Weill Cornell Medical College

CLINICAL STUDY PROTOCOL

TITLE:	Phase II Clinical Study of the Clinical Efficacy and Safety of Tosedostat in Patients with Myelodysplastic Syndromes (MDS) after Failure of Hypomethylating Agent-based Therapy
STUDY NUMBER:	WCMC IST-CTI-MDS
INVESTIGATIONAL MEDICINAL PRODUCT:	Tosedostat
IND No.	125244
INDICATION:	High or Very High Risk Myelodysplastic Syndrome (MDS)
PRINCIPAL INVESTIGATOR:	Gail J. Roboz, MD Director of the Leukemia Program Weill Medical College of Cornell University and NewYork-Presbyterian Hospital 525 East 68th Street Payson Pavilion, 3 New York, NY 10065, USA Telephone: (646) 962-2700 Fax: (646) 962-1605
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STATISTICIAN	Paul Christos, DrPH (Statistics consultant)
PROTOCOL VERSION AND DATE:	Version 1.2 dated 06 October 2016
CROSS REFERENCE	CTI BioPharma Corp – IND No. 75,503: Tosedostat (CHR-2797)

PROTOCOL SYNOPSIS

Purpose of the Study	Study WCMC IST-CTI-MDS evaluates the safety and tolerability of tosedostat in adult patients with pathologically confirmed myelodysplastic syndromes (MDS) after failure of hypomethylating agent-based therapy.
Primary Objectives	The primary objective the study is to evaluate the safety and efficacy of tosedostat patients with myelodysplastic syndrome who have relapsed after or are refractory or intolerant to azacitidine or decitabine. The primary endpoint is overall survival.
Secondary Objectives	The following secondary endpoints will be evaluated in high and very high risk MDS patients: • Hematological improvements (erythroid response [ER], platelet response [PLR] and neutrophil response [NR]) according to 2006 IWG criteria (Appendix 3), including reduction in RBC and/or PLT transfusion needs • Overall response (complete remission [CR], partial remission [PR], bone marrow complete response [BMCR], and stable disease [SD] according to 2006 International Working Group (IWG) criteria, including, among responders, the distribution of time to response and the duration of response. (Appendix 3) • Improvements of cytogenetics as evaluated by the change in aneuploidy in BM according to 2006 IWG criteria • Safety and tolerability of tosedostat • Time to AML transformation
Study Design	This is a single-center, open label, phase II study of clinical activity of tosedostat in adult patients with MDS who have failed prior hypomethylating agent-based therapy. In this study, approximately 80 patients will be enrolled at Weill Cornell Medical College. The dose of tosedostat will be 120 mg once a day continuously for each 28 day treatment cycle. The dose of tosedostat should be taken orally with a glass of water after food preferably in the morning at about the same time every day to ensure an even dose interval. Patients will be assessed for disease response every two cycles as defined in the protocol. If patient has no response as defined by the protocol after two cycles, azacitidine 75 mg/m^2 SC or IV for 5 days may be combined with tosedostat, at the investigator's discretion. Subjects will be permitted to interrupt tosedostat treatment, to a maximum of 14 days, under circumstances described in Section 6.5. If a subject requires multiple, or prolonged (greater than 14 days) study medication interruptions, the principal investigator will be consulted for a discussion on the subject's continued participation in the study. Investigators are encouraged to avoid unnecessary subject withdrawal. Late response to therapy has been seen in earlier trials, particularly in those who have shown at least stabilization of disease. However, the safety of the subject is paramount and subject's right to withdraw at any time is absolute.
Duration of Clinical Study	Enrollment in this clinical study is expected to be completed in approximately 24 months, and the total study duration, including the 30-day follow up period, will be approximately 36-48 months.
Inclusion Criteria	1. Able to understand and to provide written informed consent 2. At least 18 years of age with pathologically confirmed MDS (IPSS-R high or very high) or 20-30% blasts in bone marrow per FAB classification (RAEB-T)

	3. Must have received at least 4 cycles of decitabine-based or azacitidine-based therapy and are either refractory to, relapsed after or intolerant to prior therapy with either agent. • *Primary failure/refractory:* Stable or worsening disease after a minimum of 4 cycles of decitabine-based or azacitidine-based therapy • *Secondary failure/relapse:* Bone marrow blast count increase or loss of hematologic response after initial treatment response with hypomethylating agent-based therapy • *Intolerance:* Intolerance of hypomethylating agent-based therapy regardless of number of cycles completed and clinical response 4. Progression (according to 2006 IWG criteria) at any time after initiation of subcutaneous or intravenous azacitidine or decitabine treatment per labeling during the past 2 years, defined as follows: • For patients with <5% BMBL, ≥ 50% increase in BMBL to >5% BMBL • For patients with 5-10% BMBL, ≥ 50% increase in BMBL to >10% BMBL • For patients with 10-20% BMBL, ≥ 50% increase in BMBL to >20% BMBL • For patients with 20-30% BMBL, ≥ 50% increase in BMBL to >30% BMBL • Any of the following: o ≥ 50% decrease from maximum remission/response levels in granulocytes or PLT o Decrease in Hgb concentration by ≥2 g/dL o Transfusion dependence, defined as administration of at least 4 RBC units in the past 8 weeks before Screening (patients must have Hgb values < 9 g/dL prior to transfusion to be considered), in the absence of another explanation. 5. Has failed to respond to, relapsed following, not eligible, or opted not to participate in BM transplantation 6. Off azacitidine or decitabine for at least 2 weeks, off all other anticancer treatments for at least 2 weeks. Filgrastim (G-CSF) and EPO are allowed before and during the study as clinically indicated 7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-3 8. Subjects must have adequate hepatic and renal function including the following: • Total bilirubin ≤ 1.5 x upper limit of normal (in the absence of Gilbert's syndrome) • AST and ALT ≤ 2.5 x upper limit of normal • Serum creatinine ≤ 1.5 x upper limit of normal 9. Must have acceptable recovery from clinically significant non-hematologic toxicity after prior therapy. 10. Must have a life expectancy of at least 2 months 11. Screening left ventricular ejection fraction (LVEF) > 50% as documented by transthoracic echocardiogram (TTE) 12. Female subjects of child-brearing potential and male subjects with female partners of reproductive potential must use acceptable contraceptive methods (hormonal or barrier method of birth control; abstinence) for the duration of time on study and continue to do so for a further 3 months after the end of tosedostat treatment. Should a female subject become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. 13. Able to comply with all study procedures during the study including all visits and tests

	14. Willing to adhere to the prohibitions and restrictions specified in this protocol 15. Patient must sign an informed consent form (ICF) indicating that s/he understands the purpose of and procedures required for the study and is willing to participate.
Exclusion Criteria	1. Presence of serious illness, medical condition, or other medical history, involving the heart, kidney, liver, or other organ system, including abnormal laboratory parameters, which, in the opinion of the Investigator, would be likely to interfere with a subject's participation in the study or with the interpretation of the results. 2. Have known active central nervous system disease or active, uncontrolled, clinically significant infection(s) 3. Have other active malignancies or other malignancies within 12 months before enrollment, except non-melanoma skin cancer or cervical intraepithelial neoplasia 4. Are receiving any other investigational therapy or protocol-prohibited therapy 5. Have received previous treatment with tosedostat 6. Pregnant or breastfeeding females 7. Any prior or co-existing medical condition that in the Investigator's judgment will substantially increase the risk associated with the subject's participation in the study 8. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or completion of the necessary study procedures 9. Significant* cardiovascular disease defined as: a. Active heart disease including myocardial infarction within 6 months prior to study entry b. Symptomatic coronary artery disease c. Uncontrolled or clinically significant arrhythmia, angina, congestive heart failure d. Presence of clinically significant valvular heart disease e. Presence of clinically significant conduction defect on screening ECG f. Uncontrolled hypertension (i.e., systolic BP >160mmHg, diastolic >90 mmHg in repeated measurements) despite adequate therapy g. Clinically significant atrial fibrillation *Grade 3/4 in the CTCAE v4.0 grading would generally be considered clinically significant, although this remains a judgment for the Investigator to make. 10. LVEF ≤ 50% 11. Baseline troponin I and b-type natriuretic peptide > Grade I 12. Prior exposure cardiotoxic agent, such as anthracycline within 3 months of enrollment 13. Concomitant use of drugs that prolong QT/QTc interval except antibiotics, antifungals, and other antimicrobials used as standard of care for the treatment and prevention of infection and/or other such drugs clinically indicated for patient care. When use of concomitant medications with QT-prolonging potential is necessary, ECG must be repeated 4 hours post-dose on Day 1 (+1 day), on Day 3 (±1 day), and on Day 7 (±1 day), and as clinically indicated, relative to start of agent with QT-prolonging potential. QTc will be calculated using the Fridericia formula. For subsequent use of same concomitant medication, ECG may not be repeated if it did not cause QTc prolongation with tosedostat. 14. Gastrointestinal disorders that may interfere with absorption of drug 15. Active serious infection or sepsis 16. Clinically significant interstitial lung disease
Study duration	24 months
Safety	Safety evaluations will include monitoring of adverse events (AEs); laboratory safety testing,

	including hematology and blood chemistry; urinalysis; physical examinations; vital signs; ECGs; and left ventricular ejection fraction (LVEF) determination. All reported symptoms and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized. Crude incidence rates will be based on the maximum intensity grade for each subject. Descriptive statistics for other safety parameters will be produced. All subjects who receive any amount of tosedostat will be included in these analyses.

