Phase Ib/II study of the glutaminase inhibitor telaglenastat (CB-839) in combination with azacitidine in subjects with advanced myelodysplastic syndrome

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1. OBJECTIVES

1.1 Primary Objectives

The primary objectives of this study are to determine the safety, tolerability and clinical activity of telaglenastat (CB-839) in combination with azacitidine (AZA) for patients with advanced MDS.

1.2 Secondary Objectives

The secondary objectives of the study are:

1.2.1. To explore the pharmacokinetics (PK) of telaglenastat in combination with AZA

1.2.2. To explore the pharmacodynamics (PDn) of telaglenastat in combination with AZA

1.2.3. To assess overall survival, event-free survival and duration of response of telaglenastat in combination with AZA

2. BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Background

Myelodysplastic syndromes (MDS) are malignant clonal disorders characterized by ineffective hematopoiesis, bone marrow dysplasia, peripheral cytopenias including thrombocytopenia, and a propensity to transform into acute myeloid leukemia (AML).(1, 2) Classically, MDS is associated with apoptosis and excessive proliferation, resulting in a paradoxical combination of a hyper-cellular marrow and peripheral cytopenias.(3) The incidence of MDS in the United States is rising, with approximately 20,000 to 30,000 new cases of MDS diagnosed annually, and a median age at diagnosis of 70 years.(3, 4)

Over the past decade, clinical use of the hypomethylating agent azacitidine has been shown to improve patient quality of life, decrease transfusion requirements, and improve outcome parameters in MDS patients, and is now a standard of care for MDS patients requiring therapy. With current HMA regimens, achievement of an ORR is estimated at 28-70%, with a CR rate of only 6-34% in patients with MDS treated with front-line HMA therapy, and with a median length of response in the HMA-responders of only 8 to 10 months.(5-10)

MDS patients requiring therapy include those with intermediate-2 or High-risk disease by IPSS, or high or very-high risk by R-IPSS.(11) In addition, patients with otherwise intermediate MDS with high-risk molecular features including *TP53*, *ASXL1*, *EZH2*, and/or *RUNX1* mutations have been identified as a subgroup that may benefit from early therapeutic intervention.(12)

2.2 Rationale for Glutaminase Inhibition:

Tumor cells including MDS cells exhibit an altered metabolic profile compared with normal cells, presumed to favor rapid growth and proliferation as well as augmented survival in hypoxic environment. As first noted by Warburg in 1924, tumor cells display “aerobic glycolysis” in lieu of oxidative phosphorylation, and thereby generate limited ATP from glucose. Consequently, many tumor cells require a continuous supply of exogenous glutamine (GLN) that is used to fuel the tricarboxylic acid (TCA) cycle for the generation of ATP and as a precursor in the generation of amino acids, nucleic acids, and fatty acids. This enhanced utilization of GLN requires the activity of glutaminase, a mitochondrial enzyme which converts GLN to glutamate (GLU). GLU, in turn, has a number of important bioenergetic and biosynthetic functions including as an anaplerotic intermediate fueling the TCA cycle via conversion to α-ketoglutarate (αKG). Many tumors have been found to have a pronounced upregulation of glutaminase. These tumors are sensitive to withdrawl of GLN from growth medium, usually have a high cellular ratio of GLU to GLN, and are very sensitive to the inhibition of glutaminase by telaglenastat .

Anti-tumor activity of glutaminase knock-down with shRNA or inhibition with small molecules has been reported both *in vitro* and *in vivo*.(13, 14) Mutations in the TCA cycle enzyme isocitrate dehydrogenase (IDH), either in the cytoplasm (IDH1) or mitochondria (IDH2), have been identified in both AML and MDS. These mutations result in conversion of the TCA cycle intermediate aKG into 2-hydroxyglutarate (2HG). 2HG, considered an oncometabolite, accumulates in the cell resulting in dioxygenase blockade, DNA and histone hypermethylation, and ultimately, impaired cell differentiation.

