 of the subsequent oral decitabine/cedazuridine cycle. The Medical Monitor should be notified of any planned dose delays.

If a magrolimab dose reduction is considered, an initial 33% dose reduction (from 30 to 20 mg/kg) should be done first. If no improvement is observed within at least 28 days, further magrolimab dose reductions from 20 to 15 mg/kg may be warranted. For persistent BM hypocellularity or peripheral cytopenias (where both oral decitabine/cedazuridine and magrolimab may have a contribution), the dose of oral decitabine/cedazuridine should be reduced first. Subjects can re-escalate to higher doses of magrolimab up to the original 30 mg/kg dose if AEs improve, after discussion with the sponsor's Medical Monitor.

6.6.2.1 Repriming for Magrolimab

Given the large CD47 antigen sink on normal cells, subjects who have a dose delay of magrolimab equivalent to 28 days or more are required to be reprimed with magrolimab to resaturate the CD47 antigen sink. Within 24 hours prior to each of the repriming doses of magrolimab, all subjects must have a documented Hgb ≥9 g/dL. Subjects who do not meet these criteria must be transfused and

have their Hgb rechecked to meet the minimum Hgb threshold prior to each of the first 2 doses of magrolimab. During the first 2 doses of repriming, blood testing of Hgb will be required 3 to 6 hours after a magrolimab dose and the results must be reviewed prior to discharging the subject from clinic. The subject should be transfused as clinically appropriate.

Repriming differs depending on where the participant is in their treatment period as follows:

1) For subjects who have not reached Day 57 of magrolimab, up to 14 days between doses is permitted.
2) For subjects who have received Day 57 (or beyond) dose of magrolimab, up to 28 days between doses is permitted.

After Day 22 of repriming, subjects should return to their original maintenance dose schedule.

Please notify the Medical Monitor of any planned dose delays.

6.6.3 Temporary Discontinuation of Oral Decitabine/Cedazuridine

Study drug dosing should be withheld anytime a toxicity would have qualified as a DLT (Section 8.5.6). Dosing may resume, at the investigator's discretion, if and when the following conditions are met:

- When study treatment-related toxicity has:
  - Completely resolved or returned to baseline (all AEs), or
  - Partially recovered to Grade 2 or less (anemia, fatigue, malaise, alopecia), or
  - Partially recovered to Grade 1 or less (all other toxicities)

If toxicity, other than cytopenias, has not resolved as described above within 21 days, the investigator should consider permanently discontinuing study treatment.

If cytopenia-related toxicity has not resolved as described above within 42 days, the investigator should consider permanently discontinuing study treatment.

If and when dosing is resumed following an oral decitabine/cedazuridine-associated DLT, the individual's dosing of oral decitabine/cedazuridine should be adjusted to the next lower dose and should follow what is outlined in Section 6.6.

6.7 Missed or Vomited Doses

Oral decitabine/cedazuridine

If a dose is missed within 12 hours of the time it is usually taken, the subject should take the missed dose as soon as possible. If a dose is missed by more than 12 hours, the subject should not take the

missed dose. In either scenario, the subject should resume the usual dosing schedule the next day and proceed with completing the full 5 days (unless previously adjusted) of treatment per cycle.

If the subject vomits after dosing, the vomiting episode and the time it occurred should be recorded in the dosing diary. No additional dose should be taken that day. The next dose should be taken at the usual time. Investigators should consider pre-medicating the subject with antiemetics if vomiting is anticipated to be a recurring issue.

Magrolimab

If a dose of magrolimab is missed, it should be given as soon as possible. If delayed by more than 3 days (excluding priming or repriming), the timing of subsequent doses needs to be reset so that the subsequent dose is offset by the appropriate number of days. If there is a delay of magrolimab dosing then oral decitabine/cedazuridine dosing should be delayed to align the 2 study drugs (See Section 6.6.2).

6.8 Treatment of Overdose

For this study, any administered dose of magrolimab or oral decitabine/cedazuridine greater than the assigned daily dose defined in the treatment administration (Section 6.1) will be considered an overdose. A dose given on a day that is not prescribed by the protocol is also considered an overdose. Based on the clinical experience of decitabine, an overdosage of oral decitabine/cedazuridine may result in more profound or prolonged myelosuppression and its consequences such as infection, or bleeding, or GI toxicity, and subjects should be managed accordingly. Based on the clinical experience of magrolimab, there is no known or expected effect from a single overdose of magrolimab. There is no specific treatment for an overdose with oral decitabine/cedazuridine alone or in combination with magrolimab.

In the event of an overdose:

- Inform the Astex medical monitor immediately.
- Closely monitor the subject for AEs/serious adverse events (SAEs) and laboratory abnormalities.
- Obtain a plasma sample for PK analysis.
- Record the actual dose of study drug administered in the source document and on the Dosing eCRF page.
- Record any adverse clinical signs and symptoms associated with an overdose on the AE eCRF page.
- Report signs and symptoms of an overdose that meet SAE criteria (Section 10.5.2) to Astex on the SAE form within 24 hours (Section 10.5.4).
- Treat any AE (including SAE) based on SOC for the specific signs and symptoms.

- Record as a protocol deviation.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Astex medical monitor based on the clinical evaluation of the subject.

6.9 Concomitant Therapy

All medications a subject takes, starting from 14 days before first dose administration and ending 30 days after the last dose of study treatment, including supportive or palliative treatment (see below) whether prescription or over-the-counter, vitamin and mineral supplements, herbs, and medications taken for procedures (eg, biopsy) should be reported on the Concomitant Medication eCRF. This reporting includes antacids, proton pump inhibitors, H_2 antagonists and cold medications. The following information is expected: medication name, start/stop dates, and indication for use. Medications used for premedication before infusion should be entered and noted as premedications.

6.9.1 Supportive, Prophylactic, or Other Treatments Allowed

Premedication is permitted while on study treatment (Section 6.5). Localized non-CNS radiotherapy, erythroid and/or myeloid growth factors, hormonal therapy with luteinizing hormone-releasing hormone agonists for prostate cancer, and treatment with bisphosphonates receptor activator of nuclear factor kappa beta inhibitors are permitted. Blood transfusions are permitted during screening or before first dose administration to ensure adequate Hgb levels. Blood transfusions are also permitted during the study as clinically indicated for management of cytopenias. On-study blood transfusion should be reported in the dedicated transfusion eCRF. Hydroxyurea (up to 4 g/day) can be used during the first 56 days to reduce the WBC to $\leq 20 \times 10^3/\mu L$. In nonclinical studies, coadministration of magrolimab and hydroxyurea in human leukemia engrafted immunodeficient mice did not cause phagocytosis of normal BM cells, suggesting limited on-mechanism toxicity in subjects. No gross safety abnormalities were observed in these nonclinical studies. While no formal analyses have been performed in clinical studies no significant safety concerns have been observed in subjects who have received concomitant magrolimab and hydroxyurea.

6.9.2 Prohibited Medications/Therapies

Prohibited concomitant therapies while on study are as follows: CNS or systemic radiation therapy, chemotherapy, immunotherapy, or any experimental therapy. Drugs and supplements that are metabolized by cytidine deaminase should be used with caution or held on days when oral decitabine/cedazuridine is administered.

Vaccination with live vaccines is prohibited while subjects remain on study treatment.

6.9.3 Rescue Medicine

There is no specific rescue medication that would be considered standard as this differs by subject disease and by regional or institutional standards. If a subject develops progressive disease while on treatment or the treatment is not tolerated, subjects should permanently discontinue treatment. Any subsequent or rescue therapy will be based on individual case and local site standards of management.

6.9.4 COVID-19 Vaccine

COVID-19 vaccines should not be considered investigational agents for the purposes of this study; approved and authorized COVID-19 vaccines should be listed as concomitant medication and entered in the electronic record as such (Desai et al 2021).

6.10 Study Treatment After the End of the Study

The investigator is responsible for ensuring that consideration is given for poststudy care of the subject's medical condition whether Astex is providing specific poststudy treatment or not. As defined in Section 4.7, the sponsor provides the opportunity to continue treatment with the study drugs through expanded access, or the local equivalent, and collect, at a minimum, safety information from subjects who are still deriving benefit from continued treatment, until the subject is withdrawn from study treatment, or the treatment is commercially available for this indication.

7.0 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Permanent Discontinuation of Study Treatment

It may be necessary for a subject to permanently discontinue study treatment. Treatment discontinuation refers to the discontinuation of both oral decitabine/cedazuridine and magrolimab. If study treatment is permanently discontinued, the subject will remain in the study to be evaluated for safety and long-term health status. See the SoA for data to be collected at the time of treatment discontinuation (Table 1 and Table 2).

A subject may choose to permanently discontinue study treatment at any time (described in further detail in Section 7.2). In addition, subjects may be required to permanently discontinue study treatment at any time for the following reasons:

- Investigators can discontinue subjects from study treatment in case of unacceptable toxicity, non-compliance, disease progression, or if the investigator determines it is in the subject's best interest.
- Astex Pharmaceuticals may require that a subject is discontinued from treatment for safety reasons or for noncompliance.
- Any female participant who becomes pregnant while participating in the study will permanently discontinue study treatment.