Table 1: LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APL	Acute Promyelocytic Leukemia
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BP	Blood pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CFU/c	Colony-Forming Unit in Culture
CML	Chronic Myeloid Leukemia
CPK	Creatinine Phosphokinase
CR	Complete Remission
CPMP	CHMP - Committee for Medicinal Product for Human Use
CRm	Molecular Complete Remission
CRp	Complete Remission with Incomplete Platelet Recovery
CRc	Complete Remission, cytogenetic
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data & Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor

Hb	Hemoglobin
HUVEC	Human Umbilical Vein Endothelial Cell
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
INN	International Non-proprietary Name
IRB	Institutional Review Board
ITT	Intent To Treat
IVRS	Interactive Voice Response System
IWG	International Working Group for Diagnosis, Standardization
LVEF	Left Ventricular Ejection Fraction
MDACC	MD Anderson Cancer Center
MDS	Myelodysplastic Syndrome
MeDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphological Leukemia Free State
MM	Multiple Myeloma
mRNA	messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
NYHA	New York Heart Association
PD	Progressive Disease
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PT	Prothrombin Time
SAE	Serious Adverse Event
SD	Stable Disease
SOP	Standard Operating Procedure
tRNA	transfer Ribonucleic Acid
ULN	Upper Limit of Normal
USAN	United States Adopted Name
WBC	White Blood Cells
WCMC	Weill Cornell Medical College
WHO	World Health Organization

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1 INTRODUCTION

Background

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis and variable cytopenias. As the myeloid dysplasia progresses, patients develop severe anemia requiring frequent transfusions, and develop neutropenia and thrombocytopenia from progressive bone marrow failure. About a third of patients with MDS progress to acute myeloid leukemia (AML), usually within months to years.[1]

MDS is the most commonly diagnosed myeloid neoplasm in the United States. Incidence of MDS is approximately 4.6 per 100,000 people according to the SEER database. It is predominantly a disease of the elderly, with approximately 86% patients older than 60 at the time of diagnosis. The incidence of MDS is projected to increase significantly over time as a result of the aging worldwide population, increasing rates of secondary MDS in patients previously treated with chemotherapy and/or radiation for other cancers, and increased awareness of and therapeutic options for the disease.[2] The prognosis of MDS is generally poor, but survival ranges from a few months to many years depending on several important prognostic factors. Prognostic factors that confer poor prognosis include severe cytopenias, increased bone marrow blasts (5-20%), complex or unfavorable cytogenetics, and somatic point mutations (*TP53*, *EZH2*, *ETV6*, *RUNX1*, *ASXL1*).[3-5]

The treatment aims of MDS are to control symptoms, improve quality of life, improve overall survival, and decrease progression to AML. For lower risk MDS, typically supportive care with blood products and growth factors (i.e. erythropoietin, granulocyte-macrophage colony stimulating factors) are utilized.[6] There are currently only three agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDS: lenalidomide (Revlimid®, Celgene Corporation), azacitidine (Vidaza®, Celgene Corporation), and decitabine (Dacogen®, Eisai Inc.). Lenalidomide is only approved for transfusion dependent patients with a deletion 5q cytogenetic abnormality.[7] Azacitidine and decitabine are hypomethylating agents (HMA) approved for all MDS patients, and are typically utilized upfront for higher risk patients or for lower risk patients who have progressed on supportive care.[8,9] Intensive chemotherapy and allogeneic stem cell transplantation are other options, however they are not suitable options for majority of elderly MDS patients due to serious and potentially fatal side effects.

The prognosis for MDS patients who fail to respond or lose their response to azacitidine or decitabine is dismal and there is a compelling unmet medical need for novel therapeutic strategies for these patients. For patients who have failed or progressed after HMA, overall survival ranges from 4-5 months in advanced patients[10,11] and is about 15 months in low and int-1 disease (Jabbour et al, ASH 2014, abstract 388). In a recent phase III trial, the investigational agent rigosertib failed to achieve a statistically significant prolongation of overall survival versus supportive care (8.2 vs. 5.8 mos) in high-risk MDS patients who failed therapy with HMA (ASCO 2014, data in preparation) Thus, there are currently no FDA approved

agents for MDS in this setting. Hypomethylating agents azacitidine and decitabine have demonstrated single-agent efficacy in AML. In single center studies, repeated 10-day cycles of decitabine produce CR in 40-50% of newly diagnosed older patients with AML with a favorable extramedullary toxicity profile compared to standard chemotherapy.[12] Still, as with intensive chemotherapy, the median duration of remission is only 12-18 months and survival after failure of hypomethylating agent is poor. Thus, there is significant unmet need for novel agents after progression of hypomethylating agents.

1.1 THE AMINOPEPTIDASE INHIBITOR TOSEDOSTAT

1.1.1 Mechanism of Anti-leukemic Activity of Tosedostat

Tosedostat is a new orally bioavailable inhibitor of members of the M1 and M17 classes of aminopeptidases that includes the Zn^{2+}-dependent aminopeptidases.[13] Aminopeptidases catalyze the hydrolysis of the terminal amino acids from peptides or polypeptides generated by proteasomal degradation, and are involved in the continuous cycle of protein synthesis and degradation.

The aminopeptidase inhibitor tosedostat is converted in the intracellular compartment into a poorly membrane-permeable active metabolite (CHR-79888), which inhibits the M1 family of aminopeptidases, particularly puromycin-sensitive aminopeptidase and leukotriene A4 hydrolase and the M17 family member leucine aminopeptidase. Inhibition of aminopeptidases by tosedostat and its metabolite leads to an intracellular accumulation of small peptides, which in transformed cells of the haematopoietic lineage, appears to result in a deficiency of free amino acids for new protein synthesis.[14] As malignant cells may be more dependent on protein cycling and availability of amino acids than the normal cells, interrupting this pathway is, therefore, a potential therapeutic target for novel agents. Microarray analysis of sensitive tumor cell lines treated with aminopeptidase inhibitors indicated that the expression of a number of genes involved in amino acid synthesis, sensing (tRNA synthetases) and transport were increased.[14] These genes belong to a cohort of stress-response genes previously shown to be up-regulated in response to amino acid deprivation. In response to amino acid deprivation, the expression of pro-apoptotic proteins such as CHOP and Noxa are up-regulated, which serves to prime the cell for apoptosis and have an antiproliferative effect.[15]

In preclinical experiments, tosedostat exerts anti-neoplastic activity in a wide variety of cell lines *in vitro*, including solid tumor, leukemia and myeloma cell lines and has demonstrated anti-neoplastic activity in a range of *in vivo* solid tumor models.[14]

1.1.2 Preclinical Data on the Anti-leukemic Activity of Tosedostat

1.1.2.1 Activity of Tosedostat in AML Models in vitro

To determine the differential sensitivity of primary AML blasts and normal bone marrow progenitor cells to tosedostat, bone marrow samples were taken from AML patients (n=52) and controls (n=10), and the anti-proliferative effects of tosedostat were tested in a cell

proliferation assay. Tosedostat inhibited cell proliferation in the AML blast samples with a median IC_{50} of 1.1 µM, compared to 9µM in the normal bone marrow progenitor samples. Although there were no statistically significant differences between the different classes of AML, there was a trend towards a better response in the monocytic leukemias and the cytogenetic groups associated with a good prognosis.[13]

In addition to its effect on inhibiting proliferation and inducing leukemic cell apoptosis, tosedostat was found to induce differentiation of acute promyelocytic cells to mature myeloid cells.[13]

1.1.3.2 Inhibition of Endothelial Proliferation and the Anti-angiogenic Effect of Tosedostat

Endothelial cells isolated from human umbilical vein (HUVEC) were found to be very sensitive to the inhibitory effects of tosedostat; proliferation was inhibited with an IC_{50} of 30 to 40 nM. Tosedostat has also been shown to inhibit vascular endothelial growth factor-induced angiogenesis in an *in vitro* model based on a co-culture system of HUVEC and stromal fibroblasts.[13]

1.1.3.3 Evaluation of CYP450 inhibition

Currently available *in vitro* data suggest that tosedostat may be a moderate inhibitor of selected catalytic activities of cytochrome $P_{450}3A4$. Therefore, it may participate in, or contribute to, drug-drug interactions *in vivo*, which are mediated by cytochrome $P_{450}3A4$.[13]

1.1.3 Aminopeptidase Inhibition in MDS: Bestatin

Bestatin is another aminopeptidase inhibitor that is utilized in oncology and hematological malignancies. It has antitumor and immunostimulant activity.[16]

Bestatin has been widely investigated in the clinic, albeit almost exclusively in Japan. Bestatin is approved in Japan, Korea, and China as a maintenance therapy in patients with non-lymphocytic leukemia after it was shown that it prolonged survival and remission duration, especially in elderly patients. A stimulating effect was also observed on colony forming units in culture (CFU/c). In one study, bestatin, in a daily oral dose of 30 mg, was given for as long as possible even after recurrence of disease and it prolonged overall survival, especially in the elderly Japanese population (50 to 65 years old).

Bestatin has been studied in MDS patients in Japan. In one single-arm study in MDS, 10 out of 13 patients responded after 1 month of oral therapy.[16] In another study of 71MDS patients, overall response was 7%, with median duration of response 10.5 weeks.[17]

The clinical activity of bestatin supports aminopeptidase inhibition as a possible therapeutic approach in MDS and supports evaluation of tosedostat in MDS. Tosedostat's pharmacologic activity is improved compared to bestatin in two aspects. First, tosedostat has at least 500-fold greater anti-proliferative activity against AML cell lines than bestatin. Secondly, unlike bestatin, tosedostat is a membrane-permeable ester that is converted inside cells to an active, charged acid. The active metabolite accumulates within the cell and reaches the high

intracellular concentration required to block aminopeptidase activity.[14]

1.1.4 Clinical Experience with Tosedostat

1.1.4.1 Pharmacokinetic Information

Available phase I pharmacokinetic (PK) data indicate that tosedostat has a terminal half- life of 1 to 2 hours. The active metabolite CHR-79888 has a terminal half-life of between 8 and 11 hours, justifying once daily dosing. Intracellular exposure of tosedostat and CHR-79888 is good.[13]

1.1.4.2 Clinical Experience with tosedostat in hematologic malignancies

As of February 23, 2014, there have been two published studies of tosedostat in hematologic malignancies.