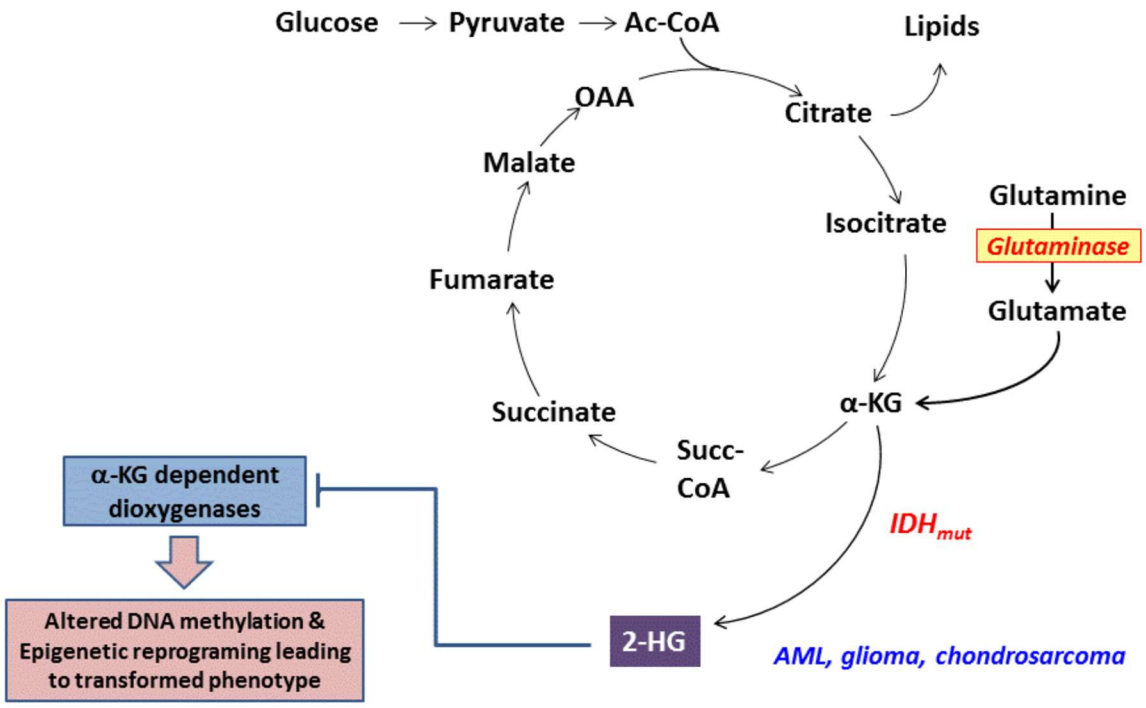

Figure 1: Metabolic pathway associated with IDH1 and IDH2 mutations.

Telaglenastat is a potent and selective reversible inhibitor of glutaminase activity. Two alternative splice variants of glutaminase (GLS), GAC and KGA, are found in tumors and in normal tissues including lung, liver, heart, kidney, spleen, intestine and brain. A separate gene encodes glutaminase-2 (GLS2), found mainly in the liver. Telaglenastat is an allosteric and noncompetitive inhibitor of both GAC and KGA isoforms of glutaminase, but does not inhibit GLS2. Incubation of recombinant human glutaminase with CB-839 results in time-dependent and slowly reversible inhibition of glutaminase activity (IC50 = 34 nM with 1 hour pre-incubation). Glutaminase inhibition is associated with antiproliferative activity in a wide range of tumor cell lines. Pro-apoptotic activity

has been observed in triple-negative breast cancer (TNBC), multiple myeloma, mesothelioma, and many additional solid and hematologic tumors.

Recent experimental data suggest that glutamine metabolism is very important for leukemic blasts. Removal of glutamine from the culture media of AML cell lines inhibits mTORC1 and induces apoptosis, and shRNA knockdown of SLC1A5, a high-affinity transporter for GLN, inhibits tumor formation in mouse AML xenografts. Leukemic cells may be dependent on glutamine utilization pathways to provide carbon skeletons for TCA activity (Matre et al, ASH 2013).

The antiproliferative and pro-apoptotic effect of telaglenastat has been evaluated alone and in combination with the hypomethylating agent azacitidine in two different AML cell lines (data from OCI-AML3 cell line shown in Figure 2). Both telaglenastat and azacitidine showed significant antiproliferative effects in both cell lines. In combination, substantially greater inhibition of cell number and induction of apoptosis was observed. The mechanism whereby these agents act together has not been fully established. However, recent findings indicate that telaglenastat significantly depletes the cellular pool of aspartate, which is a substrate for the synthesis of purine and pyrimidine nucleotides. In multiple myeloma cells, telaglenastat caused a significant depletion of intracellular pools of aspartate, adenylosuccinate and total adenylate. Azacitidine is a prodrug that is metabolized to 5-aza-2'-deoxycytidine-triphosphate, which is incorporated into DNA and result in DNA damage (Stresemann C and Lyko F, Int. J. Cancer 123:8-13 (2008). The combination of nucleotide depletion and induction of DNA damage may result in enhanced impairment of DNA replication.