In all cases, the reason(s) for discontinuation from study treatment must be recorded in the source document and on the relevant page of the subject's eCRF.

At the time of permanent discontinuation of treatment, a Treatment Discontinuation Visit should be conducted, as detailed in the SoA (Table 1 and Table 2). At minimum, subjects should be followed up for safety until 30 days after the last dose of study treatment.

Every effort must be made to undertake protocol specified follow-up procedures. For subjects willing to continue study follow-up procedures, the investigator should review the follow-up procedures with the subject, including the number of visits, the specific procedures to be done, and the total length of the follow-up period.

7.2 Subject Discontinuation/Withdrawal From the Study

A study subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for behavioral, compliance, or administrative reasons. This is expected to be uncommon. It is important to distinguish between the decision for a subject to permanently discontinue treatment and the decision for a subject to withdraw completely from the study. The term study withdrawal/withdrawal of consent should only be restricted to those subjects who wish to completely withdraw from the study and stop all study follow-up procedures including long-term follow-up that may be conducted remotely. A subject’s decision to discontinue treatment or discontinue certain follow-up procedures IS NOT considered study withdrawal.

In all cases, the reason(s) for withdrawal from study must be recorded in the source document and on the relevant page of the subject's eCRF.

- The investigator must also ensure the subject understands that his or her medical records will continue to be available for the follow-up period as described in the approved ICF for the entire study period.
- If a subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Additionally, if a subject withdraws consent from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records and inform the sponsor within 24 hours.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a study subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the study subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1 and Table 2). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Biological samples which are collected as part of routine medical care or as part of protocol procedures may be stored and analyzed as part of secondary endpoint analysis (eg, genetic, PK) and will follow all applicable local regulatory guidelines.

8.1 Demographics, Medical History, and Prior Anticancer Therapy

Demographic data will be recorded at screening. Investigators will obtain subject's relevant medical and surgical history including date [month (if available) and year], and prior anticancer therapies (including best response) at screening, using the investigator's best judgement, and record it on the appropriate medical history eCRF page.

8.2 Safety Assessments

Planned time points (including the visit windows) for all safety assessments are provided in the SoA (Table 1 and Table 2).

8.2.1 Physical Examinations

A complete and/or symptom directed physical examination (PE) will be performed per the SoA (Table 1). A complete PE will be performed per the institutional standard practice, and at a minimum should include assessment of the cardiovascular, respiratory, GI, lymphatics, skin, and neurological systems at screening, predose on Cycle 1 Day 1, and at treatment discontinuation. For subjects who had a complete PE performed at screening within 3 days before the first dose of study drug(s), it is not necessary to repeat the complete PE on Cycle 1 Day 1; a symptom-directed PE on Cycle 1 Day 1 can be done instead. A symptom directed PE will be performed at all other time points detailed in the SoA (Table 1). If the subject has no subjective complaints, a symptom-directed PE is not necessary and should be noted as such in the eCRF. Height and weight will also be measured before study treatment at visits specified in the SoA. The symptom-directed PE can be performed the day before the visits if more convenient.

8.2.2 Vital Signs

On magrolimab dosing days and on Day 1 of any cycle of oral decitabine/cedazuridine, all vital signs will be measured **predose** per the institutional standard practice at the time points outlined in the SoA (Table 1 and Table 2). On non-dosing days (Table 1 and Table 2), vital signs measurements should be conducted per institutional standard practice. Vital signs to be measured are resting systolic and diastolic blood pressure, resting heart rate, resting respiration rate, oxygen saturation, and body temperature. In addition to the vital signs measured predose on Cycle 1 Day 1, systolic and diastolic blood pressure and heart rate will also be obtained 2 hours (±30 minutes) **postdose** on Cycle 1 Day 1.

The date and time of collection and measurements will be recorded on the appropriate eCRF.

8.2.3 Twelve-lead Electrocardiograms

Twelve-lead electrocardiogram (ECG) will be obtained predose and at the time points indicated in the SoA (Table 1) using an ECG machine that automatically calculates the heart rate and measures RR interval, PR segment, QRS duration, and QT duration. Postdose ECGs will also be obtained during PK assessment per Section 8.4.

Electrocardiograms will be read locally and ECG parameters including clinical interpretation will be recorded in the eCRF.

8.2.4 Clinical Safety Laboratory Assessments

The list of clinical safety laboratory tests (including serum/plasma chemistry, hematology, and urinalysis) to be performed in this study are detailed below.

Hematology must include complete blood count (CBC) with either manual or automated differential and platelet counts. If manual and automated differentials are done, the manual counts will be entered into the eCRF. Urinalysis includes dipstick test (if available).

If sites do not have the capability to perform extended RBC genotyping or phenotyping analysis, samples will be sent to the central laboratory for RBC genotyping.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Pregnancy testing should be conducted as detailed in Table 1 (a serum test [from whole blood] is required at screening; serum or urine testing may be used at subsequent time points, as required by local regulations). Testing should also be conducted at the end of relevant systemic exposure plus an additional 30 days and correspond with the time frame for female participant contraception in Section 5.1.

Analytes to be assessed by the local laboratory or specialty laboratories at screening are presented in Table 10.

Table 10: Laboratory Analyte Listing (To Be Performed at Screening)

Chemistry (Serum or Plasma)	Hematology	Urinalysis	Other Laboratory Measurements
Sodium	RBC	RBC	Pregnancy test (serum at screening)
Potassium	Hgb	Glucose	
Chloride	Hematocrit	Protein	Blood phenotyping or blood genotyping
Bicarbonate	Platelets	Urine pH	
Total protein	WBC	Ketones	
Albumin	Neutrophils	Bilirubin	Type and screen (ABO/Rh)
Calcium	Eosinophils	Urine specific gravity	
Magnesium	Basophils		DAT
Phosphorus	Lymphocytes		
Glucose	Monocytes		ADA
BUN or urea	Reticulocytes		
Creatinine	Haptoglobin		Hepatitis B and hepatitis C assessments: HBsAg, anti-HBc, HCV antibody; HBV DNA and HCV RNA (as required)
Uric acid	PT		
Total bilirubin	INR aPTT or PTT		
Direct bilirubin	PB smear		
Indirect bilirubin			
LDHAST (SGOT)			HIV antibody (if clinically indicated)
ALT (SGPT)			Molecular study to determine IPSS-M, including p53 status[a]
Alkaline phosphatase			

ABO=any of the 4 blood groups (A, B, AB, and O); ADA=antidrug antibody; ALT=alanine aminotransferase; anti-HBc=antibody against hepatitis B core antigen; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; DAT=direct antiglobulin test; HBV=hepatitis B virus; HCV=hepatitis C virus; HBsAg=hepatitis B surface antigen; Hgb=hemoglobin; HIV=human immunodeficiency virus; INR=international normalized ratio; IPSS-M=Molecular International Prognostic Scoring System for myelodysplastic syndromes; LDH=lactate dehydrogenase; PB=peripheral blood; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; Rh=Rhesus factor; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; WBC=white blood cell.

Note: Refer to the Schedules of Activities (Table 1 and Table 2) for collection time points.

[a] Please see Section 10.4 for further details on the molecular markers used for IPSS-M.

Analytes to be assessed by the local laboratory or specialty laboratories during the study are presented in Table 11.

Table 11: Laboratory Analyte Listing (To Be Performed During the Study)

Chemistry (Serum or Plasma)[a]	**Hematology**	**Other Laboratory Measurements**
Sodium	RBC	Pregnancy test[c]
Potassium	Hgb	PK[d]
Chloride	Platelets	ADA[d]
Bicarbonate	WBC	Cytogenetics
Albumin	Neutrophils	MRD[d,e]
Glucose	Lymphocytes	
BUN or urea	Reticulocytes	
Creatinine	Haptoglobin[b]	
Total bilirubin	PB smear	
Direct bilirubin	Peripheral blasts	
Indirect bilirubin		
LDH[b]		
AST (SGOT)		
ALT (SGPT)		
Alkaline phosphatase		

ABO=any of the 4 blood groups (A, B, AB, and O); ADA=antidrug antibody; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; DAT=direct antiglobulin test; Hgb=hemoglobin; IEC=Independent Ethics Committee; INR=international normalized ratio; IRB=Institutional Review Board; LDH=lactate dehydrogenase; MRD=minimal residual disease; PB=peripheral blood; PK=pharmacokinetic(s); RBC=red blood cell; Rh=Rhesus factor; SAE=serious adverse event; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; SOC=standard of care; ULN=upper limit of normal; WBC=white blood cell.

Note: Refer to the Schedules of Activities (Table 1 and Table 2) for collection time points.

[a] All events of ALT ≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and INR >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[b] Collection of LDH and haptoglobin is not required after Day 29 except during repriming cycles.