CHR-2797-002 was a phase I-II study to evaluate the safety, tolerability and anti-disease activity of the aminopeptidase inhibitor tosedostat, in elderly and/or treatment refractory subjects with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) or multiple myeloma (MM).[18] In the study, 51 subjects had AML, 4 had MDS, and 2 had MM. In the phase I portion, four of 13 AML patients (31%), two at 60mg and two at 130mg, achieved complete marrow responses. Among the 4 subjects with high risk MDS, one subject met the criteria of stable disease and another subject reached a partial response with a complete morphological bone marrow response. These responses were evident at the end of treatment and confirmed 12 weeks later. In addition, 1 of 2 subjects with MM achieved stable disease at the end of the study, which was confirmed 3 months later.[18]

The dose of tosedostat selected in phase I of CHR-2797-002 was 130 mg. This was based on the occurrence of one DLT of raised alanine aminotransferase (ALT) (grade 3) at 130 mg and 2 cases of thrombocytopenia (grade 4) at 180 mg. On the basis of these results, 130mg was considered to be a suitable dose for ongoing or maintenance treatment of AML subjects.[18]

Overall, in the CHR-2797-002 study, 7 out of 51 AML (2 on 60 mg, and 5 on 130 mg) subjects had a reduction in bone marrow blast counts (<5% blastocytes) and achieved a complete response, at some stage during the study. One of the 7 responders (on 60 mg) had a fibrotic bone marrow but became completely transfusion independent and had a hypocellular bone marrow sample suggestive of a complete response, and is counted as such. Four of the AML complete responders also showed hematological recovery, with recovery of neutrophils, platelets and hemoglobin, such that they met the criteria for a complete remission of their AML (duration of complete remission between 4 and 11 months). Seven further AML subjects had reductions in bone marrow blast counts (between 5 and 15% blastocytes) and achieved a partial response, at some stage during the study. Two of these were short duration responses, noted during treatment, whilst 5 subjects remained on treatment, and the responses lasted until 4 to 12 weeks after the end of the protocol-defined treatment period.[18]

The OPAL study was a randomized open-label phase II study that evaluated tosedostat in

elderly (≥60 years) AML patients who had relapsed after achieving first complete remission lasting less than 12 months or who had not achieved previous complete remission. One cohort received tosedostat at 120mg once daily for 6 months, and the other cohort received tosedostat for 240mg once daily for 2 months followed by 120mg for 4 months. Overall, seven patients (10%) had complete remission or complete remission with incomplete platelet recovery; two in the 120mg cohort and five in the 240mg to 120mg cohort. Sixteen (22%) patients had partial remission or better, and 21 (29%) patients had stable disease. Median time to response was 56 days, median duration of response was 39 days. Median overall survival was 126 days; 175.5 days for the 120mg cohort and 88 days in the 240mg to 120mg cohort.[19]

1.1.4.3 Safety Results from the OPAL study[19]

The most common AEs according to two dosing schedules from the OPAL are summarized in Table 2. The most common adverse events were diarrhea, edema, fatigue, and dyspnea. Most common grade 3-4 side effects were febrile neutropenia, fatigue, and thrombocytopenia.

Table 2: Most Common Adverse Events Observed in >20% of Subjects

	Tosedostat 120 mg (n=38)			Tosedostat 240 mg to 120 mg (n=35)		
	All	Grade 3-4	Grade 5	All	Grade 3-4	Grade 5
Patients with at least one adverse event	38 (100%)	21 (55%)	13 (34%)	35 (100%)	16 (46%)	17 (49%)
Diarrhea	20 (53%)	2 (5%)	0	22 (63%)	1 (3%)	0
Peripheral edema	18 (47%)	0	0	22 (63%)	0	0
Fatigue	16 (42%)	7 (18%)	0	20 (57%)	8 (23%)	0
Dyspnea	16 (42%)	5 (13%)	0	14 (40%)	7 (20%)	0
Nausea	13 (34%)	0	0	15 (43%)	0	0
Decreased appetite	12 (32%)	1 (3%)	0	15 (43%)	1 (3%)	0
Hypotension	12 (32%)	3 (8%)	0	14 (40%)	4 (11%)	0
Febrile neutropenia	13 (34%)	11 (29%)	0	13 (37%)	8 (23%)	2 (6%)
Dizziness	12 (32%)	0	0	13 (37%)	0	0
Cough	12 (32%)	0	0	11 (31%)	1 (3%)	0
Pyrexia	12 (32%)	2 (5%)	0	11 (31%)	0	0
Asthenia	9 (24%)	1 (3%)	0	11 (31%)	3 (9%)	0
Hypokalemia	10 (26%)	2 (5%)	0	10 (29%)	3 (9%)	0
Constipation	10 (26%)	0	0	7 (20%)	0	0
Insomnia	9 (24%)	1 (3%)	0	8 (23%)	0	0
Rash	9 (24%)	2 (5%)	0	8 (23%)	0	0
Pneumonia	8 (21%)	3 (8%)	1 (3%)	9 (26%)	3 (9%)	3 (9%)
Vomiting	8 (21%)	0	0	8 (23%)	0	0
Thrombocytopenia	8 (21%)	8 (21%)	0	8 (23%)	8 (23%)	0

Serious adverse events are summarized in table 3. Most commonly reported serious adverse events were febrile neutropenia, disease progression, atrial fibrillation, pneumonia, pyrexia, and cardiac failure. In the study, discontinuation for tosedostat-related toxicity occurred in 14 (19%) of patients; 9 in 120mg cohort and 5 in the 240mg to 120mg cohort. There were five adverse events with outcome of death possibly related to tosedostat; three in the 120mg cohort, and two in the 240mg cohort. The adverse events were acute hepatitis, repiratory failure, pneumonia, atrial fibrillation, and left ventricular dysfunction.

Table 3: Serious adverse events occurring in ≥3% of Subjects

	Tosedostat 120 mg (n=38)	Tosedostat 240 mg to 120 mg (n=35)
Patients with at least one serious adverse event	32 (84%)	30 (86%)
Febrile neutropenia	9 (24%)	12 (34%)
Disease progression	6 (16%)	5 (14%)
Atrial fibrillation	1 (3%)	5 (14%)
Pneumonia	1 (3%)	5 (14%)
Pyrexia	3 (8%)	1 (3%)
Cardiac failure, congestive	1 (3%)	2 (6%)
Cellulitis	2 (5%)	1 (3%)
Dyspnoea	1 (3%)	2 (6%)
Multiorgan failure	2 (5%)	1 (3%)
Rectal hemorrhage	0	3 (9%)
Respiratory failure	3 (8%)	0

1.1.4.4 Tosedostat with Azacitidine

Tosedostat was studied in combination with azacitidine in older patients with AML or high-grade MDS.[19] This was a phase I/II trial of older, relapsed/refractory AML or high-risk MDS patients having failed prior hypomethylating agents. All subjects received tosedostat 120mg orally once daily for 28 day cycles with azacitidine at 50mg/m2 or 75mg/m2 for 7 days per cycle. There were 10 subjects enrolled. Median age of the subjects was 73, with majority with antecedent MDS and complex cytogenetics. 6 subjects were evaluable for response with 50% overall response rate: 2 subjects with morphologic leukemia free state, 1 with partial remission, 1 with stable disease, and 2 with progressive disease. 4 subjects discontinued prior to completion of cycle 1 for reasons other than study-drug related toxicity or progressive disease. The most common non-hematologic grade 3 or higher toxicities regardless of attribution included lung infection (4/10), wheezing (2/10), and somnolence (2/10). One fatal acute coronary event on cycle 2, day 2 of tosedostat 180mg/m2 and azacitidine 75mg/m2 was considered possibly related to the drug.

1.1.4.3 Safety Results from the OPAL study[19]

1.2 DOSE RATIONALE

In study CHR-2797-002, described above, the optimal dose of tosedostat was determined to be

130 mg once daily. Interpolation of the relationship between dose of tosedostat and PK parameters (Cmax, AUC), indicates little or no difference between doses of 120 and 130 mg. There were increased cardiovascular events with higher dosing schedules, including atrial arrhythmias. Therefore, for this study, 120 mg was chosen to provide the safest and most convenient dosing for subjects.

1.3 SUMMARY AND STUDY RATIONALE

The prognosis of MDS patients refractory to or relapsed after hypomethylating agents is poor and there is no effective therapy in this setting. There is an urgent need for novel compounds and treatment strategies for these patients. Tosedostat is a novel aminopeptidase inhibitor, which in preclinical experiments has shown potent activity in both *in vitro* and *in vivo* cancer models as a single agent. Early clinical trials mainly in AML demonstrated that it is safe and well tolerated, and has activity in refractory and relapsed AML patients. This study aims to evaluate the efficacy of tosedostat in MDS patients refractory to hypomethylating agents.

2 STUDY OBJECTIVES

Primary Objective:

The primary objective of the study is to evaluate the safety and efficacy of tosedostat in patients with myelodysplastic syndrome who have relapsed after or are refractory or intolerant to azacitidine or decitabine. The primary endpoint for patients is overall survival.

Secondary Objectives:

The following secondary endpoints will be evaluated:

- Hematological improvements (erythroid response [ER], platelet response [PLR] and neutrophil response [NR]) according to 2006 IWG criteria (Appendix 3), including reduction in RBC and/or PLT transfusion needs
- Overall response (complete remission [CR], partial remission [PR], bone marrow complete response [BMCR], and stable disease [SD] according to 2006 International Working Group (IWG) criteria, including, among responders, the distribution of time to response and the duration of response. (Appendix 3)
- Improvements of cytogenetics as evaluated by the change in aneuploidy in BM according to 2006 IWG criteria
- Safety and tolerability of tosedostat
- Time to AML transformation

3 INVESTIGATIONAL PLAN

3.1 CLINICAL STUDY DESIGN AND PLAN

This is a single-center, open label, phase II study of clinical activity of tosedostat in adult patients with MDS who have failed prior hypomethylating agent-based therapy. In this study, approximately 80 patients (80 patients;) will be enrolled at Weill Cornell Medical College. The dose of tosedostat will be 120 mg once a day continuously for each 28 day treatment cycle.