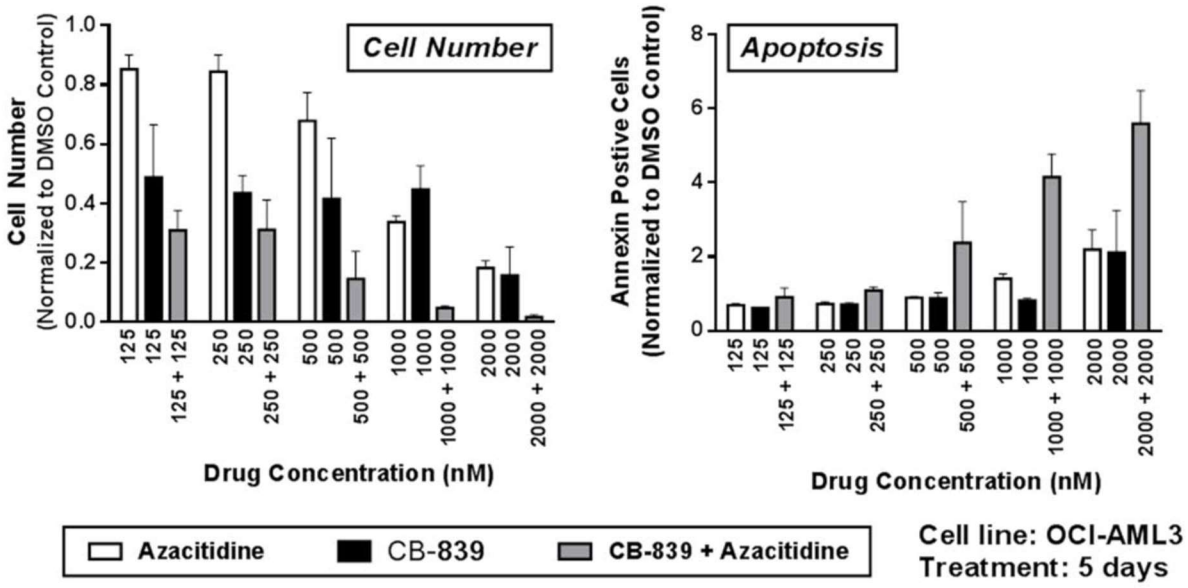

Figure 2: Anti-proliferative and pro-apoptotic effects of Telaglenastat and azacitidine in AML cell line in vitro. OCI-AML3 cells were incubated with increasing concentrations of

Telaglenastat, azacitidine, or Telaglenastat + azacitidine for 5 days. The antiproliferative effect of single agent or combination treatment was determined by cell counting. The induction of apoptosis was determined by staining with Annexin V. This work was carried out in the laboratory of Dr. Marina Konopleva at MD Anderson Cancer Center.

2.3 *In Vivo* Pharmacodynamics of telaglenastat :

Telaglenastat inhibition of cellular glutaminase activity has been assessed in rodents. These studies have demonstrated that oral administration of Telaglenastat results in a rapid, dose-dependent inhibition of glutaminase in mice bearing established human tumor xenografts. Moreover, all tissues examined with the exception of brain (where there is limited exposure) and liver (where GLS2 predominates) showed evidence of glutaminase inhibition, although less dramatic than in tumors.

When telaglenastat was administered to immunocompromised mice bearing established human TNBC and myeloma xenografts, there was a significant inhibition of tumor growth, both as a single agent and in combination with standard of care chemotherapeutics. Telaglenastat administration was well-tolerated up to 400mg/kg BID and resulted in substantial inhibition of tumor growth.

2.4 PK and PD of telaglenastat in Tumors and Tissues in Mice

The tissue distribution and PD response to CB-839 was evaluated in mice bearing the human TNBC tumor HCC1806 by measurement of drug concentration and glutaminase inhibition, respectively. Telaglenastat was administered as a 200 mg/kg single oral dose to female SCID/bg mice. Excellent exposure to telaglenastat was observed in plasma, in the tumor, and in all other tissues examined except brain, where exposure was 20-fold lower than in plasma. GLN concentration increased, while GLU and ASP decreased substantially in tumors relative to untreated controls. GLU and ASP remained essentially unchanged in non-tumor tissues, suggesting that despite significant exposure to telaglenastat , inhibition of glutaminase does not result in product depletion in normal tissues. Other metabolic pathways appear to resupply the intracellular pools of GLU in non-tumor tissues with the exception of the spleen.

2.5 Nonclinical Metabolism and Pharmacokinetics:

Please refer to the Investigator's Brochure (IB) for a more detailed description of the nonclinical metabolism and PK.

Systemic exposure to telaglenastat following oral administration is highly species dependent due to significant cross-species differences in absorption and metabolism.

Based on the *in vitro* and *in vivo* ADME data, good oral exposure of telaglenastat in humans is predicted.
The oral exposure in female rats was found to be higher than in male rats because of more extensive metabolism in male rats. *In vitro* studies also showed more rapid metabolism of telaglenastat in male rat liver microsomes and hepatocytes than in female, whereas no differences were observed *in vitro* using human hepatocytes. Oral exposure of telaglenastat in rats was also affected by feeding status. Systemic exposure to telaglenastat was higher in fasted rats than in fed rats following oral administration.

2.5.1 Absorption

The apical-to-basolateral permeability of telaglenastat in human Caco-2 monolayers was determined to be 9.6 x 10^-6 cm/s and is predictive of good absorption in humans. The oral bioavailability of 44-70% in mice and 66-157% in rats demonstrated good absorption of telaglenastat in these species.

2.5.2. Distribution:

High *in vitro* plasma protein binding of telaglenastat was observed in mouse, rat, dog, and human plasma using an ultracentrifugation approach. The mean plasma protein binding was 98.0, 97.0, 97.9, and 99.1%, respectively. As described in Section 2.4, following a single oral dose of 200 mg/kg to SCID/bg mice, telaglenastat was broadly distributed to tissues including heart, lung, spleen, muscle, and subcutaneously-implanted tumors; brain had 20-fold lower telaglenastat levels.

2.5.3. Metabolism:

In vitro metabolic stability of telaglenastat was evaluated using cryopreserved hepatocytes derived from mice, rats, dogs, monkeys (cynomolgus, rhesus, and marmoset), and humans. Telaglenastat was most stable in human hepatocytes. Gender differences were observed only in rats; CB-839 was more stable in rat hepatocytes from females. The *in vitro* clearance derived from the hepatocyte stability is well correlated with *in vivo* clearance in mice, rats, dogs, marmoset monkeys, and cynomolgus monkeys.

Two pathways of metabolic transformation of telaglenastat have been identified *in vitro* in hepatocytes and *in vivo*: amide hydrolysis and P450-mediated hydroxylation. There are considerable differences in the mechanism of metabolism across species. All metabolites resulting from amide hydrolysis and hydroxylation of CB-839 have a low abundance (<10%) in human hepatocyte incubations up to 4 hr. Significant exposure of the human metabolites identified thus far is anticipated in the non-clinical GLP toxicity studies.