[c] Pregnancy testing after screening can be performed on either urine or serum based on local preferences and testing requirements of local regulation or Institutional Review Boards/Independent Ethics Committees.

[d] This assay will be performed at a central laboratory.

[e] Information on MRD will be collected from sites per SOC.

8.2.5 Pregnancy Testing

Pregnancy testing will be performed at the time points indicated in the SoA (Table 1) for women of childbearing potential only. A serum test is required at screening; serum or urine testing may be used at subsequent time points, as required by local regulations. Results must be reviewed prior to dosing and must be recorded in the eCRF.

8.2.6 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group PS scores are detailed in Table 12 and will be recorded per the SoA (Table 1). The timing and frequency of ECOG performance score assessments are detailed in the SoA (Table 1) and can be performed on the day before the visit if more convenient.

Table 12: Eastern Cooperative Oncology Group Performance Status

Score	ECOG Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: ECOG Performance Status — https://ecog-acrin.org/resources/ecog-performance-status/ (accessed 10 August 2022)

8.3 Efficacy Assessments

Efficacy (response) assessments should be performed within the prespecified windows indicated in the SoA (Table 1).

8.3.1 Disease Response Assessment

Disease assessment will follow IWG 2006 criteria (Section 10.6) and will include CR, HI, and ORR (including CR, mCR, or any HI). Other assessments will include duration of PFS, LFS, undetectable disease assessed by MRD, DOR, and OS. Disease response assessment will be determined based on BM evaluations and a corresponding PB sample along with transfusion requirements. Bone marrow evaluations must include aspirate (when feasible), biopsy, and cytogenetics. If hematologic recovery is in progress, a repeat CBC may be done no more than 7 days after the BM evaluation for response assessment. The BM biopsy and aspirate procedure will be conducted according to local standard practice at time points shown in the SoA (Table 1).

BM and PB samples adequate for analysis must be obtained in order to confirm response. BM biopsy and aspirate and a CBC must be repeated if the BM and/or PB sample are not interpretable by the investigator. A local laboratory will be used to assess BM and PB samples. BM samples should be Wright Giemsa or May Grunwald Giemsa stained. Detailed instructions for processing BM samples will be provided in the Laboratory Manual.

BM evaluations should be performed at screening and on Day 1 of every cycle (or within a 3-day window prior to Day 1) until an mCR is achieved (BM myeloblasts ≤5% and decrease by ≥50% over pretreatment). If an mCR is achieved, without meeting CR criteria, a follow-up BM evaluation should occur on Day 1 of the next cycle (or within a 3-day window prior to Day 1) to assess or confirm the possibility of CR. Thereafter, BM evaluation may occur as clinically indicated to monitor DOR as appropriately guided by PB counts after achieving a confirmed CR

but should occur at least every 3 cycles for the first year, then as clinically indicated. Results do not have to be fully available to start study treatment for that cycle.

Response will be assessed by the investigator and derived programmatically based on the 2006 IWG criteria (Cheson et al 2006). Further details of the IWG criteria can be found in Section 10.6.

8.3.2 Long-term Follow-up

Beginning 3 months after the 30-day Safety Follow-up visit (for subjects who permanently discontinued treatment), subjects will be followed in long-term follow-up for health status information, which will be gathered every 3 months (±2 weeks) until death, the subject withdraws consent, the subject is lost to follow-up, or the study ends, whichever occurs first. Long-term follow-up may be accomplished through a telephone call to the subject or next of kin, contact with the local treating physician, or medical record review. If the subject did not have disease progression prior to treatment discontinuation, the absence of disease progression should be monitored according to standard practice during long-term follow-up contact. For subjects who discontinued treatment before documented disease progression and have a telephone visit, they should be asked if they have had disease progression (bone marrow blast count ≥5% and MDS conversion to AML) or any transfusion requirements since last contact. Follow-up contact will also permit BM biopsy reports to be obtained from subjects that discontinue treatment to receive an SCT, allowing efficacy to be followed at this stage. The investigator or designee should record the subject's survival status in the eCRF. Date of death may be collected and recorded in the EDC system from public sources in cases of subjects who withdraw consent or who are lost to follow-up. In the event of death, a death form detailing the primary cause of death must be completed for the subject.

8.4 Pharmacokinetics

PK samples will be collected as described in the SoA (Table 1 and Table 2) and evaluated for magrolimab and oral decitabine/cedazuridine concentrations. Serum magrolimab and plasma decitabine and cedazuridine assessments will be done using validated assays. This could include using leftover serum for alternative PK assay development and analysis.

Table 13 shows the schedule for PK sample collection for serum magrolimab and Table 14 shows assessments for oral decitabine/cedazuridine (for determination of plasma levels of decitabine and cedazuridine). PK collections for oral decitabine/cedazuridine require special pretreatment with tetrahydrouridine (THU, for stabilization) of blood collection tubes and details for this procedure will be included in the Laboratory Manual.

Table 13: Serum Collection Schedule for Pharmacokinetic Analysis and Antidrug Antibodies (ADA) for Serum Magrolimab

Day	Dosing Day?	Predose	End of Infusion[a]
Day 1	Yes	✓	
Day 50	Yes	✓	
Day 57	Yes	✓	✓ (PK Only)
Day 141	Yes	✓	
End of treatment	NA	✓	

NA=not applicable; PK=pharmacokinetic(s).
Note: ✓=PK blood sample is to be collected at the indicated time point.
[a] Magrolimab should be infused over 3 hours (±30 minutes).

Table 14: Plasma Collection Schedule for Pharmacokinetic Analysis for Oral Decitabine/Cedazuridine

Day	Dosing Day?	Predose[b]	Hours Postdose
Cycle 1 Day 1	Yes	NA	2.0 (±30 minutes)[c,d]
Cycle 1 Day 4[a,e]	Yes	✓[c]	0.5 (±5 minutes), 1.0 (±5 minutes)[c,d], 1.5 (±5 minutes), 2.0 (±30 minutes)[c,d], 3.0 (±10 minutes), 4.0 (±10 minutes)[c,d], 6.0 (±20 minutes), 8.0 (±30 minutes)
Cycle 1 Day 5[e]	Yes	Predose (24 ±1.0 hours after Cycle 1 Day 4 dose)[c]	
Cycle 2 Day 4[e]	Yes	✓[c]	1.0 (±30 minutes)[b,c], 2.0 (±30 minutes)[c,d], 4.0 (±60 minutes)[c,d]
Ad-hoc PK sample	NA	NA	Optional (if needed)

ECG=electrocardiogram; NA=not applicable; PK=pharmacokinetic(s).
Notes: ✓=PK blood sample is to be collected at the indicated time point.
[a] If there are 2 or more dose reductions, then PK should be done on Day 3 and Day 4 instead of Day 4 and Day 5.
[b] On dosing days, predose samples are to be collected within 60 minutes before administration of study treatment.
[c] The PK sample is a time-matched blood sample to be taken immediately following (within 5 minutes) the ECG assessment) as described in Section 8.2.3.
[d] ECG assessment is to be taken postdose at this time point.
[e] If the oral decitabine/cedazuridine dosing level falls below Level 4 (please refer to Table 9 for further details), the timing of PK acquisition at this time point will be adjusted to be 1 day earlier.

8.5 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs or SAEs can be found in Section 10.5.

8.5.1 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Event Information

All AEs and SAEs will be collected from the time the ICF is signed until 30 days after the last dose of study treatment. Any clinically significant findings that begin before the start of study treatment but after the ICF is signed will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not in the AE section. However, if the event is related to a screening procedure it will be captured and recorded as an AE in the eCRF. Any clinically significant finding(s) observed after the start of study treatment will be recorded as an AE in the eCRF.

If the subject starts a new anti-cancer treatment, including a new investigational treatment, the stop date for reporting obligations for this study will be based on whichever occurs earlier (ie, 30 days after the last dose of study drug or initiation of a new anticancer therapy). Details for recording AEs and SAEs are provided in Section 10.5.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours after the investigator is aware of the SAE, as indicated in Section 10.5. The investigator will submit any updated SAE data to the sponsor within 24 hours of the data becoming available.

Investigators are not obligated to actively seek AE or SAE information ≥30 days after the last dose of study treatment. However, if the investigator becomes aware of an SAE or of a death at any time beyond 30 days after the last dose, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor as described in Section 10.5.4.

8.5.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.5.

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the study subject is the preferred method to inquire about AE occurrences (such as “Have you had any new symptoms, injuries, illnesses since your last visit?”).

8.5.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until clinically relevant information is complete and reported to the sponsor; details are provided in Section 10.5.3.

Additional information for follow-up requirement of AEs/SAEs is provided in Section 10.5.3.

8.5.4 Regulatory Reporting Requirements for Serious Adverse Events

- The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- Investigator safety reports must be prepared by the sponsor or sponsor's designee for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5 Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of study treatment and until 180 days plus 5 half-lives of magrolimab (70 days), totaling 250 days (approximately 8.5 months), after the last dose of either study treatment. Details of pregnancies in female partners of male subjects will be collected after the start of study treatment and until 90 days plus 5 half-lives of magrolimab (70 days), totaling 160 days (approximately 5 months), after the last dose of either study treatment.
    - Magrolimab has a longer half-life than oral decitabine/cedazuridine, which forms the basis of the requirements above.
- If a pregnancy is reported, the investigator should follow the procedures outlined in Section 10.2.