The dose of tosedostat should be taken orally with a glass of water after food preferably in the morning at about the same time every day to ensure an even dose interval.

Patients will be assessed for disease response every two cycles as defined in the protocol. If patient has no response as defined by the protocol after two cycles, azacitidine 75 mg/m2 SC or IV for 5 days may be combined with tosedostat, at the investigator's discretion.

Subjects will be permitted to interrupt tosedostat treatment, to a maximum of 14 days, under circumstances described in Section 6.5. If a subject requires multiple, or prolonged (greater than 14 days) study medication interruptions, the principal investigator will be consulted for a discussion on the subject's continued participation in the study. Investigators are encouraged to avoid unnecessary subject withdrawal. Late response to therapy has been seen in earlier trials, particularly in those who have shown at least stabilization of disease. However, the safety of the subject is paramount and subject's right to withdraw at any time is absolute.

3.1.1 Screening (Study Day -14 to Day 1)

Initiate and complete screening activities within 14 days before Cycle 1, Day 1 treatment, with the exception that informed consent may be obtained within 28 days before Cycle 1, Day 1.

3.1.2 Treatment (Cycle 1, Day 1 through End-of-Treatment Visit)

This period begins on the day the patient first receives tosedostat and ends at the End-of-Treatment Visit.

3.1.3 Follow-up

After completion of the End-of-Treatment Visit, all patients are followed up for 30 days.

3.1.4 Clinical Study Endpoints

The primary endpoint the study is to evaluate the safety and efficacy of tosedostat in patients with myelodysplastic syndrome who have relapsed after or are refractory or intolerant to azacitidine or decitabine. The primary endpoint for patients is overall survival.

The following secondary endpoints will be evaluated:

- Hematological improvements (erythroid response [ER], platelet response [PLR] and neutrophil response [NR]) according to 2006 IWG criteria (Appendix 2), including reduction in RBC and/or PLT transfusion needs
- Overall response (complete remission [CR], partial remission [PR], bone marrow complete response [BMCR], and stable disease [SD] according to 2006 International Working Group (IWG) criteria, including, among responders, the distribution of time to response and the duration of response (Appendix 2). All responses of CR must be confirmed 4 weeks after achievement.
- Improvements of cytogenetics as evaluated by the change in aneuploidy in BM according to 2006 IWG criteria
- Safety and tolerability of tosedostat

- Time to AML transformation

3.2 DISCUSSION OF STUDY DESIGN

While the prognosis of MDS patients who are refractory to or have relapsed after treatment with hypomethylating agents is universally poor. For higher risk MDS patients, overall survival is extremely short, with estimates ranging from 3-6 months. Therefore, for this group, the primary endpoint is doubling of overall survival from 6 to12 months. The tosedostat dose of 120 mg per day for this study was chosen based safety, efficacy and convenience established in the prior studies CHR-2797-002 and OPAL. Based on preliminary clinical and in vitro data, it is possible that tosedostat may synergize with and/or restore sensitivity to the hypomethylating agent azacitidine. Therefore, for patients who have stable disease, but no hematological improvement after 2 cycles with tosedostat, the investigator may add azacitidine 75 mg/m^2 IV or SC for 5 days to tosedostat.

4 SELECTION OF STUDY POPULATION

4.1 INCLUSION CRITERIA

Male and female MDS patients who meet all of the following criteria are eligible for enrollment in the trial:

1. Able to understand and to provide written informed consent

2. At least 18 years of age with pathologically confirmed MDS (IPSS-R high or very high) or 20-30% blasts in bone marrow per FAB classification (RAEB-T)

3. Must have received at least 4 cycles of decitabine-based or azacitidine-based therapy and are either refractory to, relapsed after or intolerant to prior therapy with either agent.
   - *Primary failure/refractory:* Stable or worsening disease after a minimum of 4 cycles of decitabine-based or azacitidine-based therapy
   - *Secondary failure/relapse:* Bone marrow blast count increase or loss of hematologic response after initial treatment response with hypomethylating agent-based therapy
   - *Intolerance:* Intolerance of hypomethylating agent-based therapy regardless of number of cycles completed and clinical response

4. Progression (according to 2006 IWG criteria) at any time after initiation of subcutaneous or intravenous azacitidine or decitabine treatment per labeling during the past 2 years, defined as follows:
   - For patients with <5% BMBL, ≥ 50% increase in BMBL to >5% BMBL
   - For patients with 5-10% BMBL, ≥ 50% increase in BMBL to >10% BMBL
   - For patients with 10-20% BMBL, ≥ 50% increase in BMBL to >20% BMBL
   - For patients with 20-30% BMBL, ≥ 50% increase in BMBL to >30% BMBL
   - Any of the following:
     - ≥ 50% decrease from maximum remission/response levels in granulocytes or PLT

- Decrease in Hgb concentration by ≥2 g/dL
- Transfusion dependence, defined as administration of at least 4 RBC units in the past 8 weeks before Screening (patients must have Hgb values < 9 g/dL prior to transfusion to be considered), in the absence of another explanation.

5. Has failed to respond to, relapsed following, not eligible, or opted not to participate in BM transplantation

6. Off azacitidine or decitabine for at least 2 weeks, off all other anticancer treatments for at least 2 weeks. Filgrastim (G-CSF) and EPO are allowed before and during the study as clinically indicated

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-3

8. Subjects must have adequate hepatic and renal function including the following:
   - Total bilirubin ≤ 1.5 x upper limit of normal (in the absence of Gilbert's syndrome)
   - AST and ALT ≤ 2.5 x upper limit of normal
   - Serum creatinine ≤ 1.5 x upper limit of normal

9. Must have acceptable recovery from clinically significant non-hematologic toxicity after prior therapy.

10. Must have a life expectancy of at least 2 months

11. Screening left ventricular ejection fraction (LVEF) $>$ 50% as documented by transthoracic echocardiogram (TTE)

12. Female subject of child-bearing potential and male subjects with female partners of reproductive potential must use acceptable contraceptive methods (hormonal or barrier method of birth control; abstinence) for the duration of time on study and continue to do so for a further 3 months after the end of tosedostat treatment. Should a female subject become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

13. Able to comply with all study procedures during the study including all visits and tests

14. Willing to adhere to the prohibitions and restrictions specified in this protocol

15. Patient must sign an informed consent form (ICF) indicating that s/he understands the purpose of and procedures required for the study and is willing to participate.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following exclusion criteria at Screening will not be enrolled in the

study:

1. Presence of serious illness, medical condition, or other medical history, involving the heart, kidney, liver, or other organ system, including abnormal laboratory parameters, which, in the opinion of the Investigator, would be likely to interfere with a subject's participation in the study or with the interpretation of the results.

2. Have known active central nervous system disease or active, uncontrolled, clinically significant infection(s)

3. Have other active malignancies or other malignancies within 12 months before enrollment, except non-melanoma skin cancer or cervical intraepithelial neoplasia

4. Are receiving any other investigational therapy or protocol-prohibited therapy

5. Have received previous treatment with tosedostat

6. Pregnant or breastfeeding females

7. Any prior or co-existing medical condition that in the Investigator's judgment will substantially increase the risk associated with the subject's participation in the study

8. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or completion of the necessary study procedures

9. Significant* cardiovascular disease defined as:
   a. Active heart disease including myocardial infarction within 6 months prior to study entry
   b. Symptomatic coronary artery disease
   c. Uncontrolled or clinically significant arrhythmia, angina, congestive heart failure
   d. Presence of clinically significant valvular heart disease
   e. Presence of clinically significant conduction defect on screening ECG
   f. Uncontrolled hypertension (i.e., systolic BP >160mmHg, diastolic >90 mmHg in repeated measurements) despite adequate therapy
   g. Clinically significant atrial fibrillation

* Grade 3/4 in the CTCAE v4.0 grading would generally be considered clinically significant, although this remains a judgment for the Investigator to make.

10. LVEF ≤ 50%

11. Baseline troponin I and b-type natriuretic peptide > Grade I

12. Prior exposure cardiotoxic agent, such as anthracycline, within 3 months of enrollment

13. Concomitant use of drugs that prolong QT/QTc interval except antibiotics, antifungals, and other antimicrobials used as standard of care for the treatment and prevention of infection and/or other such drugs clinically indicated for patient care. When use of concomitant medications with QT-prolonging potential is necessary, ECG must be repeated 4 hours post-dose on Day 1 (+1 day), on Day 3 (±1 day), and on Day 7 (±1 day), and as clinically indicated, relative to start of agent with QT-prolonging potential. QTc will be calculated using the Fridericia formula. For subsequent use of same concomitant medication, ECG may not be repeated if it did not cause QTc prolongation with tosedostat.

14. Gastrointestinal disorders that may interfere with absorption of drug

15. Active serious infection or sepsis

16. Clinically significant interstitial lung disease

4.3 DURATION OF CLINICAL STUDY

Enrollment in this clinical study is expected to be completed in approximately 24 months, and the total study duration, including the 30-day follow up period, will be approximately 36-48 months. Patients have up to 4 cycles of treatment to achieve a response to tosedostat; responding patients may continue treatment indefinitely, at the discretion of the treating investigator, in collaboration with the sponsor.

5 STUDY ASSESSMENTS

Each treatment cycle consists of 28 days. Visits have a ± 2-day visit window. Day 28 visits may be combined with day 1 visits of subsequent visits to reduce the travel burden of patients.