2.5.4. Excretion:

About 0.3-1.2% of orally dose CB-839 was eliminated via biliary excretion in bile duct-cannulated rats. And biliary excretion happened predominately in the first 2 hr after dosing. On the other hand, when CB-839 was dosed orally to bile duct-cannulated rats, 41 to 49 reduction in systemic exposure to CB-839 was seen relative to normal rats, suggesting a significant amount of CB-839 is flowing through the bile, and perhaps undergoing enterohepatic recirculation in normal animals. Further studies are needed to better understand biliary excretion of CB-839 in rats.

2.5.5. Drug-drug interaction

Direct and time-dependent inhibition (TDI) of human cytochrome P450 (CYP) enzymes by telaglenastat was evaluated in human liver microsomes (HLM). CB-839 was not an inhibitor for CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP3A. CB-839 appears to be an inhibitor of CYP2C9 with an IC50 of 1.8 - 6.7 μM. Further studies are needed to understand the time-dependency of inhibition. Telaglenastat was not an inducer of human CYP1A2, 2B6, or 3A4 in cryopreserved hepatocytes from three donors. Telaglenastat is a moderate substrate of efflux transporters with an efflux ratio of 6.2 in Caco-2 monolayers.

2.6 Genotoxicity

The genotoxicity of telaglenastat in bacteria was evaluated in a GLP-compliant Ames test. There were no findings of mutagenicity of telaglenastat .

2.7 Clinical Data

The safety, pharmacokinetics (PK), and pharmacodynamics (PDn) following oral administration of telaglenastat is being evaluated in three ongoing Phase 1 clinical trials in CX-839-001 (solid tumors), CX-839-002 (MM and NHL), and CX-839-003 (acute leukemia). Increasing doses of telaglenastat resulted in an increase in plasma concentration of telaglenastat and in inhibition of glutaminase activity in platelets and in tumors. As of January 26, 2016, 147 subjects have been treated with telaglenastat monotherapy across the 3 studies, at doses of 100 – 1000 mg orally TID fasted, or 600 – 1000 mg BID orally with food. To date, 2 DLT events (elevated creatinine and elevated LFTs) have been reported for the monotherapy. Although a maximum tolerated dose (MTD) has not been defined, 800 mg BID is the highest dose that is confirmed to be safe and well tolerated as monotherapy. The most frequent drug-related grade 3-4 toxicity has been reversible elevations in liver function tests, primarily ALT, AST and GGT, although the frequency of Grade 3/4 LFT elevations is substantially reduced with BID dosing with food as compared to the original TID regimen. CB-839 has been evaluated at doses up to 1000 mg TID in patients with hematologic malignancies.

In the CX-839-003 study the safety and tolerability of telaglenastat is being evaluated in patients with hematological malignancies (acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), or myelodysplastic syndrome (MDS) either as monotherapy or in combination with azacitidine. A total of 11 leukemia patients have received telaglenastat as monotherapy on the BID schedule with food and treatment related AEs are presented in TABLE 1. Overall, 81.8% of patients experienced an AE that was considered at least possibly related to CB-839. The most frequent CB-839-related AEs were hematological (thrombocytopenia and anemia) with other AEs including Grade 1/2 elevated AST, elevated creatinine, constipation and dyspnea. The hematological AEs were all Grade 3/4 whereas the non-hematological AEs were typically mild to moderate in intensity (Grade 1/2), reversible and manageable without dose interruption or modification. No Grade 3/4 elevations in LFTs were noted. CB-839-related Grade 3/4 events included thrombocytopenia (4), neutropenia (2), anemia (2), lymphopenia (1), hyponatremia (1) and stomatitis (1).

Table 1: CX-839-003 Treatment-Related Adverse Events in ≥ 2 patients – BID fed

BID Monotherapy (N=11)		
MedDRA Preferred Term	**Number (%) of patients**	
	All Grades	**≥Grade 3**
Patients with Any CB-839-Related AE	9 (81.8)	5 (45.5)
THROMBOCYTOPENIA	4 (36.4)	4 (36.4)
ASPARTATE AMINOTRANSFERASE INCREASED	2 (18.2)	0
BLOOD CREATININE INCREASED	2 (18.2)	0
CONSTIPATION	2 (18.2)	0
DYSPNOEA	2 (18.2)	0
NEUTROPENIA	2 (18.2)	2 (18.2)

Reductions in blast counts were achieved in 2 patients with AML receiving monotherapy telaglenastat including one with CRi.

On the CX-839-003 study telaglenastat also is being evaluated at escalating doses (400 mg BID – 800 mg BID) in combination with standard dose azacitidine (75 mg/m^2 dosed IV or SC for 7 days of every 28-day cycle). As of the data cutoff for this document 4 patients have received telaglenastat in the 400 mg BID dose cohort in combination with azacitidine One of 4 patients has experienced a treatment-related AE considered at least possibly related to telaglenastat . To date, no DLTs have occurred. Efficacy data are not yet available for patients receiving telaglenastat in combination with azacitadine.