The investigator should counsel any female subject with a positive pregnancy test after the start of treatment, discussing any risks of continuing the pregnancy and any possible effects on the fetus. The investigator will record any occurrence of pregnancy on the Pregnancy Exposure Report Form Part I and email to Astex Clinical Safety and Risk Management (CS&RM; **drugsafety@astx.com**). After the outcome of the pregnancy, collect information by completing the Pregnancy Exposure Report Form Part II.

8.5.6 Definition of Dose-limiting Toxicities

Dose-limiting toxicities are defined as any of the following toxicities at least possibly related to the treatment regimen as determined by the DSRC:

- Drug-related Grade ≥3 non-hematologic events (except nausea, vomiting, or diarrhea if the events do not require tube feeding, total parenteral nutrition, or require or prolong hospitalization).
- Grade 4 neutropenia and thrombocytopenia, not present prior to dosing, that last 28 days or longer should be considered a DLT unless clearly and solely due to the underlying disease.

- If the investigator suspects that the development of Grade 4 neutropenia or thrombocytopenia is drug related and the event continues for 7 days in Cycle 1, a BM assessment (no later than the 14th day of Grade 4 cytopenia) may be done, at the discretion of the investigator, to assist with the determination of DLT.

- Delay of >2 weeks after Cycle 1 is complete due to drug-related toxicity. That is, if initiation of Cycle 2 is delayed for drug-related toxicity, the DLT window will expand accordingly.
- Establishment of an MTD is not a goal of this study. However, the DSRC will assess the occurrence of DLTs in the DLT cohort (Section 4.1.1) to help ensure the study drug combination is safe. The DLT period has been defined as the first 2 cycles of oral decitabine/cedazuridine (from the start of administration to Cycle 1 Day 28) in the first 6 to approximately 18 subjects.

8.5.7 Specific Safety Management Guidelines

8.5.7.1 Anemia, Blood Cross-matching, and Packed Red Blood Cell Transfusion Procedures

Magrolimab binds to RBCs and leads to erythrophagocytosis. In clinical studies, anemia is the most common treatment-related AE and is typically manifested as a decline in Hgb observed in the first 1 to 2 weeks of treatment. Subjects with low baseline Hgb level, especially those with cardiac history, should be monitored closely after initial administrations of magrolimab as preexisting anemia could be exacerbated. In general, a Hgb level of at least 9.5 g/dL or higher for subjects with cardiac comorbidities prior to the first magrolimab dose is recommended. Hgb ≥9 is required prior to the first two doses in priming and repriming of magrolimab. Red blood cell transfusions are permitted prior to study treatment to ensure adequate Hgb level. This, coupled with anemia from other causes in participants with cancers, means that care has to be taken with RBC cross-matching and packed RBC transfusions. There is a possibility that treatment with magrolimab may obscure assessment of RBC phenotyping, although this has not been observed in the subjects treated to date.

Prior to initiation of magrolimab, extended RBC phenotyping or genotyping for minor antigens, type and screen (ABO/Rh), and DAT will be performed for each subject as described in Section 5.3.3. This, together with using the prior phenotype, will facilitate allocation of properly matched blood, should a blood transfusion be warranted.

8.5.7.2 Management of Infusion-related Reactions

Infusion-related reactions are defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0 (under the category “General disorders and administration site conditions”) as “a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances” (Section 10.5). For the purposes of this study, the time frame for infusion-related reaction assessment is the 24-hour period beginning from the start of the infusion. Premedication use described in Section 6.5 will be used to manage infusion-related reactions preemptively.

Recommendations for the management of infusion-related reactions are provided below.

- For Grade 1 infusion-related reactions, described as mild transient reaction, infusion interruption is not indicated, and intervention not indicated.
  - Remain at bedside and monitor participant until recovery from symptoms.
- For Grade 2 infusion-related reaction, infusion interruption is indicated, but participant responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids), and prophylactic medications are indicated for ≤24 hours:
  - Stop the magrolimab infusion, begin an IV infusion of normal saline, and consider treating the participant with diphenhydramine 50 mg IV (or equivalent) and/or 500 mg to 750 mg of oral acetaminophen.
  - Remain at bedside and monitor participant until resolution of symptoms.
  - Corticosteroid therapy may also be given at the discretion of the investigator.
  - If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate.
  - If no further complications occur after 1 hour (± 10 minutes), the rate may be increased to 100% of the original infusion rate. Monitor the participant closely.
  - If symptoms recur, stop infusion and disconnect participant from the infusion apparatus. No further magrolimab will be administered at that visit.
  - Premedications should be considered before any future infusions.
  - The amount of magrolimab infused must be recorded on the eCRF.
  - Participants who experience a Grade 2 infusion-related reaction during the postinfusion observation period that does not resolve to ≤ Grade 1 during that time should be observed until the AE resolves or stabilizes, with vital sign measurements as medically indicated for the management of the AE.
- For Grade 3 or Grade 4 infusion-related reaction, where Grade 3 is described as prolonged infusion-related reactions (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion), or recurrence of symptoms following initial improvement, or where hospitalization is indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) and Grade 4 is described as having life-threatening consequences and where urgent intervention is indicated.
  - Immediately discontinue infusion of magrolimab.
  - Begin an IV infusion of normal saline and consider treating the participant as follows: Administer bronchodilators, epinephrine 0.2 mg to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 mg to 0.25 mg of a 1:10,000 solution injected slowly

for IV administration and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.

- The participant should be monitored until the Investigator is comfortable that the symptoms will not recur.
- Participants who have Grade 4 infusion-related reactions occurring with the first dose (priming dose) will be permanently discontinued from study treatment.
- Participants who experience Grade 3 or 4 infusion-related reactions must be given premedication prior to subsequent doses. In this setting, premedication with oral acetaminophen (650 mg to 1000 mg), oral or IV diphenhydramine (25 mg to 50 mg), and IV dexamethasone (4 mg to 20 mg), or a comparable regimen, is recommended for the subsequent 2 doses. Continued premedication with corticosteroids beyond these 2 doses may be administered at the discretion of the treating physician.
- Participants who receive premedication and still experience a Grade 3 or 4 infusion-related reaction will be permanently discontinued from the study treatment.
- For anaphylaxis, investigators should follow their institutional guidelines for treatment.
- All participants with Grade 3 or greater infusion-related reactions will be observed until the AE resolves or stabilizes, with vital sign measurements and additional evaluations as medically indicated for the management of the AEs.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

The CR rate with HMA monotherapy varies between studies and depends on severity of disease with an estimated overall range of approximately 10% to 20%. In Study ASTX727-02, for higher-risk MDS (IPSS-R >3) subjects, the observed CR rate with oral decitabine/cedazuridine was 22% (95% confidence interval [CI] of 14% to 32%).

The combination of magrolimab plus azacitidine seems promising with better efficacy compared to azacitidine monotherapy, including a 50% CR rate, objective response rate of 92%, with an acceptable safety profile, suggesting that this combination offers advantages beyond HMA monotherapy (Garcia-Manero et al 2020). Assuming treatment of higher-risk MDS subjects with HMA oral decitabine and cedazuridine or with azacitidine is similar and that the combination of HMA oral decitabine/cedazuridine with magrolimab will result in a CR rate of approximately 40%, a sample size of approximately 100 subjects will allow for a greater than 80% power to rule out an HMA response rate of 20% (ie, lower bound of the exact 95% CI for the response rate will be greater than 20%). In addition, assuming that the response rate for this study will be approximately 40%, a sample size of approximately 100 subjects will allow for 80% power to estimate a CI with half-width of approximately 10%. This sample size represents a preliminary estimate of the study size, however, the final sample size for the study may be revised based on the final response rate to be observed in the Phase 3 Magrolimab ENHANCE study.

9.2 Analyses Sets

For purposes of analysis, the following populations are defined:

Table 15: Analysis Populations

Population	Description
Enrolled	All subjects who sign an ICF and meet all eligibility criteria as assessed by the investigator and sponsor.
Efficacy	All subjects who receive any study treatment.
Safety	All subjects who receive any study treatment.
PK	All subjects who have received study treatment and for whom PK samples were collected and successfully analyzed.

ICF=informed consent form; PK=pharmacokinetic

9.3 Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to any efficacy assessment (first interim analysis for futility), and it will include a technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.3.1 General Considerations

All efficacy and safety endpoint parameters will be summarized descriptively. Continuous efficacy and safety endpoints will be summarized using the mean, standard deviation, median, minimum, and maximum, 25 and 75 percentiles). Frequency distributions (counts and percentages) will be used to summarize categorical endpoints.

The primary efficacy analysis will be performed using a 2-sided 0.05 significance level. No adjustments for multiple endpoints is planned.