5.1 SCREEN PERIOD ASSESSMENT (Study Days -28 to 1)

Initiate and complete all screening activities within 14 days before Day 1 of study. Screening tests may be repeated if minor or transient abnormalities are found in lab values or vital signs. The following assessments will be performed:

- Obtaining and signing informed consent
- Review of inclusion and exclusion criteria
- Recording of subject demographics
- Recording of relevant medical history, to record all relevant past and present medical and surgical conditions, diseases or events including allergies or transplants. Recording should also include prior malignancies (whether primary/secondary MDS and other relevant etiology) and its previous treatment (including chemotherapy regimens and doses)
- Physical examination, including assessment of extramedullary disease
- Recording of ECOG performance status
- Vital signs, including body temperature (°C), pulse rate and systolic and diastolic blood

pressures, height (cm), weight (kg), and body surface area
- Determination of LVEF by echocardiography (ECHO)
- Perform 12-lead ECG
- Collect blood samples for hematology, chemistry, cardiovascular panel (including troponin I, b-type natriuretic peptide), coagulation
- Collect Urinalysis
- Recording of concomitant medications and concomitant significant non-drug therapies, including blood product transfusions
- Bone marrow aspirate and biopsy for assessment of bone marrow morphology, cytogenetics, flow cytometry, and immunophenotyping

Once the patient meets the inclusion and exclusion criteria, a request for registration must be sent. Patients will be registered with the Weill Cornell Medical College (WCMC) Joint Clinical Trials Office (JCTO). To register a patient, email the following documents to the regulatory assistant and regulatory coordinator:

- WCMC Patient registration form
- First and last page of the fully executed informed consent form, plus additional pages if checkboxes for correlative studies are required.
- Fully executed short form, if applicable
- Fully executed HIPAA research authorization form
- Eligibility checklist signed and dated by investigator and research nurse/study coordinator
- Documentation of any eligibility waivers granted
- Source documentation to confirm eligibility
- For inpatients, signed consent documentation template (WCMC only)

Documentation of patient registration will be faxed to the Investigational Pharmacy to allow for release of study agent. Patient is eligible to begin treatment once a confirmation email has been sent to study team.

5.2 TREATMENT PERIOD ASSESSMENTS

5.2.1 Cycle 1

Study visits have a ± 2-day visit window

5.2.1.1 Day 1 (Baseline)

If subjects meet all inclusion and exclusion criteria, they will return to the Investigational site within 28 days after the Screening Visit and the following assessments will be performed:

- Review of any changes since the Screening Visit which may affect inclusion/exclusion criteria
- Recording of any changes to medical history since the Screening Visit
- Recording of baseline signs and symptoms
- Physical examination
- Assessment of ECOG performance status

- Vital signs, including body temperature (°C), pulse rate and systolic and diastolic blood pressures, weight (kg), and body surface area
- Collect blood samples for hematology, troponin I, b type natriuretic peptide, coagulation, and blood chemistry (may be omitted if obtained within 7 days as part of the screening visit)
- Collect urinalysis (may be omitted if obtained within 7 days as part of the screening visit)
- Perform 12-lead ECG
- Recording of concomitant medications and significant non-drug therapies including blood product transfusions
- Assess and record of AEs
- Dispense tosedostat
- Instruct subjects on satisfactory completion of treatment diary

5.2.1.2 Days 8, 15, 22

- Physical examination
- Vital signs, including body temperature (°C), pulse rate and systolic and diastolic blood pressures, weight, and body surface area
- Collect blood samples for hematology, chemistry, troponin I, b-type natriuretic peptide
- Perform 12-lead ECG
- Recording of concomitant medications and significant non-drug therapies including blood product transfusions
- Recording of AEs

5.2.1.3 Days 28

- Physical examination
- Vital signs, including body temperature (°C), pulse rate and systolic and diastolic blood pressures, weight, and body surface area
- Collect blood samples for hematology, chemistry, troponin I, b-type natriuretic peptide
- Perform 12-lead ECG
- Transthoracic echocardiogram
- Recording of concomitant medications and significant non-drug therapies including blood product transfusions
- Recording of AEs

5.2.2 Cycles 2

Patients with a documented response of CR, PR, hematologic improvement or stable disease at the end of Cycle 2 may be eligible to continue treatment indefinitely with tosedostat, at the discretion of the Investigator.. Study visits during Cycles 2+ have a 2-day window. Patients must have returned to at least baseline hematological parameters at the start of each cycles unless investigator deems cytopenias are secondary to underlying disease, and all drug-related non-hematological toxicities must have resolved to < grade 2.

5.2.2.1 Day 1

- Recording of any changes to medical history since the Screening Visit

- Recording of baseline signs and symptoms
- Physical examination, including assessment of extramedullary disease
- Assessment of ECOG performance status
- Vital signs, including body temperature (°C), pulse rate and systolic and diastolic blood pressures, weight (kg), and body surface area
- Collect blood samples for hematology, troponin I, b type natriuretic peptide, coagulation, and blood chemistry (blood samples may be omitted if obtained within 7 days)
- Collect urinalysis (may be omitted if obtained within 7 days)
- Perform 12-lead ECG
- Transthoracic echocardiogram, only if patient has been off of tosedostat for more than 2 weeks since prior cycle
- Recording of concomitant medications and significant non-drug therapies including blood product transfusions
- Assess and record of AEs
- Examination of subject treatment diary and return of unused tosedostat
- Dispense tosedostat

5.2.2.2 Days 8, 15, 22

- Physical examination, including assessment of extramedullary disease
- Vital signs, including body temperature (°C), pulse rate and systolic and diastolic blood pressures, weight, and body surface area
- Collect blood samples for hematology, chemistry, troponin I, b-type natriuretic peptide

Perform 12-lead ECG

- Recording of concomitant medications and significant non-drug therapies including blood product transfusions
- Recording of AEs

5.2.2.3 Days 28

- Physical examination, including assessment of extramedullary disease
- Vital signs, including body temperature (°C), pulse rate and systolic and diastolic blood pressures, weight, and body surface area
- Collect blood samples for hematology, chemistry, troponin I, b-type natriuretic peptide
- Perform 12-lead ECG
- Transthoracic echocardiogram
- Recording of concomitant medications and significant non-drug therapies including blood product transfusions
- Recording of AEs

5.2.3 Even Cycles Day 28

Response to be assessed through examination of bone marrow and peripheral blood according to the 2006 IWG criteria.[20]

- Collect samples for local laboratory evaluation for hematology
- Bone marrow aspiration and/or biopsy for confirmation of response
- Record concomitant medications
- Assess and record AEs

Patients with noted responses of CR or PR must have their responses confirmed 4 weeks after initial documentation of response. Patients with noted responses of hematologic improvement at the end of Cycle 2 must have their responses confirmed 8 weeks after initial documentation of response.

5.3 END-OF-TREATMENT SAFETY EVALUATION VISIT

Patients will have an End-of-Treatment Safety Evaluation Visit at discontinuation of tosedostat treatment and before the start of a new cancer therapy. Ideally, the End-of-Treatment Visit occurs on the day the decision to discontinue study treatment is made, but should be within 7 days of discontinuation of tosedostat.

If a patient is lost to follow up and does not complete the End-of-Treatment Visit per protocol, the investigator reports any known AEs that occurred up to last study visit. If at the End-of-Treatment Visit a patient is experiencing ongoing AEs assessed as possibly related to tosedostat, follow up the events until each related AE has returned to baseline, has stabilized and is considered irreversible, or the patient has died.

Complete the following at the End-of-Treatment Safety Evaluation Visit:

- Update concomitant medications
- Perform complete physical examination and weight
- Assess ECOG performance status
- Perform a 12-lead ECG
- Transthoracic echocardiogram
- Measure and record vital signs
- Collect samples for hematology and serum chemistry
- Collect BM biopsy or aspirate (if clinically indicated) for patients who have relapsed
- Assess and record AEs

5.4 UNSCHEDULED VISITS

An unscheduled visit may be performed for a variety of reasons, including confirmation of bone marrow or hematologic responses, safety investigations, additional treatments such as transfusions, and case reviews. Where an unscheduled visit is performed for safety reasons, the Investigator should consider performing appropriate investigations from those listed below. Appropriate investigations for a CR/PR confirmation visit should include:

- Hematology sample
- Bone marrow aspirate and biopsy for assessment of morphology, cytogenetics, flow cytometry

Appropriate investigations in other circumstances may include:

- Physical examination, including assessment of extramedullary disease, height, weight,

and body surface area
- Vital signs, including body temperature (°C), pulse rate and systolic and diastolic blood pressures
- Blood samples for hematology, troponin I, b-type natriuretic peptide, chemistry
- Urinalysis
- Cardiovascular panel and LVEF assessment (ONLY if the unscheduled visit is for a possible cardiovascular AE)
- Recording of concomitant medications and concomitant significant non-drug therapies including blood product transfusions
- Recording of AEs
- Bone marrow aspiration and biopsy

5.5 SUBJECT FOLLOW-UP

Survival data for subjects who complete the study or withdraw from the study will be collected every 3 months and recorded until the time of death or the subject is lost to follow-up. LVEF assessment by transthoracic echocardiogram as well as electrocardiogram will be done every 12-24 weeks after study discontinuation or through study completion if possible for those subjects who experience at least a grade II decrease of ejection fraction at end of treatment. Adverse events must be recorded for 28 days after last dose of study drug. All adverse events must be followed until resolution as outlined in Section 7.3.6.5.

5.6 DEFINITION OF END OF TRIAL

The End of Trial will be the date of the last subject's end-of-treatment visit.

5.7 PROTOCOL DEVIATIONS, PATIENT DISCONTINUATION, AND STUDY TERMINATION CRITERIA

5.7.1 Protocol Violations/Deviations

Protocol violations are defined as a departure from the protocol that affects patient safety or benefit potential, or confounds assessments of safety or clinical activity. A protocol deviation is a departure from the protocol that does not meet the above criteria. Protocol violations or deviations may be grouped into the following classes:

- Enrollment criteria
- Study activities
- Noncompliance to dose or schedule, including dose calculations, administration, and
- interruption; reduction; or discontinuation criteria
- Clinical trial handling including storage and accountability
- Informed consent and ethical issues

Protocol violations/deviations will be reported as per IRB policy.

5.7.2 Patient Withdrawal

Inform patients that they may withdraw from this clinical study at any time without jeopardizing their relationship with their health care providers. Follow up details are provided in Section 5.7.5.