3. STUDY ELIGIBILITY

3.1 Inclusion Criteria

1. Signed, informed consent must be obtained prior to any study specific procedures.

2. Subjects must be $\geq$ 18 years of age at the time of informed consent

3. Subjects with a histologically confirmed diagnosis of MDS, including both MDS and RAEB-T (AML with 20-30% blasts and multilineage dysplasia by FAB criteria) by World Health Organization (WHO) and chronic myelomonocytic leukemia (CMML) are eligible.

4. Subjects with high-risk MDS (i.e. IPSS Intermediate-2 or high-risk; or R-IPSS high or very-high risk). Patients with Intermediate-1 risk by IPSS or Intermediate risk by R-IPSS and with IDH1 or IDH2, or high-risk molecular features including TP53, ASXL1, EZH2, and/or RUNX1 mutations are also eligible.

5. Subjects with prior hypomethylating agent therapy exposure may be eligible based on discussion with the PI.

6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2.

7. Adequate liver function, as evidenced by a serum bilirubin $\leq$ 2x the ULN (except for patients with Gilbert's disease) and ALT or AST $\leq$ 3x the laboratory ULN.
8. Adequate renal function including creatinine clearance $\geq$ 30 mL/min based on the Cockcroft-Gault equation.

9. Able to understand and voluntarily sign a written informed consent, and willing and able to comply with protocol requirements.

10. Resolution of all clinically significant treatment-related, non-hematological toxicities, except alopecia, from any previous cancer therapy to $\leq$ Grade 1 prior to the first dose of study treatment

11. Female patients of childbearing potential must have a negative serum or urine pregnancy test within 3 days of the first dose of study drug and agree to use dual methods of contraception during the study and for a minimum of 3 months following the last dose of study drug. Post-menopausal females (> 45 years old and without menses for > 1 year) and surgically sterilized females are exempt from these requirements. Male patients must use an effective barrier method of contraception during the study and for a minimum of 3 months following the last dose of study drug if sexually active with a female of childbearing potential.

3.2 Exclusion Criteria:

1. Any prior or coexisting medical condition that in the investigator's judgment will substantially increase the risk associated with the subject's participation in the study.

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

3. Active uncontrolled infection at study enrollment including known diagnosis of human immunodeficiency virus or chronic active Hepatitis B or C infection.

4. Clinically significant gastrointestinal conditions or disorders that may interfere with study drug absorption, including prior gastrectomy.

5. Patients with known active CNS disease, including leptomeningeal involvement.

6. Impaired cardiac function, uncontrolled cardiac arrhythmia, or clinically significant cardiac disease including the following: a) New York Heart Association Grade III or IV congestive heart failure, b) myocardial infarction within the last 6 months

7. Subjects with a QTc > 480 ms (QTc > 510 msec for subjects with a bundle branch block at baseline).

8. Nursing or pregnant women.

9. Subjects with known hypersensitivity to study drugs or their excipients.

4. TREATMENT PLAN

4.1 Study Design

This is a Phase 1b/II clinical trial designed to assess the safety, tolerability and efficacy of telaglenastat in combination with AZA for the treatment of advanced MDS. Patients will be treated with standard AZA (IV or SQ 75mg/m2 IV daily x 7 days) and telaglenastat orally twice daily continuously for 28 days per treatment cycle. A cycle will consist of 28 days of dosing. Patients will continue on study therapy unless they have evidence of progressive disease or unacceptable toxicity. Other objectives include exploring the PK and PDn of telaglenastat in combination with AZA.

4.1.1. Phase 1b:

In the Phase 1b portion, telaglenastat will be administered at the goal starting dose level 0 of 600mg BID continuously. The MTD is defined as the highest dose level with </= 1 out of 6 patients experiencing a DLT during the first cycle.

The first 6 patients will be treated at dose level 0. If </= 1 out of the 6 patients experience a DLT during the first cycle, this level will be identified as the RP2D and the study will progress to the Phase II portion. If ≥ 2 out of the 6 patients experience a DLT during the first cycle, this dose level would exceed the MTD, and an additional 6 patients will be treated at the next lower dose level. Reduced dose level -1 is defined in Table 1 below. Patients treated in the Phase 1b portion that are removed from study before day 28 for any reason other than toxicity, and have not experienced DLT, will be replaced.

AZA will be administered subcutaneously (SQ) or intravenously (IV) for 7 days of every cycle (days 1-7) as determined by the treating physician. Both SQ and IV forms of administration are FDA-approved and are considered interchangeable, based on patient and physician preference.

Table 1: Dose de-escalation for telaglenastat and AZA

Dose Level	CB-839 (oral)	AZA (IV or SQ)
0	600 mg BID days 1-28	75 mg/m2 days 1-7
-1	400 mg BID days 1-28	75 mg/m2 days 1-7

Dose reductions beyond those mentioned in this table or different to the doses specified should be discussed with the PI and documentation of the justification recorded in the medical record.