It is anticipated that statistical summaries will be performed using SAS Version 9.4 or higher (SAS Institute, Inc., Cary, NC, USA) or higher. Additional software may be used to produce graphics and for statistical methodology not available in SAS.

9.3.2 Primary Endpoint(s)

The primary efficacy endpoint for this study is the proportion of subjects who achieve CR. Response rate will be based on the investigator assessment for all treated subjects. Exact Clopper-Pearson 95% CI will be presented.

The analysis of duration of CR, ORR, OS, and PFS will be conducted using the Kaplan-Meier method based on subjects who achieved CR. Median duration of CR will be estimated with its 95% CI for each treatment arm based on the Kaplan-Meier method. For the time-to-event

endpoints of the duration of CR and DOR will be based on subjects who achieved ORR. The median duration will be estimated with its 95% CI for each treatment arm.

Analysis for all secondary efficacy endpoints will also be performed by pre-specified subgroups. Details of this analysis will be presented in the SAP.

No formal hypothesis testing will be conducted for any key secondary endpoint.

9.3.3 Other Analysis

PK analyses will be described in the SAP finalized before database lock. The population PK analysis will be presented separately from the main clinical study report.

9.4 Interim Analysis

This is an open-label study. Ongoing analyses to help manage the study and support the DSRC reviews for safety and antitumor activity will be undertaken.

One formal interim assessment of futility is planned after approximately 40 subjects have been treated with the oral decitabine/cedazuridine plus magrolimab and completed a minimum of 6 cycles of treatment. The number of subjects to include in the interim analysis was chosen to minimize the chance of exposing subjects to an ineffective treatment. The expected CR is approximately 40%. However, the expected response rate may be revised once the results of the Phase 3 magrolimab ENHANCE study are available. If the achievement of the expected CR rate is questionable, possible study modification will be discussed with the DSRC.

The decision to continue enrollment will be informed by the observed number of CRs (ie, CRs) and safety of the combination (ie, incidence and severity of adverse events). Table 16 provides the probabilities of observing varying frequency of response under different true response rates for a sample of approximately 40 subjects. For example, observing 8 or fewer responses out of 40 treated subjects would suggest a low likelihood (11% chance) that the true response rate is >30% and 0.6% chance that the true response rate is >40%. On the other hand, observing 14 or more responses out of the 40 treated subjects would suggest a high likelihood (80% chance) that the true response is greater than 30%. Therefore, when 40 subjects are treated and evaluable for response assessment, if 8 or fewer responses are observed, the study will be discontinued.

Similarly, if a two-stage Simon design is implemented to test whether the proportion responding (P) warrants continuation to the next phase (ie, H0: $P \leq 0.2$ versus H1: $P \geq 0.3$), Type I error rate of 0.05, 80% power, and a total sample size of approximately 100 subjects, at the first stage (n approximately 40) the trial should be discontinued if 8 or fewer subjects respond to the treatment. Otherwise, the study will continue to the next stage.

This calculation will be revised once the results of the Phase 3 magrolimab ENHANCE study are available and the true expected response is confirmed.

Table 16: Probabilities of Observing Varying Frequency of Response Under Different True Response Rates (40 Subjects)

		Event Rate			
No. Response (r)	**Probability**	**20%**	**30%**	**40%**	**50%**
8	Prob(no. resp <= r| true p)	0.593	0.111	0.006	0.000
9	Prob(no. resp <= r| true p)	0.732	0.196	0.016	0.000
10	Prob(no. resp <= r| true p)	0.839	0.309	0.035	0.001
11	Prob(no. resp <= r| true p)	0.912	0.441	0.071	0.003
12	Prob(no. resp <= r| true p)	0.957	0.577	0.129	0.008
13	Prob(no. resp <= r| true p)	0.981	0.703	0.211	0.019
14	Prob(no. resp <= r| true p)	0.992	0.807	0.317	0.040
15	Prob(no. resp <= r| true p)	0.997	0.885	0.440	0.077
16	Prob(no. resp <= r| true p)	0.999	0.937	0.568	0.134

Prob=probability; No.=number.

9.5 Toxicity Stopping Rule

Any dosing adjustment made during assessment of DLTs in the DLT cohort will be applied as the dosing schedule for remainder of the study. During the study, a stopping rule for observation of excess toxicity will be implemented. The rate of AEs that would meet the DLT criteria (Section 8.5.6) of the study will be used to establish stopping guidelines for excess toxicity. For the duration of therapy, any event that occurs and is at least possibly related to study treatment, and that meets the criteria set out for DLT, will be counted. Sequential boundaries will be used to monitor the DLT rate (Ivanova et al 2005). Accrual will be halted if excessive numbers of subjects with DLTs are observed, that is, if the number of subjects with DLTs is equal to or exceeds b_n out of n subjects who start Cycle 1. This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 20% for DLTs when the presumed rate of DLTs is equal to approximately 20% (Table 17). In addition to this stopping rule, Astex may stop enrollment and/or terminate the study for safety concerns.

Table 17: Criteria for Excess Toxicity for an Acceptable Dose-limiting Toxicity Rate of 20%

Number of Subjects, n	1	2	3-4	5-7	8-10	11-14	15-17	18-21	22-25	26-28
Boundary, b	-	2	3	4	5	6	7	8	9	10
Number of Subjects, n	29-32	33-36	37-40	41-44	45-48	49-52	53-56	57-60	61-64	65-69
Boundary, b	11	12	13	14	15	16	17	18	19	20
Number of Subjects, n	70-73	74-77	78-81	82-85	86-90	91-94	95-98	99-100		
Boundary, b	21	22	23	24	25	26	27	28		

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the prospective subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative [defined in 21 CFR 50.3 (L)] will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A signed copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

Subjects who are rescreened are required to sign a new ICF.

10.1.4 Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

All data generated in this study required to be publicly available will follow all local and global regulations. Requests to delay submission of study results will follow the appropriate regulatory procedures, if warranted.

Peer reviewed publication(s) of the study results will follow the publication policy detailed in Section 10.1.9.

10.1.6 Data Quality Assurance

- All subject data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues, study treatment storage and accountability, and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Source Documents

- Definition of source data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the study center.

- The goal is to maximize data transmitted directly from source to the EDC system. For data transcribed in the eCRF from source documents, the data must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8 Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further study intervention development.

10.1.9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10 Clinical Trial Insurance

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating study centers upon request.

10.2 Appendix 2: Contraceptive and Barrier Guidance

10.2.1 Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are considered women of nonchildbearing potential:

1) Premenarchal
2) Premenopausal female with 1 of the following:
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.

3) Postmenopausal female
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
      i) A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 follicle stimulating hormone measurement is required.
      ii) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.2.2 Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods[b] That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)

Azoospermia a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.

Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly Effective Methods[b] That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - Oral
  - Injectable
- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

10.2.3 Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy (drugsafety@astx.com). The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Information on any children born will be collected until 1 year of age. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant:

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's pregnancy (drugsafety@astx.com).
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the sponsor. Information on any children born will be collected until 1 year of age. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication, abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death [<20 weeks gestation], stillbirth [>20 weeks gestation], congenital anomalies, ectopic pregnancy), or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor as described in Section 10.5.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
    - Any subject who becomes pregnant while participating in the study will immediately discontinue study treatment.

10.3 Appendix 3: Revised International Prognostic Scoring System for Myelodysplastic Syndromes (IPSS-R)

The Revised International Prognostic Scoring System for myelodysplastic syndromes (IPSS-R) prognostic score values and prognostic risk categories/scores are presented in Table 18 and Table 19, respectively.

The IPSS-R is an algorithm that uses clinical features of subjects with MDS (percentage BM blasts, Hgb, platelets, absolute neutrophil count) and 5 cytogenetic categories (very good, good, intermediate, poor, very poor) to stratify subjects into risk categories, which can then be used to inform appropriate treatment pathways.

Table 18: Revised International Prognostic Scoring System for Myelodysplastic Syndromes Prognostic Score Values

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor
BM blast, %	≤2	-	>2% to <5%	-	5% to 10%	>10%	-
Hemoglobin	≥10	-	8 to <10	<8	-	-	-
Platelets	≥100	50 to <100	<50	-	-	-	-
ANC	≥0.8	<0.8	-	-	-	-	-

"-"= not applicable; ANC=absolute neutrophil count; BM=bone marrow

Source: Greenberg et al 2012

Table 19: Revised International Prognostic Scoring System for Myelodysplastic Syndromes Prognostic Risk Categories/Scores

Risk Category	Risk Score
Very low	≤1.5
Low	>1.5-3
Intermediate	>3-4.5
High	>4.5-6
Very high	>6

Source: Greenberg et al 2012

10.4 Appendix 4: Molecular International Prognostic Scoring System for Myelodysplastic Syndromes (IPSS-M)

The Molecular International Prognostic Scoring System for myelodysplastic syndromes (IPSS-M) is a recently designed and validated scoring system that incorporates molecular diagnostic testing into the risk stratification that is described above in Section 10.3 (Bernard et al 2022).