5.7.3 Investigator Discontinuation of Patient

The Investigator may exercise medical judgment to discontinue a patient's treatment with tosedostat because of clinically significant changes in any clinical or laboratory parameter. Follow up details are provided in Section 5.7.5.

5.7.4 Criteria for Protocol-Defined Required Discontinuation of Treatment

- Discontinue treatment with tosedostat if patients experience any of the following:
- Do not achieve CR, PR, hematologic improvement, or bone marrow remission after four cycles of treatment with tosedostat alone or 4 cycels of azacitidine if azacitidine is added to tosedostat.
- Experience disease progression
- Develop an intercurrent illness that prevents further treatment with tosedostat
- Develop unacceptable/intolerable AE(s)
- Withdraw from the clinical study
- Become pregnant
- Receive other systemic cancer therapy or protocol-prohibited medications
- Have general or specific changes that render the patient unsuitable for further treatment with tosedostat, in the judgment of the Investigator

5.7.5 Follow Up at Treatment Discontinuation or Early Withdrawal

Patients treated with tosedostat should have an End-of-Treatment Visit within 7 days of last dose of tosedostat and before the start of a new cancer therapy. End-of-Treatment Visit assessments are listed in Section 5.3.

5.7.6 Study Termination

The Investigator has the right to terminate this clinical study at any time. Reasons for terminating the clinical study or a clinical site's participation include, but are not limited to, the following:

- The incidence or severity of an adverse reaction in this or other studies, indicating a potential health hazard to patients
- Unsatisfactory patient enrollment
- Inaccurate or incomplete data recording
- Site personnel noncompliance to study procedures

Request from regulatory body such as the FDA or IRB

5.8 Correlative Studies

Samples will be collected for studies related to MDS. The samples consist of peripheral blood and bone marrow aspirate. Approximately 10 - 30mL of bone marrow aspirate and up to 20mL of peripheral blood will be collected at the following time points:

- Screening
- Cycle 1 Day 15 (peripheral blood only)
- End of C2
- Any clinically relevant points thereafter as indicated to be safe by the Investigator

The collection of these samples occurs during standard of care timepoints. Patients will not undergo a separate procedure for the collection of these samples. Samples will also be stored for possible future studies. The appropriate future research language and genetic testing language is included in the consent form for subject notification and information.

Samples will be stored indefinitely unless the patient provides a written request for destruction of their specimens.

6 STUDY TREATMENTS

6.1 IDENTITY OF INVESTIGATIONAL PRODUCT(S)

Basic information about the study treatments is provided in Table 4.

Table 4: Study Treatments

Test Product:	CHR-2797
Trade Name	Tosedostat
Manufacturer	Patheon UK Ltd.
Dose	120 mg daily
Route of administration	Oral
Formulation	Hard gelatin capsules, in blister packs
Capsule strengths	60 mg

Tosedostat will be provided by CTI BioPharma Corp. in bottles of 30, 60 mg capsules. A 120 mg once daily dose will require the subject to take 2 capsules per day. Shelf life details will be clearly printed on the packaging labels and accompanying documentation. The product should be stored below 30°C (86°F), protected from moisture and light. Do not freeze.

6.2 ADMINISTRATION AND TIMING OF DOSE

The dose regimens of tosedostat will be 120 mg once daily.

The dose of tosedostat should be taken orally with a glass of water after food, preferably in the morning at about the same time every day to ensure an even dose interval.

6.3 ADDITION OF AZACITIDINE FOR NON-RESPONSE

If at end of two cycles of tosedostat, patient does not have response as defined as above, the investigator has discretion of adding azacitidine in addition to tosedostat. Dosing will be standard dosing (azacitidine 75mg/m^2), either subcutaneously or intravenously, for 5 continuous days every 28 days.

6.4 MONITORING OF CARDIAC FUNCTION

In view of possible cardiotoxic potential of tosedostat, cardiac monitoring includes routine troponin I, BNP, EKG, and transthoracic echocardiogram every cycle. If a patient has been off tosedostat for more than 2 weeks, then an additional transthoracic echocardiogram will be done prior to starting subsequent cycle (day 1 of the next cycle). Clinically significant cardiaovascular events will be assessed by the investigator, and investigator may reduce or hold dose of tosedostat until cardiovascular studies return back to baseline.

6.5 DOSE MODIFICATIONS AND INTERRUPTIONS

The Investigator may temporarily discontinue dosing of tosedostat for safety reasons, for example if the Investigator considers that an AE is related to tosedostat. The Investigator should document the reasons for discontinuation, and should contact the Medical Monitor to discuss the case and possible options. In addition, the Investigator may reduce the dose of tosedostat to 60 mg once daily for safety reasons for which the Investigator considers temporary or permanent discontinuation is unnecessary.

Throughout the clinical study, safety is assessed for all patients through laboratory evaluations, vital signs, physical examinations, ECGs, echocardiogram, and the incidence and severity of AEs/SAEs. Doses may be reduced or held based on the toxicity of drug-related hematologic and non-hematologic toxicities that occur during the preceding cycle.

There will be no dose adjustments based on hematologic parameters EXCEPT for grade 4 hematologic toxicities. Dose adjustments pertaining to non-hematologic and hematologic toxicities should be performed as follows:

DRUG-RELATED AE	ACTION
CTCAE Grade 1	No adjustments needed
CTCAE Grade 2	Investigator's option to reduce or hold dose
CTCAE Grade 3[a]	• If non-hematologic toxicity, withhold dose until recovery to baseline. If it persists for more than 14 days, Investigator will determine if patient will discontinue treatment. • If hematologic toxicity, no dose adjustments will be made.
CTCAE Grade 4	• If hematologic toxicity, Investigator will determine if the patient may continue on study with appropriate dose reduction.

- If non-hematologic toxicity, patient will discontinue treatment.

a Excluding nausea, vomiting, or diarrhea controlled with antiemetic or antidiarrheal therapy; alopecia; Grade ≥ 3 mucositis lasting < 5 days; Grade ≥ 3 AST or ALT elevation lasting < 7 days; and infection/febrile neutropenia controlled with antibiotics.

The reasons for any dose adjustments for any patient should be documented in the patient's source record.

Adverse events to be excluded from consideration for dose adjustments include:

- Alopecia
- Grade ≥ 3 mucositis lasting < 5 days
- Grade ≥ 3 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation lasting < 7 days
- Infection/febrile neutropenia controlled with antibiotic therapy
- Grade 4 hematologic AE: anemia, neutropenia, or thrombocytopenia persisting after cycle 2 in the presence of residual MDS
- Other grade 3 or higher non-hematologic toxicity that are clearly and incontrovertibly due to extraneous causes
- Grade 3 or greater nausea, diarrhea, or vomiting that is managed with the use of medical intervention

6.6 PRIOR AND CONCOMITANT TREATMENTS

Medications taken by, or administered to, the subject within 28 days prior to first dose of tosedostat, or up to 28 days after the final dose of tosedostat, should be recorded. The entry should include the generic name, dose regimen, route, indication, and dates of use.

6.6.1 Best Supportive Care

All subjects should receive best supportive care including, but not limited to, transfusions of red cells (with iron chelation therapy as needed), platelets, and medication for the prevention and treatment of infections and hyperuricaemia. These are all given at the discretion of the Investigator and should be fully documented in the eCRF. Best Supportive Care should be recorded for treatments given in the 28 days prior to first dose of tosedostat, or up to 28 days after the final dose of tosedostat.

6.6.2 Allowed Medications

The following medications may be used within the recommendations of nationally applicable marketing approvals and the following limits:

- Anticoagulant Therapy: subjects who are taking warfarin (or equivalent) may participate in this study; however, it is recommended that prothrombin time (PT) be monitored carefully at least twice per week for the first month, followed by the pre-study level of monitoring if the international normalized ratio is stable. Subcutaneous heparin is permitted

- Colony Stimulating Factors: the routine use of granulocyte colony stimulating factors (GCSFs or GM-CSFs) is permitted for the treatment of neutropenic sepsis during this study. Subjects should not receive G-CSFs prophylactically in general.

- When use of concomitant medications with QT-prolonging potential is necessary, ECG must be repeated 4 hours post-dose on Day 1 (+1 day), on Day 3 (±1 day), and on Day 7 (±1 day), and as clinically indicated, relative to start of agent with QT-prolonging potential. QTc will be calculated using the Fridericia formula.

6.6.3 Excluded Medications

Immunotherapy, hormonal cancer therapy, high-dose corticosteroids (other than topical, intra-articular, inhaled, short courses for the prevention of hypersensitivity, for example during blood product transfusions, or other locally administered steroids), radiation therapy (except small field radiotherapy with palliative intent) or experimental medications are not permitted at any time after randomization.

6.6.4 Cytochrome P450 Interactions

Currently available *in vitro* data suggest that tosedostat may be a moderate inhibitor of selected catalytic activities of CYP4503A4. Therefore, it may participate in, or contribute to, inhibitory drug-drug interactions *in vivo*, which are mediated by cytochrome P4503A4. Drugs that are known to be substrates for CYP4503A4 should be used with caution, examples of which include acetaminophen, carbamazepine, cyclosporin, digitoxin, diazepam, erythromycin, felodipine, fluoxetine, nifedipine, quinidine, saquinavir, terfenadine, triazolam, verapamil, and warfarin.

It is not expected, however, that tosedostat will reach sufficiently high, prolonged concentrations to significantly impact upon the metabolism of such drugs. Tosedostat has little effect on the enzyme activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

6.7 TREATMENT COMPLIANCE

The prescribed dosage, timing, and mode of administration may not be changed, except as stipulated in Section 6.3. Any departures from the intended regimen must be documented. Overdoses should be reported to a CTI BioPharma Corp. representative or designee. The clinical manifestation (if any) of an overdose should be reported as an AE or SAE, as appropriate.

Subjects will be issued with a diary in which they should record study drug taken or omitted. Reasons for omission should be recorded. At the end of each month during the study, prior to dispensing further study medication, the treatment diary will be reviewed, previously dispensed study medication will be retrieved by the Investigator and compliance assessed. Subjects exhibiting poor compliance as assessed by capsule counts should be counselled on the importance of good compliance to the study dosing regimen.