4.1.1.2. Dose De-escalation Procedures:

A dose-limiting toxicity (DLT) is defined as any Grade 3 or higher non-hematologic adverse event or abnormal laboratory value occurring during the first cycle (i.e. the first 28 days) on study except those that are clearly and incontrovertibly due to disease progression or extraneous causes, with the following exceptions:

- CTCAE v4.03 Grade 3 AST or ALT that resolves to ≤ Grade 2 within 14 days without an associated rise in bilirubin
- Grade 3 nausea, vomiting or diarrhea that can be managed to ≤ Grade 2 with standard antiemetic or antidiarrheal medications
- Grade ≥ 3 electrolyte abnormality that lasts < 24 to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
- Grade 3 biochemical abnormalities of amylase or lipase without clinical evidence of pancreatitis

Hematologic DLT is defined as Grade ≥ 3 neutropenia and/or thrombocytopenia with a hypocellular bone marrow lasting for 6 weeks or more after the start of a course in the absence of underlying MDS. Anemia will not be considered for the definition of DLT.

4.1.1.3. The first 6 patients will be treated at dose level 0. If DLT occurs in ≥ 2/6 evaluable patients, this dose level would exceed the MTD, and an additional 6 patients will be treated at the lower dose level. The highest dose level at which 0-1/6 patients experience DLT will be used as the RP2D. Should ≥2/6 DLTs occur in dose level -1, the combination may be considered too toxic in this indication and the study may be discontinued.

4.1.2. Phase II:

The Phase II portion will open after determination of the RP2D of the combination of telaglenastat and AZA from the Phase 1b portion. The RP2D will be selected based on the totality of the clinical data (safety, tolerability, PK, PDn, and efficacy) and will not exceed the MTD. A total of 28 evaluable MDS patients, which includes 22 Phase II patients and 6 patients treated at the RP2D from Phase 1, will be enrolled.
We will enroll 16 patients in the first stage. If 6 or fewer patients achieve response, enrollment will be halted. If 7 or more out of the first 16 patients achieve response, accrual will continue until a total of 28 patients have been enrolled. If 15 or more out of these 28 patients achieve response, the treatment will be considered efficacious and worthy of further investigation. Toxicities will be monitored closely using the method of Thall et al (1995) in Section 8.1.3.

4.2. Study Duration:

4.2.1. All subjects must complete a screening visit, day 1 visits for each new cycle, and an end-of-treatment visit.

4.2.2. Treatment will continue until discontinuation due to relapse, unacceptable toxicity, or disease progression as defined by the IWG 2006 criteria for MDS. This includes:

- clinically significant progressive disease at any time, or

- a lack of clinical benefit after 5 cycles of treatment at the highest dose of study medication, or

- Possibility of undergoing allogeneic stem cell transplantation

- discontinuation of study drug for more than 6 weeks, or

- intercurrent illness that prevents further administration of treatment, or

- unacceptable adverse event(s), or

- patient decision for study withdrawal, or

- general or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator

Patients may remain on study for up to 12 cycles if the patient demonstrates clinical benefit and no excessive toxicity (i.e. no clinically significant study-drug related grade $\geq$ 3 toxicity). Patients who are experiencing clinical benefit and have not experienced excessive toxicity may be eligible to continue therapy after discussion with the PI and the discussion documented in the patient's medical record.

If one of the study agents is discontinued due to toxicity, the patient may remain on study until the occurrence of significant disease progression, severe toxicity that requires all study agents to be permanently discontinued, or at the discretion of the PI.

4.2.3. Cycle Length:

Study cycles will be administered every 28 days $\pm$ 5 days or upon resolution of any clinically significant study drug related AE to grade 0-2, whichever occurs first.

4.2.4. Cycle Administration:

4.2.4.1. AZA may be administered by MDACC or local physician, inclusive of the regional care centers. Commercial supplies and institutional standards for administration of AZA will be used and records will be obtained from the local physician as indicated in the Dear Doctor Letter. Institutional standards include administration of AZA on the "5-2-2" schedule.

4.2.4.2. Telaglenastat should be taken orally twice daily with food. The first telaglenastat dose of the day will be administered immediately after breakfast. The evening/second dose should be taken with a meal approximately 12 hours (+/- 2 hours) after the morning dose.

4.2.4.3. Telaglenastat will be self-administered primarily on an outpatient basis; but may be administered as an inpatient.

4.2.4.4. Patient compliance will be documented using the MDACC Research Medication Diary and will be assessed at each study visit.

4.2.4.5. Missed doses should be skipped. If a patient forgets to take a dose of study drug and they are outside the allotted protocol window (+/- 6 hours) they should be instructed NOT to take extra study drug at their next administration. If a dose is delayed by <6 hours, they should be instructed to take the dose and then to take the next dose at the normal time.

4.3. Identity of Investigational Product:

International Non-proprietary name	Telaglenastat
Manufacturer	Calithera
Dose	As per protocol
Route of Administration	oral
Formulation	Capsule or tablet formulation (200 mg)

Telaglenastat will be provided by Calithera.

For oral administration only
Store at room temperature 15-30^{0}C (59-86^0 F). Do not refrigerate or freeze. Keep bottle tightly closed.
The Expiry date will be provided by Calithera (based on Certificate of Analysis)

4.4 Supportive Care Guidelines and Concomitant Medications:

4.4.1. Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drug. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an adverse event), the treatment must be recorded on the eCRF, including the reason for treatment, name of the drug, dosage, route, and start and stop dates of administration

4.4.2. Supportive measures including blood and platelet transfusions, antimicrobials, and analgesics are permitted.

4.4.3. The administration of anticancer therapies, other investigational cytotoxic agents, or prophylactic use of hematopoietic colony stimulating factors are not permitted.