The model was developed by profiling mutations in 152 genes in pretreatment diagnostic or peridiagnostic samples from 2957 subjects with MDS. The IPSS-M score was constructed from an adjusted Cox multivariable regression for LFS and used a weighted sum of prognostic variables observed for each subject (Table 20).

Table 20: IPSS-M Risk Score Construction From an Adjusted Cox Multivariable Regression for Leukemia-Free Survival

Category and Variable	Adjusted Hazard Ratio (95% CI)[a]	Model Weight[b]
Clinical		
BM blast, %	1.07 (1.05–1.09)	0.0704
Min *platelets,250), $\times 10^9$/L	0.998 (0.997–0.999)	−0.00222
Hemoglobin, g/dL	0.84 (0.81–0.88)	−0.171
Cytogenetic		
IPSS-R cytogenetic category[c]	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)[d]		
TP53$^{\text{multihit}}$	3.27 (2.38–4.48)	1.18
MLL$^{\text{PTD}}$	2.22 (1.49–3.32)	0.798
FLT3$^{\text{ITD+TKD}}$	2.22 (1.11–4.45)	0.798
SF3B1$^{\text{5q}}$	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B$^{\alpha}$	0.92 (0.74 1.16)	−0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)[e]		
min(Nres,2)	1.26 (1.12–1.42)	0.231

BM=bone marrow; CI=confidence interval; IPSS-M=International Prognostic Scoring System–Molecular; IPSS-R=International Prognostic Scoring System–Revised; ITD=internal tandem duplication; min=minimum; PTD=partial tandem duplication; TKD=tyrosine kinase domain.

[a] Hazard ratio is for the risk of leukemic transformation or death, adjusted for age, sex, and secondary/therapy-related versus primary myelodysplastic syndrome. Cox regression was performed for 2428 subjects with available covariables and leukemia-free survival data.

[b] Model weights were derived from the logarithm of the raw hazard ratios up to three significant digits. The following formula applies: IPSS-M score = 1.15467 + $(\sum_{\text{variables } j} w_j x_j)/\log(2)$, where w_j denotes the weight of variable j, and x_j the value of the variable j observed in a given patient.

[c] IPSS-R cytogenetic categories were as follows: 0 denotes very good, 1 good, 2 intermediate, 3 poor, and 4 very poor.

[d] *SF3B1*$^{\text{5q}}$ is the *SF3B1* mutation in the presence of isolated del(5q) — that is, del(5q) only or with one additional aberration excluding -7/del(7q). *SF3B1*$^{\alpha}$ is the *SF3B1* mutation without comutations in *BCOR*, *BCORL1*, *RUNX1*, *NRAS*, *STAG2*, *SRSF2*, and del(5q).

[e] Nres is defined as the number of mutated genes within the following list: *BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, and *WT1*. The variable min(Nres,2) can therefore take the value 0, 1, or 2.

Source: Bernard et al 2022

10.5 Appendix 5: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Adverse events and/or adverse drug reactions will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.

View the National Cancer Institute (NCI) CTCAE electronically at the following web link: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

10.5.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a subject or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition(s) detected or diagnosed after administration of study treatment(s) even though condition(s) may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • A complication that occurs as a result of a protocol-specified procedure. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured as progressive disease and recorded on the appropriate eCRF. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• The disease being studied, and any symptoms, safety, laboratory, or other diagnostic findings due to underlying disease (including disease progression), unless judged by the investigator to be more severe than expected for the participant's condition. See Section 10.5.3 for clarification on reporting SAEs in the setting of disease progression. • Medical or surgical procedures (eg, endoscopy, appendectomy, or other procedures for general health maintenance) are not considered AEs. The condition, excluding general health maintenance, that leads to the procedure is the AE and should be recorded on the appropriate eCRF. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations (without worsening in intensity) of signs and symptoms related to pre-existing disease(s) or condition(s) that were present before first dose and were not related to screening procedures.

10.5.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE.

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. Is life-threatening • The term 'life-threatening' in the definition of 'serious' adverse event refers to an event in which the participant was at immediate risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization should be considered AEs if they are deemed clinically significant by the investigator. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE or AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.5.3 Recording, Severity, Relationship, and Follow-Up of AEs and/or SAEs, Lost to Follow-up and Stopping of AE/SAE Collection

AE and SAE Recording

- The reporting of AE/SAEs will start at the signing of the informed consent form (ICF) and continue through 30 days after the last and final dose of study treatment (see section on Stopping of AE/SAE Collection and Section 8.5.1).
- If the subject starts a new anticancer treatment within those 30 days, including a new investigational treatment, the stop date for reporting obligations for this study will be the date when the subject started the anticancer therapy, or the 30 days whichever occurs earlier.
- If an AE/SAE occurs between signing ICF and first dose administered, the AE/SAE will be recorded as medical history and not in the AE section. However, if the event is related to a screening procedure it will be captured and recorded as an AE in the eCRF. Any clinically significant finding(s) observed after the start of study treatment will be recorded as an AE in the eCRF (Section 8.5.1).
- When reporting AE/SAE after one or more doses of study treatment has been administered, the AE/SAE will be considered a treatment emergent adverse event.

- Death should not be recorded or reported as AE/SAE but should be recorded as an outcome of a single event, eg, the cause of death. The condition that resulted in the death should be recorded and reported as the AE/SAE.
- Disease progression as a term should not be reported as AE/SAE. When an SAE occurs in a subject and it is presumed to be, but not yet confirmed to be the cause of disease progression, the SAE must be reported. When and/or if disease progression is confirmed to be the cause, the previously reported SAE WILL NOT be retracted; therefore, the SAE shall remain in the database.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) pertaining to the event.
- The investigator or delegated site staff will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Astex CS&RM in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Astex CS&RM. In these cases, all participant identifiers, except for the participant number, will be redacted on the copies of the medical records before submission to Astex CS&RM.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- If there is a change in the serious criteria of an event such that a non-serious event becomes serious, an end date of the non-serious event will be entered. Then, the serious event will be entered as a separate event with the next day as the starting date.
- In the example below, hypotension would be listed twice in the eCRF (once for the nonserious event and once for the serious event).

  Nonserious event (no serious criteria met): **hypotension, Grade 2, onset 01 February 2021, end date 07 February 2021.**

  Serious event (as hospitalization was added): **hypotension, Grade 3, onset 08 February 2021, end date 10 February 2021.**

  Note that the dates do not overlap; the nonserious event must end prior to the serious event beginning.
- If a serious event is downgraded to nonserious, a new entry will be created in the eCRF to note that change as described above.

AE Assessment of Severity

Use the definitions found in the CTCAE v5 for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, use the following grading system to assess severity:

- Grade 1 – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- Grade 2 – Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living, such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3 – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care of activities of daily living, such as bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Grade 4 – Life-threatening consequences; urgent intervention indicated.
- Grade 5 – Death related to AE.

NOTE: If a nonserious event is continuous, but changes in severity (CTCAE grade) over time, the site will have one record of the one unique event (preferred term) with the highest severity grade recorded for the entire duration of the event. Only a change from nonserious to serious requires a new entry.

For example: If there is a change in severity, the highest severity should be recorded for the entire duration.

For the AEs:

Hypertension Grade 1, onset 15 January 2021, end date 20 January 2021.

- Hypertension Grade 2, onset 21 January 2021, end date 30 January 2021.
- Hypertension Grade 1, onset 31 January 2021, end date 19 February 2021.

Record as:

- Hypertension Grade 2, onset 15 January 2021 end date 19 February 2021.

AE Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment(s) and each occurrence of each AE/SAE as related or not related to study treatment(s).
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

- The investigator will also consult the IB and/or Product Information (for marketed products) to assist in his/her assessment of a causality.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Astex CS&RM. However, **it is very important that the investigator always assesses causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information by modifying the SAE eCRF with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- After the initial AE/SAE report, the investigator is required to actively follow each subject at subsequent visits/contacts. If any information necessary to evaluate the suspected adverse reaction/event is missing or unknown, the investigator should seek such information from the source of the report when available and without delay forward it to Astex CS&RM, as soon as the information is available.
- It is the investigator's responsibility to follow all SAEs and any additional information pertaining to an SAE, such as, but not limited to clinically relevant information and SAE outcomes. This additional information should be reported to Astex CS&RM without delay as soon as the information is available.
- Additionally, the sponsor may request necessary information to evaluate serious adverse reaction/event and it is the investigator's responsibility to report this information without delay to Astex CS&RM, as soon as possible.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Astex CS&RM with a copy of any post-mortem findings including histopathology, if available.
- New or updated information will be recorded in the eCRF or otherwise communicated to Astex CS&RM within 24 hours of receipt of the information. If the new or updated information is entered into the EDC system, it will automatically be sent to Astex CS&RM.