Non-compliance is defined as taking less than 80% of study medication during any evaluation

period (visit to visit). Protocol permitted dose discontinuations will not be counted towards this percentage. Subjects exhibiting poor compliance may be withdrawn from the study. A discussion between the Investigator and the Medical Monitor must occur before this happens.

6.8 STUDY MEDICATION ACCOUNTABILITY

The Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all trial medication using a Drug Accountability Form. These forms must be available for inspection at any time.

7 EFFICACY, SAFETY AND PHARMACOKINETICS MEASURES

7.1 SCHEDULE OF ASSESSMENTS

A Schedule of Assessments is presented in Appendix 1, Sections 11.1.

7.2 EFFICACY MEASURES

Primary and secondary endpoints include evaluation of efficacy by determination of the number of patients who achieve a response (i.e. CR, PR, stable disease, disease progression, or hematologic improvement). Response will be evaluated every 2 cycles or more frequently at the discretion of the investigator. Determination of disease response is based on the 2006 IWG response criteria (see Appendix 3).

7.3 SAFETY MEASURES

Safety assessments will be performed at intervals indicated in the Schedule of Assessments (Appendix 1, Sections 11.1) and at any time deemed necessary by the Investigator.

7.3.1 Physical Examination

Physical examinations may include examination of general appearance, skin, head and neck (including thyroid), eyes, ears, nose, throat, heart, lungs, chest (including breasts), abdomen, genitalia, anorectal area, musculoskeletal, lymph nodes, extremities, nervous system, and assessment of extramedullary disease. An AE form must be completed for all changes from condition at the Baseline Visit that are identified as clinically noteworthy.

7.3.2 Vital Signs

Vital signs will include body temperature (°C), pulse rates, and systolic and diastolic blood pressures. Height in centimeters (without shoes) and weight in kilograms will be recorded. Body surface area (BSA) will be calculated automatically in the eCRF at screening using the following formula: BSA is square root of (height in cm x weight in kg)/3600.

7.3.3 Electrocardiography (ECG)

Standard 12-lead ECGs will be conducted during the Screening Visit, and as indicated in the schedule of assessments (Appendix 1).

7.3.4 Left Ventricular Ejection Fraction

The left ventricular ejection fraction (LVEF) will be measured by transthoracic echocardiogram

at end of each cycle. If patient has been off tosedostat for more than 2 weeks after Day 28, then a transthoracic echocardiogram will be repeated prior to start of subsequent cycle.

7.3.5 Laboratory Parameters

The laboratory tests comprise:

- Hematology: Hgb, erythrocyte count, leukocyte count (with differential), platelet count, mean corpuscular volume, lymphocyte count, ANC
- Coagulation: PT, activated partial thromboplastin time (APTT).
- Chemistry: blood urea nitrogen (BUN), , chloride, albumin, ALT, alkaline phosphatase, aspartate aminotransferase (AST), bilirubin-total, calcium, creatinine, glucose, potassium, total protein, sodium, and magnesium.
- Cardiovascular panel: Troponin I, N-terminal Prohormone Brain Natriuretic Peptide,
- Urinalysis (dipstick): pH, specific gravity, ketones, protein, glucose, bilirubin, and blood. In addition, a microscopic examination is to be performed if more than 1 test is positive.

In the event of an unexplained clinically noteworthy abnormal laboratory test value, the test should be repeated immediately and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered an AE; however, if the laboratory value abnormality is consistent with a current diagnosis, it may be documented accordingly. A change in CTCAE grading of 2 or more grades in any laboratory value should be reported as an AE. All grade 3 or higher CTCAE side effects should be reported as an AE.

7.3.6 Adverse Events

The Investigator is responsible for recording all AEs observed during the study (screening, treatment and a 28-day period after last dose of study drug). Events which occur during the screening period will be considered baseline signs and/or symptoms unless caused by a study-related procedure or intervention, in which case they will be considered AEs.

Definition of AE in this study: an AE is any untoward medical occurrence in a subject administered a pharmaceutical product (or associated with a study-related procedure) and which does not necessarily have a causal relationship with this treatment.

Definition of Serious Adverse Event (SAE): an AE that:

- Results in death
- Is life-threatening (the subject is at a 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)
- Requires inpatient hospitalization or prolongation of existing hospitalization: hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Other: medically significant events, which do not meet any of the criteria above, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. An example of such an event would be convulsions that do not result in hospitalization.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

7.3.6.1 Severity

The severity of the AE will be defined by the CTCAE v4.0

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

7.3.6.2 Relationship

The causal relationship between the study medication and the AE has to be characterized as 'related' or 'unrelated'as defined below:

Related to study drug: Any AE (serious or not) that appears to have a reasonable possibility of causal relationship to the use of the study drug (i.e., a relationship cannot be ruled out). Guidelines to determine whether an event might be considered related include (but are not limited to) the following:

- The event occurred in close temporal relationship to study drug administration.
- The event abated (diminished) or disappeared when treatment with the study drug was down-titrated, interrupted, or discontinued.
- The event re-occurred when treatment was re-introduced.
- Environmental factors such as clinical state and other treatments could equally have caused the event.

Unrelated to study drug: This category applies to any AE (serious or not) that does not appear to have a reasonable relationship to the use of study drug (see above guidelines).

7.3.6.3 Reporting of Adverse Events

All AEs, regardless of severity and whether or not they occurred during the screening, treatment or follow-up period, are to be recorded on the appropriate AE pages (either 'serious' or 'non-serious') in the eCRF. Events which occur during the screening period will be considered baseline signs and/or symptoms unless caused by a study-related procedure or intervention,

in which case they will be considered AEs. The Investigator should complete all the details requested including dates of onset, resolution, severity, action taken, outcome, relationship to study drug. Each event should be recorded separately.

7.3.6.4 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

As Sponsor, Weill Cornell Medical College is responsible for ensuring the expedited reporting of serious, unexpected adverse drug reactions to regulatory authorities and IRBs/IECs. Expectedness assessments will be made by the IRB using the most current, approved Tosedostat Investigator Brochure or approved product labeling (e.g. for Azacitidine) The PI is responsible for submission of expedited reports to the IRB. A written report will be submitted to the Institutional Review Board (IRB) in accordance with the IRB's policy. SAEs should also be reported to CTI BioPharma Corp. (CTI). SAE reports [(including the voluntary MedWatch Form (Form FDA 3500) if criteria are met] should be sent to:

NAME: CTI Pharmacovigilance
FAX #: + 1 866 660 8967
E-mail: pv@ctiseattle.com

The study number, WCMC IST-CTI-MDS, should be referenced on the fax or subject line of the e-mail. Additional follow-up information should be completed on a SAE follow-up form as soon as it becomes available.

7.3.6.5 Follow-Up of Adverse Events

The Investigator will continually monitor any subject with an AE and SAE until either the event has returned to the baseline grade or ≤ grade 1 or, if the AE is determined to be chronic, a cause is identified, or until the subjects starts another type of anti-neoplastic therapy.

Follow-up of all AEs must be documented in the subject's medical record and on the eCRF. A narrative outlining the details of the SAE, treatment, and outcome are to be included on the SAE form and additional information which the investigator thinks is relevant.

All Serious AEs that occur within 28 days of the last dose of study drug should also be reported to CTI BioPharma Corp. and followed up in the same manner. New SAEs assessed as causally related to Tosedostat and occurring at any time after the End-of-Study or after the 28-day follow-up period after study drug discontinuation (whichever comes first) should be reported to the Sponsor promptly after the Investigator becomes aware of the event.

7.4 QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted and monitored according to GCP and training will be given to all study personnel on all relevant aspects of the protocol.

According to the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), CTI BioPharma Corp. is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, and efficacy data for all enrolled patients.

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

The PI ensures all completed CRFs and completed data correction forms are accurate.

In addition, CTI BioPharma Corp. may conduct periodic audits of the study processes, including, but not limited to investigational site, site visits, central laboratories, vendors, clinical database, and final clinical study report. When audits are conducted, access must be authorized for all study related documents including medical history and concomitant medication documentation to authorized CTI BioPharma Corp. representatives and regulatory authorities.

Additionally, as the WCM DSMB serves as the primary monitoring entity for the trial, the WCM DSMB will have access to the RedCap database to verify data integrity.

7.4.1 Safety Monitoring

This is an investigator-initiated trial. The Principal Investigator will be responsible for the study and will ensure that the protocol is being followed in accordance with current local IRB, FDA, and ICH regulations/guidelines.

In this research study, safety data is reviewed on a rolling basis. A formal safety interim analysis will take place after 40 patients have been enrolled and completed at least one cycle of treatment. The Investigator will review the following safety:

- Physical exam
- Vital signs
- Electrocardiogram (ECG)
- Left ventricular ejection fracture (LVEF)
- Laboratory parameters, includes blood counts, blood chemistries, urinalysis, coagulation, and cardiac panel
- Adverse events and serious adverse events

Based on the results of the interim analysis, the investigator may allow the study to proceed as is, modify the study, or terminate the study.

7.4.2 Data Management/Coding

Data generated within this clinical trial will be handled according to the relevant SOPs ofWCMC. Adverse events and concomitant diseases should be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications and prior MDS therapies will be coded using the WHO Drug dictionary.

7.4.3 Quality Assurance Audit

Investigator sites, the study database and study documentation may be subject to Quality Assurance audit during the course of the study by CTI BioPharma Corp. or a third party auditor on behalf of CTI BioPharma Corp. In addition, inspections may be conducted by regulatory bodies at their discretion.

7.4.4 Data Safety Monitoring Board (DSMB)

Weill Cornell Medical College requires that all research approved by the WCMC IRB include an appropriate plan for the monitoring of data to ensure the safety of human subjects. Research supported by Federal agencies will be monitored according to all regulations and guidelines of the relevant Federal agency.