Lost to Follow-up and Stopping of AE/SAE Collection

- If the investigator has determined that the subject is lost to follow-up, no further collection of AE/SAE information is required. Investigator shall document in the appropriate CRF that the subject was lost to follow-up.
- All AE/SAE should be collected and reported to the sponsor (Astex CS&RM), 30 days following the last dose of the study treatment (investigational drug or control drug). However, if the investigator becomes aware of an SAE or of a death at any time beyond 30 days after the last dose, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor and the information should be reported without delay and as soon as the information is available (Section 8.5.1).
- If the subject starts a new anticancer treatment within those 30 days, including a new investigational treatment, the stop date for reporting obligations for this study will be the date when the subject started the anticancer therapy, or the 30 days whichever occurs earlier.
- If the subject has withdrawn full informed consent to participate in the study, investigator should not collect AE/SAE data beyond the date of withdrawing inform consent.
- If the sponsor chooses to terminate or end the study, the sponsor will communicate expectations for data collection, including AE/SAEs.

10.5.4 Reporting of Overdose or Other Medication Errors:

It is the responsibility of the investigator/site personnel to report to Astex CS&RM overdose or other medication errors

If an overdose or other medication error should occur, please proceed as follows:

- If no AE/SAE occurred as a result of the medication error, document the medication error as a protocol deviation according to the Protocol Deviation guidance.
- If an AE occurred as a result of the medication error, document as an AE in the EDC system as well as a protocol deviation according to the Protocol Deviation guidance.
- If an SAE occurred as a result of the medication error, document as an SAE in the EDC system as well as a protocol deviation according to the Protocol Deviation guidance.

10.5.5 Reporting of SAEs

SAE Reporting to Astex CS&RM via an Electronic Data Capture Tool
• The primary mechanism for reporting an SAE to Astex CS&RM will be the electronic data capture (EDC) tool. • Study center staff will enter the SAE data into the EDC system as soon as it becomes available, but no longer than 24 hours from receipt of the information. The EDC system will automatically send a report to Astex CS&RM. • If a causality assessment is not provided, the default assessment will be 'related', for safety reporting purposes. • After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data. • If an investigational site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the investigational site staff can report this information on a paper SAE report form (see the following section).

SAE Reporting to Astex CS&RM when EDC Tool is Unavailable
• If the EDC tool is unavailable, the site will enter the SAE data via paper SAE report form within 24 hours of first becoming aware of the SAE and email to Astex CS&RM. • Contact for SAE reporting is as follows: **drugsafety@astx.com**

10.6 Appendix 6: Disease Response Assessment Based on International Working Group Criteria

Response will be assessed in patient with MDS in part by using the 2006 IWG criteria (Cheson et al 2006), as defined in Table 21. Criteria for hematologic improvement are defined in Table 22.

Table 21: Response Criteria in Myelodysplastic Syndromes (IWG 2006 Criteria)

Category	Response Criteria (responses must last ≥4 weeks)
CR	• BM ≤5% myeloblasts with normal maturation of all cell lines[a] • Persistent dysplasia will be noted[a,b] • Peripheral blood[c] • Hgb ≥11 g/dL • Platelets ≥100×10^9/L • Neutrophils ≥1.0×10^9/L[b] • Blasts 0%
PR	All CR criteria if abnormal before treatment except: • BM blasts decreased by ≥50% over pretreatment but still >5% • Cellularity and morphology not relevant
Marrow CR	BM ≤5% myeloblasts and decrease by ≥50% over pretreatment[b] Peripheral blood: if HI responses, they will be noted in addition to marrow CR[b]
Stable Disease	Failure to achieve at least PR, but no evidence of progression for >8 weeks
Failure	Death during treatment or disease progression characterized by worsening cytopenias, increase in percentage of BM blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: • Return to pretreatment BM blast percentage • Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence[d]
Cytogenetic Response	Complete: Disappearance of chromosomal abnormality without appearance of new ones Partial: At least 50% reduction of the chromosomal abnormality
Disease Progression	For patients with: • Less than 5% blasts: ≥50 increase in blasts to >5% blasts • 5%-10% blasts: ≥50% increase in blasts to >10% blasts • 10%-20% blasts: ≥50% increase in blasts to >20% blasts • 20%-30% blasts: ≥50% increase in blasts to >30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hgb by ≥2 g/dL[d] • Transfusion dependence[d]

BM=bone marrow; CR=complete response; FAB=French-American-British classification; Hgb=hemoglobin; HI=hematologic improvement; IWG=International Working Group; MDS=myelodysplastic syndromes; PR=partial remission.

[a] Dysplastic changes should consider the normal range of dysplastic changes.

[b] Modification to IWG response criteria

[c] In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

[d] Impact of anemia must be deemed disease-related and not due to study treatment.

Source: Cheson et al 2006

Table 22: Criteria for Hematologic Improvement

Hematologic Improvement	Response Criteria (responses must last ≥8 weeks)
Erythroid response (pretreatment, <11 g/dL)	1) Hgb increase by ≥1.5 g/dL and/or 2) Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation.
Platelet response (pretreatment, $<100\times10^9$/L)	1) Absolute increase of $\geq30\times10^9$/L for subjects starting with $>20\times10^9$/L platelets and/or 2) Increase from $<20\times10^9$/L to $>20\times10^9$/L and by at least 100%.
Neutrophil response (pretreatment, $<1.0\times10^9$/L)	At least 100% increase and an absolute increase $>0.5\times10^9$/L.

Hgb=hemoglobin; RBC=red blood cell
Source: Criteria from 2006 MDS criteria (adapted from Cheson et al 2006)

10.7 Appendix 7: Modifications During a COVID-19 Health Emergency

10.7.1 General Information

This section describes modifications to the study protocol which may be implemented to allow flexibility in conducting this study during the current COVID-19 public health emergency or re-emergence of the same, while maintaining safety of trial participants, maintaining compliance with GCP, and minimizing risks to trial integrity. These modifications are intended to remain in effect only for the duration of the public health emergency related to COVID-19 and only in instances where the study cannot be conducted per the protocol.

Any modifications to the study protocol must be discussed with the Astex medical monitor before implementing.

10.7.2 Study Status

In extenuating circumstances (eg, during the COVID-19 pandemic), Astex may implement all or some of the following modifications:

- Temporarily pause recruitment of new trial subjects.
- Extend the duration of the study.
- Postpone activation of study centers that have not been initiated.
- Transfer study subjects to investigational study centers away from high-risk zones or closer to their home.
- Convert physical visits to phone or video visits.
- Modify to ensure that only strictly necessary visits are performed at study centers.
- Allow laboratory tests and/or diagnostic tests to be conducted at a local laboratory/facility authorized/certified to perform such tests.
- Make changes to the per-protocol informed consent process in accordance with IRB/IEC and institutional guidelines.

10.7.3 COVID-19 Benefit/Risk Assessment

The safety of each trial participant is of primary importance. Astex will continually reassess the risks of conducting this clinical trial against the anticipated benefit for trial participants as the COVID-19 situation evolves and implement and document changes accordingly.

It is possible that local circumstances may lead to a local change in risk assessment (eg, an escalation of the pandemic within a certain region); therefore, the need to implement additional measures may arise. Investigators may be asked to complete a risk assessment questionnaire provided by Astex. This assessment should be documented in the investigator's site master file and communicated to Astex.

10.7.4 Modifications to Study Conduct

10.7.4.1 Alternative Methods for IMP Shipment

In extenuating circumstances (eg, during the COVID-19 pandemic) where standard approaches to dispensing study drug to subjects are not possible, alternative methods for dispensing study drug to subjects may be used Astex will work with individual sites to find acceptable alternative arrangements (eg, shipment of study drug from study center pharmacies to subjects) that assure compliant control of study drug and acceptable safety monitoring. Alternative methods for drug dispensing must be reviewed by Astex before implementing.

10.7.4.2 Study Visits and Procedures

Study visits and procedures should be conducted as follows:

- Study subjects may use local laboratories for standard laboratory testing (eg, hematology, serum chemistry, and urinalysis).
- Telemedicine visits (ie, conducted via telephone and/or video calls, or in-person Telehealth Visits with a health professional) may be permitted in lieu of in-person visits to monitor AEs and subject safety.
    - Telemedicine visits must be approved by Astex and aligned with Institutional practice and local regulations.
    - Telemedicine visits must be appropriately documented in source documents.
    - Additional details regarding how to conduct telemedicine visits will be provided by Astex.

In-person visits are required to assess eligibility, perform baseline assessments, and for primary outcome measures. Telemedicine visits would generally not be permitted for the following procedures unless approved by Astex:

- Screening and/or predose Cycle 1 Day 1 assessments to determine eligibility.
- Visits with blood sample collection for PK analysis.
- Bone marrow collection.
- Visits with magrolimab infusions.

10.8 Appendix 8: Summary of Changes from Original to Amendment 1.0

Protocol: ASTX727-10 Amendment 1.0; Date: 19 December 2022

Rationale for Amendment 1.0: In the original protocol the schedule of administration of oral decitabine/cedazuridine is linked to the schedule of administration of magrolimab. This amendment treats the administration of oral decitabine/cedazuridine independently from the administration of magrolimab to allow for a dose delay of either drug. In addition, other minor changes were made to add clarification to the protocol.