The WCM Data and Safety Monitoring Board (WCM DSMB) will review the IRB approved protocol, informed consent documents, and data and safety monitoring plan (DSMP). During the course of the study, the DSMB will perform a review of initial subject safety data following the treatment of five subjects with one cycle of treatment (28 days) after approval of protocol version 1.2, and then semiannually to evaluate safety, efficacy, study conduct, and scientific validity and integrity of the trial. An interim analysis for futility will be performed after the first 40 subjects are treated, and if the median overall survival is less than three months, then we will consider discontinuing the study for futility. The WCM DSMB will review interim analysis results. Subsequent enrollement should ideally resume after completion of interim analysis, however recognizing the acute and grave nature of MDS, it might not be possible to deny treatment to potential subjects for ethical reasons sufficiently long to complete interim analysis.

Given the aggressive nature of disease and expectation of serious adverse events in this study population, if there are ≥8 instances of grade V events related to the study drug, then we will considering discontinuing the study for safety.[19,21]

The WCM DSMB will also review all SAEs occurring on the trial. SAEs will be reported to the DSMB per the WCM IRB Immediate Reporting Policy: http://researchintegrity.weill.cornell.edu/institutional_review_board/irb_adv.html. The WCM DSMB may also convene as need if stopping criteria are met or other safety issues arise

that the Principal Investigator and/or IRB would like the WCM DSMB to address. The study Principal Investigator is responsible for submitting all written DSMB recommendations to the IRB upon receipt.

8 STATISTICS

This is an open-label, phase II study designed to explore the clinical activity of tosedostat in patients with MDS who have failed therapy with hypomethylating agents. The study will include 80 patients with high and very high risk MDS with the goal of doubling median overall survival from 6 to 12 months. A futility analysis will be performed after the first 40 patients are treated, and if the median overall survival is less than 3 months, then we will consider closing the study.

Sample size considerations:

The primary endpoint for is overall survival, as measured from the start of the treatment to the date of death (or date of last follow-up if no death). Previous data suggest that the median overall survival for high risk MDS patients is 6.0 months. With the administration of tosedostat, we anticipate the median overall survival to be improved to ≥9 months. A sample size of 80 patients is planned for this study, which will give us at least 85% power to detect the hypothesized improvement. This calculation assumes a Type I error of 10%, a one-sided test, and a median follow-up time of 2.5 years. It also assumes that survival times are exponentially distributed. This last assumption is for planning purposes only; actual analysis will employ nonparametric methods for estimation and testing of survival distributions. A two-sided 95% confidence interval for the median overall survival is estimated to be (6.2 months, 12.7 months) under the hypothesized improvement. At an accrual rate of 3-4 patients per month, we anticipate to complete enrollment in approximately two years.

Analysis Plan:

The median overall survival will be estimated by the Kaplan-Meier method and 95% confidence intervals for overall survival estimates will be calculated using Greenwood's formula. Descriptive statistics will be utilized to describe the parameter proportions defined above (i.e., frequency, percent). Estimated differences in the transfusion independence proportion/overall survival between categories of demographic and treatment variables (evaluated by the two-sample t-test, Wilcoxon rank-sum test, Fisher's exact test, and log-rank test, as appropriate) will serve as preliminary data (i.e., hypothesis-generating) for future studies. All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals will be calculated to assess the precision of the obtained estimates. All analyses will be performed in SAS Version 9.4 (SAS Institute, Inc., Cary, NC) and Stata Version 14.0 (StataCorp, College Station, TX).

Safety Analyses

Safety analysis will include AE summary tables using Medical Dictionary for Regulatory Activities (MedDRA) and NCI CTCAE criteria, changes in physical examination and performance status, ECG, and laboratory summary tables and figures.

Adverse Events
Adverse events occurring during the AE reporting period (see Section 7.3) will be summarized. They will be tabulated by SOC and by preferred term within SOC according to MedDRA. Severity will be graded using the NCI CTCAE. While the goal is to collect 28-day follow-up data, it is possible that patients may proceed to other anticancer therapies before completing the 28-day follow-up.

Exact 95% confidence intervals around the adverse event proportions will be calculated to assess the precision of the obtained estimates.

9 ETHICS

9.1 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

The Investigator will provide CTI BioPharma Corp. or Quintiles with documentation of IRB/Independent Ethics Committee (IEC) approval of the protocol and informed consent before the study may begin at the investigational site(s). The Investigator will supply documentation to CTI BioPharma Corp. or Quintiles of any required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of subjects or the conduct of the trial. Similarly, the Investigator will submit written summaries of the trial status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC to do so. Upon completion of the trial, the Investigator will provide the IRB/IEC with a brief report of the outcome of the trial, if required.

9.2 ETHICAL CONDUCT OF THE STUDY

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki, the applicable guidelines for GCP, or the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

9.3 SUBJECT INFORMATION AND INFORMED CONSENT

The informed consent form will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The informed consent form contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study medication. The Investigator will provide each subject with a copy of the signed and dated consent form and will document in the subject's source notes that informed consent was given.

10 STUDY ADMINISTRATION

10.1 DATA HANDLING AND RECORD KEEPING

The Investigator must maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed informed consent forms, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

10.2 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject enrolled into the study.

The Investigator will allow CTI BioPharma Corp. and authorized regulatory authorities to have direct access to all documents pertaining to the study.

10.3 INVESTIGATOR INFORMATION

10.3.1 Investigator Obligations

This study will be conducted in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP, 1997); the US Code of Federal regulations (CFR) Title 21 parts 50, 56, and 312; and European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki, sixth revision, 2008.

11 APPENDIX

11.1 APPENDIX 1: SCHEDULE OF ASSESSMENTS

Assessment	Screening Day -14 to 1	Baseline Cycle 1 Day 1	Cycle 1 Day 8, 15, and 22	Cycle 1 Day 28	Cycle 2+ Day 1	Cycle 2+ Day 8, 15, and 22	Cycle 2+ Day 28	End of Treatment Safety Evaluation Visit[5]
Obtain informed	X							
Record subject demographics	X							
Review inclusion/exclusion criteria	X	X						
Medical history[1]	X	X						
Baseline signs and symptoms		X						
Physical examination	X	X	X	X	X	X	X	X
ECOG performance	X	X			X		X	X
Vital signs[2]	X	X	X	X	X	X	X	X
Hematology including blood film	X	X[3]	X	X	X	X	X	X
Troponin I & b-type natriuretic peptide	X	X			X			X
Coagulation	X	X[3]			X		X	X
Blood chemistry	X	X[3]	X	X	X	X	X	X
Urinalysis	X	X[3]		X	X		X	X
ECG	X	X	X	X	X	X	X	X
LVEF[6]	X			X	X[7]		X	X
Concomitant medication/non-drug therapies	X	X	X	X	X	X	X	X
Bone marrow aspiration or biopsy	X						X[4]	X
Research studies (bone marrow and peripheral blood collection)[8]	X		X				X	
Adverse events		X	X	X	X	X	X	X
Administer/Dispense tosedostat		X			X			
Review treatment Diary/Return of tosedostat								X

1. Including leukemia history, previous therapy, and pre-existing diseases; new symptoms and signs occurring between screening and baseline will be recorded as medical history if completed, baseline symptoms and signs if ongoing and blood product transfusion history
2. Vital signs will include height, weight, body surface area, body temperature (°C), pulse rate, systolic and diastolic blood pressures

3. Hematology, blood chemistry, and urinalysis may be omitted if screening visit within 7 days
4. Bone marrow samples will be collected on even cycles on days 28 for response. Bone marrow biopsy has ±10 day window
5. End of Treatment Safety Evaluation Visit (Follow-up) will be 28 (+2 day window is allowed) days after last dose of study drug or before start of new anticancer therapy.
6. LVEF evaluation via transthoracic echocardiogram
7. Transthoracic echocardiogram on day 1 if patient has been off of tosedostat for more than 2 weeks since prior cycle.
8. Bone marrow aspirate and peripheral blood will be collect at baseline, week 2 during cycle 1 (blood only), the end of cycle 2, and during other clinically relevant time points deemed safe by the investigator

Note: Day 28 visits and day 1 visits of subsequent cycles may be combined to reduce travel burden on patients

11.2 APPENDIX 2: IWG RESPONSE CRITERIA

2006 International Working Group (IWG) Response Criteria for MDS[20]

Category	Response criteria (responses must last at least 4 wk)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines
	Peripheral blood‡ • Hgb ≥ 11 g/dL • Platelets ≥ 100 × 10^9/L • Neutrophils ≥ 1.0 × 10^9/L† • Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow 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 bone marrow 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
Cytogenetic response	**Complete**: Disappearance of the chromosomal abnormality without appearance of new ones
	Partial: At least 50% reduction of the chromosomal abnormality

Category	Response criteria (responses must last at least 4 wk)
Disease progression	For patients with: • Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts • 5%-10% blasts: ≥ 50% increase to > 10% blasts • 10%-20% blasts: ≥ 50% increase to > 20% blasts • 20%-30% blasts: ≥ 50% increase 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 • Transfusion dependence
Survival	**Endpoints**: • Overall: death from any cause • Event free: failure or death from any cause • PFS: disease progression or death from MDS • DFS: time to relapse • Cause-specific death: death related to MDS

IWG response criteria for hematologic improvement[20]

Hematologic improvement*	Response criteria (responses must last at least 8 wk)
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL
	Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. 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 × 10^9/L)	Absolute increase of ≥ 30 × 10^9/L for patients starting with > 20 × 10^9/L platelets Increase from < 20 × 10^9/L to > 20 × 10^9/L and by at least 100%‡
Neutrophil response (pretreatment, < 1.0 × 10^9/L)	At least 100% increase and an absolute increase > 0.5 × 10^9/L‡
Progression or relapse after HI	**At least 1 of the following:** • At least 50% decrement from maximum response levels in granulocytes or platelets • Reduction in Hgb by ≥ 1.5 g/dL • Transfusion dependence

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