Summary of Changes

Section 1.2 Schema:

- Figure 1 Schema has been modified to show the administration of magrolimab in days instead of cycle-days.

Section 1.3 Schedule of Activities

- Table 1 Schedule of Activities for Oral Decitabine/Cedazuridine and Table 2 Schedule of Activities for Magrolimab have been created from the original Table 1 Schedule of Activities for Oral Decitabine/Cedazuridine. The new tables separate the activities associated with oral decitabine/cedazuridine from the activities associated with magrolimab.
- Table 3 Dosing Schedule for Oral Decitabine/Cedazuridine and Table 4 Dosing Schedule for Magrolimab have been created from the original Table 2 Dosing Schedule for Oral Decitabine/Cedazuridine and Magrolimab. The new tables separate the dosing schedules associated with oral decitabine/cedazuridine from the dosing schedules associated with magrolimab.

Section 2.3.2 Magrolimab

- Dosing of magrolimab is changed from cycles to days.

Section 4.1 Overall Design

- The DLT group has been more clearly defined to be the first 6 to approximately 18 subjects enrolled during the first 2 cycles of oral decitabine/cedazuridine.
- Cycle is newly defined for this protocol to be “a cycle of oral decitabine/cedazuridine, which is normally 28 days”.

Section 4.1.1 Dose-Limiting Toxicity Cohort

- The DLT group has been more clearly defined to be the first 6 to approximately 18 subjects enrolled during the first 2 cycles of oral decitabine/cedazuridine.

Section 4.5 Dosing Administration

- Table 5 Treatment Administration Schedule for Oral Decitabine/Cedazuridine and Table 6 Treatment Administration Schedule for Magrolimab have been created from the original Table 3 Treatment Administration Schedule.

Section 4.6.1 Oral Decitabine/Cedazuridine

- References have been added for the justification for the dose of oral decitabine/cedazuridine. In addition to the INQOVI US Prescribing Information, prescribing information from Australia and Canada have been included.

Section 6.1 Description of Study Interventions Administered

- In Table 8 Oral Decitabine/Cedazuridine and Magrolimab Products Used in Study, the magrolimab cycle-days have been changed to days.

Section 6.6.1 Oral Decitabine/Cedazuridine Dose Modifications

- Bullets have been added to clarify when to start administration of oral decitabine/cedazuridine after delays of different numbers of days.

Section 6.6.2.1 Repriming for Magrolimab

- The requirement for the repriming for magrolimab has been defined as a dose delay of magrolimab equivalent to 28 days or more.

Section 7.1 Permanent Discontinuation of Study Treatment

- Treatment discontinuation has been defined as discontinuation of both oral decitabine/cedazuridine and magrolimab.

Section 10.5.4 Reporting of Overdose or Other Medication Errors

- Section 10.5.4 is a new section that has been added.

Section 11.0 REFERENCES

- INQOVI Australia Product Information and INQOVI Canada Product Monograph were added as references.

11.0 REFERENCES

Advani R, Flinn I, Popplewell L, Forero A, Bartlett NL, Ghosh N, et al. CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma. N Engl J Med. 2018;379(18):1711-1721.

Advani R, Bartlett NL, Smith SM, Roschewski M, Popplewell L, Flinn I, et al. The First-In-Class Anti-CD47 Antibody Hu5F9-G4 + Rituximab Induces Durable Responses in Relapsed/Refractory DLBCL and Indolent Lymphoma: Interim Phase 1b/2 Results [Abstract]. 24th Congress of the European Hematology Association (EHA); 13-16 June 2019; Amsterdam, Netherlands.

Bernard E, Tuechler H, Greenberg PL, Hasserjian RP, Arango Ossa JE, Nannya Y, et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. NEJM Evid. 2022;1(7). doi:10.1056/EVIDoa2200008.

Chao MP, Alizadeh AA, Tang C, Myklebust JH, Varghese B, Gill S, et al. Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate non-Hodgkin lymphoma. Cell. 2010;142(5):699-713.

Chao MP, Majeti R, Weissman IL. Programmed cell removal: a new obstacle in the road to developing cancer. Nat Rev Cancer. 2011;12(1):58-67.

Chen JY, McKenna KM, Choi TS, Duan J, Brown L, Stewart JJ, et al. RBC-Specific CD47 Pruning Confers Protection and Underlies the Transient Anemia in Patients Treated with Anti-CD47 Antibody 5F9 [ASH Abstract]. Blood. 2018;132(Suppl 1):2327. doi: 10.1182/blood-2018-99-115674.

Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108(2):419-25.

DACOGEN® (decitabine) for injection, for intravenous use. US prescribing information. Otsuka America Pharmaceutical, Inc.; November 11, 2021. Accessed 10 August 2022. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=deb4a13c-855b-4372-9778-6e81da598df6

Desai A, Gainor JF, Hegde A, Schram AM, Curigliano G, Pal S, et al. COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials. Nat Rev Clin Oncol. 2021;18(5):313–319. Erratum in Nat Rev Clin Oncol. 2021;18(5):320.

Ferraris D, Duvall B, Delahanty G, Mistry B, Alt J, Rojas C, et al. Design, synthesis, and pharmacological evaluation of fluorinated tetrahydrouridine derivatives as inhibitors of cytidine deaminase. J Med Chem. 2014;57(6):2582–2588.

Garcia-Manero G, Chien KS, Montalban-Bravo G. Myelodysplastic syndromes: 2021 update on diagnosis, risk stratification and management. Am J Hematol. 2020;95(11):1399–1420.

Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454-65.

INQOVI Australia Product Information, Taiho Pharmaceutical Co., Ltd; September 20, 2020. Accessed 01 December 2022. https://www.tga.gov.au/sites/default/files/auspar-decitabine-cedazuridine-210128-pi.pdf

INQOVI Canada Product Monograph, Taiho Pharmaceutical Co., Ltd; March 21, 2022. Accessed 01 December 2022.
https://www.taihopharma.ca/documents/31/INQOVI_Product_Monograph.pdf

INQOVI. US Prescribing Information. Taiho Pharmaceutical Co., Ltd; May 5, 2022. Accessed 01 August 2022. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=91a0f80b-f865-4d06-a40d-4d148d99ee71

Ivanova A, Qaqish BF, Schell MJ. Continuous toxicity monitoring in phase II trials in oncology. Biometrics. 2005;61(2):540-545.

Liu J, Wang L, Zhao F, Tseng S, Narayanan C, Shura L, et al. Pre-Clinical Development of a Humanized Anti-CD47 Antibody with Anti-Cancer Therapeutic Potential. PLoS One. 2015;10(9):e0137345.

Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. J Clin Oncol. 1997;15(1):110-115.

Ma X. Epidemiology of myelodysplastic syndromes. Am J Med. 2012;125(7 Suppl):S2-S5.

Majeti R, Chao MP, Alizadeh AA, Pang WW, Jaiswal S, Gibbs KD Jr, et al. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell. 2009;138(2):286-299.

National Comprehensive Cancer Network (NCCN). Myelodysplastic Syndromes (Version 3.2022). https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf.

Ricerca 031253 Study Report. 2013. Pharmacokinetic Study to Determine the Effect of a Staggered Oral dosing Regimen of E7727 and Decitabine in Male Cynomolgus Monkeys.

Sallman DA, Asch AS, Al Malki MM, Lee DJ, Donnellan WB, Marcucci G, et al. The First-in-Class Anti-CD47 Antibody Magrolimab (5F9) in Combination with Azacitidine Is Effective in MDS and AML Subjects: Ongoing Phase 1b Results [ASH abstract]. Blood. 2019;134(Supp 1):569. doi: 10.1182/blood-2019-126271.

Sallman DA, Al Malki MM, Asch AS, Wang ES, Jurcic JG, Bradley TJ, et al. Magrolimab in combination with azacitidine for untreated higher-risk myelodysplastic syndromes (HR-MDS):

5F9005 phase 1b study results [ASCO abstract]. J Clin Oncol. 2022;40(16 Suppl): Abstract 7017. doi: 10.1200/JCO.2022.40.16_suppl.7017

Sikic BI, Lakhani N, Patnaik A, Shah SA, Chandana SR, Rasco D, et al. First-in-Human, First-in-Class Phase I Trial of the Anti-CD47 Antibody Hu5F9-G4 in Patients With Advanced Cancers. J Clin Oncol. 2019;37(12):946-953.

Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol. 2002;20(10):2429-2440.

Steensma DP, Baer MR, Slack JL, Buckstein R, Godley LA, Garcia-Manero G, et al. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. J Clin Oncol. 2009;27(23):3842-3848.

Zeidan AM, Tsai JH, Karimi M, Schmier J, Jayade S, Zormpas E, et al. Patient Preferences for Benefits, Risks, and Administration Route of Hypomethylating Agents in Myelodysplastic Syndromes. Clin Lymphoma Myeloma Leuk. 2022;22(9):e853-e866.