4.4.4. Erythropoietin or hematopoietic colony stimulating factors for treatment of cytopenias are **discouraged**. If administered, the subject will not be eligible for a HI response assessment within one week of the receipt of epoetin alfa or filgrastim, tbo-filgrastim, filgrastim-sndz, or for one month after receipt of pegfilgrastim or darbopoetin.

4.4.5. Telaglenastat is metabolized by human hepatocytes primarily through amide hydrolysis. Telaglenastat does not appear to induce CYP drug-metabolizing enzymes and only weakly inhibits CYP2C9 (IC_{50} 1.8-6.7 μM) *in vitro*. Therefore, drug-drug interactions are not expected. Although CB-839 is not expected to inhibit CYP2C9 at the exposure levels planned, caution is warranted when administering CB-839 to patients taking drugs that are highly dependent on CYP2C9 for metabolism and have a narrow therapeutic index. (See Appendix A).

Preliminary PK data generated in this and concurrent Phase 1 studies suggest that concomitant use of agents that increase gastric pH (e.g., proton pump inhibitors, H2-receptor antagonists, antacids, etc.) may reduce absorption of telaglenastat , resulting in decreased systemic exposure. Although patients are *not required* to discontinue their use of these agents, discontinuation is recommended whenever possible.

4.5 Dosing Delays and Dose Modifications:

4.5.1. Dose Adjustments:

The doses of telaglenastat and AZA will be adjusted according to the guidelines shown in the following tables for study drug-related clinically significant toxicity. If toxicity is not covered in the table, doses may be reduced or held at the discretion of the investigator for the patient's safety.

Patients will be withdrawn from the study if they fail to recover to CTCAE v4.03 grade 0 to 1 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a clinically significant non-hematologic treatment-related toxicity within 6 weeks (leading to treatment delay of > 4 weeks) unless the investigator feels that the patient should remain in the study because of evidence that the patient is/may continue deriving benefit from continuing study treatment. Such instances will be discussed with the principal investigator on a case by case basis and the discussion documented in the medical record.

Patients with study-drug related toxicities that are manageable with supportive therapy may not require dose reductions. For patients with other drug-related toxicities, the following dose adjustment rules apply:

4.5.2.

NCI CTCAE v4.03 **Grade**	**Action**
Grade 0-2 non-hematological toxicity	No dose reduction. For grade 2 toxicities that are persistent and/or intolerable (e.g. stomatitis) patients may have a treatment interruption or dose reductions to the next lower dose level.
Grade 3-4 clinically significant non-hematological toxicity†	Hold until recover to NCI CTC AE grade 0-1 If recovery occurs within 4 weeks after treatment has been held, dose should be reduced to –1 dose level, if applicable.

Administration of subsequent cycles should be administered when neutrophils recover to ≥ 1 x 10^9/L and platelets to ≥30 x 10^9/L, or to baseline levels prior to the start of the last cycle of therapy. Patients with residual disease may start the next cycle with neutrophil and/or platelet counts lower than these if judged to be in the best interest of the patient. The decision to treat should be documented in the patient's medical record.

5. STUDY PROCEDURES

5.1 Screening (Visit 1)

The following procedures are performed during screening, staging and workup. These procedures are to be performed within 4 weeks prior to study drug administration, except where indicated. All procedures for the Phase 1b and Phase 2 are interchangeable.

A signed and dated IEC/IRB approved informed consent form must be obtained before any study specific procedures are performed. Procedures that are part of routine care are not considered study specific procedures. All subjects will be screened for eligibility before enrollment. Once the subject has met all inclusion criteria, they will be enrolled onto the study.

Table 2: Procedures during Screening, Staging and Workup

Procedures	Specifics
Informed consent	
Full History and Physical Examination	History – present illness, prior surgeries, other medical illnesses, review of systems, allergies, prior therapy for cancer and concurrent meds; Physical exam – record weight, and note abnormalities in any major organ system (including but not limited to neurologic, head and neck, lymph nodes, cardiovascular, pulmonary, abdomen, extremities), note and measure sites of disease
Concomitant Medications	
Vital signs (including temperature, pulse, and blood pressure)	
ECOG performance status	
Urine or blood pregnancy test (females of child-bearing potential only)	Within 7 days prior to first dose
Disease status (IPSS classification and WHO disease classification) Note: Bone marrow aspirate and/or biopsy within 4 weeks prior to first dose of drug in all patients.	Staging with bone marrow aspiration and biopsy for disease assessment.
Serum chemistries (repeat if screening chemistries completed greater than 72 hours prior to the first dose)	Sodium, potassium, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, AST and/or ALT, total bilirubin, alkaline phosphatase, uric acid, amylase and lipase
CBC with differential (repeat if screening test completed greater than 72 hours prior to the first dose)	Differential may be omitted if WBC $\leq 0.5 \times 10^9$/L
Standard 12-lead EKG with QTc calculation	

5.2 On-Study Procedures

5.2.1. Cycle 1 Day 1:

Pretreatment baseline procedures are acceptable if performed within 3 days prior to C1D1 except vital signs, serum chemistries, and hematology labs. *Vital signs must be taken prior to dosing on C1D1*. Patients should be instructed not to eat breakfast prior to their clinic visit on C1D1. During the C1D1 visit, patients will undergo the following procedures prior to dosing:

1. Symptom-directed physical exam including vital signs and weight. This is a focused exam performed based upon observed clinical signs and patient complaints. System exams are only required as clinically indicated.
2. Clinical laboratory evaluation
3. Pre-dose plasma sample collection for PK and correlative studies
4. Pre-dose bone marrow aspirate and/or biopsy for correlative studies (obtained after study consent is signed).
5. Recording of concomitant medications

Telaglenastat should be administered after pre-dose procedures have been completed and the patient has consumed breakfast. Azacitidine will be administered SC or IV after all safety evaluations have been performed and the appropriate premedication has been administered. Note: If institutional guidelines for pre-medication include a proton pump inhibitor (PPI), the treatment should only be administered $\geq$ 1 hour after dosing with telaglenastat . Following receipt of telaglenastat , the patients will undergo the following:

1. AE monitoring
2. ECG with QTcF (in duplicate) between 2-4 hr post-dose

Subsequent doses of telaglenastat will be self-administered by the patient per dosing instructions after all study procedures have been completed.

5.2.2. Cycle 1 Days 2-7:

During Cycle 1 and all subsequent cycles, Days 2-7, patient will undergo vital signs prior to azacitidine administration. Patients may take their telaglenastat doses prior to, during, or after their AZA according to their usual dosing schedule.

5.2.3. Cycle 1 Day 8, Day 15, Day 22 (+/- 3 days)

At these Cycle 1 mid-cycle assessments, patients will return to clinic to undergo the following procedures:

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical exam
5. Clinical laboratory evaluation (hematology, serum chemistries)
6. Plasma samples for PK analysis pre-dose on C1D15

*Patients may take their telaglenastat doses prior to, during, or after their clinic visit according to their usual dosing schedule because there are no specified pre-dose procedures ***with the exception of C1D15*** where the patient should not take their telaglenastat dose prior to arrival due to pre-dose PK sample.

5.2.4. Cycle 2 Day 1 (+/- 5 days) and all subsequent cycles on Day 1

Patients may take their telaglenastat doses prior to, during, or after their clinic visit according to their usual dosing schedule because there are no specified pre-dose study procedures ***with the exception of C2D1 and C3D1*** due to pre-dose PK samples.

1. Vital signs and weight
2. AE monitoring
3. Recording of concomitant medications
4. Symptom-directed physical exam
5. Clinical laboratory values (hematology, serum chemistry)
6. Plasma sample for exploratory biomarker analysis
7. Bone marrow evaluation of tumor/disease burden is required for all patients receiving telaglenastat on cycle 2 day 1, cycle 4 day 1, cycle 6 day 1, and every 3 cycles thereafter, +/- 5 days for all above assessments. Additional evaluations are acceptable as clinically indicated.
8. Bone marrow sample for biomarker and pharmacodynamics analysis during above protocol-defined time points.
9. Plasma samples for correlative analysis on same day as bone marrow sample timepoints are collected
10. Plasma samples for PK analysis prior to the administration of study drug, on C2D1 and C3D1.

5.3. End of Study Visit:

Subjects will undergo an End of Treatment (EOT) Visit within 28 days of discontinuation of telaglenastat . The following EOT procedures are recommended:

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Complete physical examination
5. ECOG performance status evaluation

6. Clinical laboratory values (hematology, chemistry)
7. Serum or urine pregnancy test for women of child-bearing potential
8. 12-lead ECG with QTcF
9. Bone marrow sample for biomarker and/or PDn analysis. This is only required if the reason for treatment discontinuation is relapse/disease progression following a PR or better. Patients with adequate numbers of leukemic blasts circulating in the peripheral blood may submit a whole blood sample instead of a bone marrow sample

5.4 Long Term Follow Up

All patients discontinued from study treatment for any reason other than withdrawal of consent for treatment and follow-up will continue to be assessed for survival. **Survival information (i.e. the date and cause of death) will be collected via quarterly telephone calls and/or clinical visits for a period of 5 years after the last subject has enrolled on the study.**

6. RESPONSE DEFINITIONS

6.1 Study Endpoints:

6.2.1. Efficacy Analysis: Clinical activity of telaglenastat + AZA will be assessed based on Modified IWG Response Criteria for MDS (Cheson et al, 2006).

Proposed Modified International Working Group Response Criteria for Altering Natural History of MDS Category	**Response criteria (Responses must last at least 4 weeks)**
Complete remission	Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines* Persistent dysplasia will be noted*† Peripheral blood‡ Hgb ≥11 g/dL Platelets ≥100 × 109/L Neutrophils ≥1.0 × 109/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
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

Source: (Cheson, et al. 2006) Abbreviations: MDS = myelodysplastic syndromes; CR = complete remission; Hgb = hemoglobin; HI = hematologic improvement; PR = partial remission; FAB = French-American-British; AML = acute myeloid leukemia; PFS = progression-free survival; DFS = disease-free survival. Note: Deletions to IWG response criteria are not shown. Note: To convert hemoglobin from g/L to g/dL, divide g/L by 10. *Dysplastic changes should consider the normal range of dysplastic changes (modification).

†Modification to IWG response criteria (Cheson, et al. 2003) ‡In some circumstances, protocol therapy may require the initiation of further treatment (e.g., consolidation, maintenance) before the 4-week period. Such subjects can be included in the response category into which they fit at the time the therapy is started. Transient

cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

6.2.2. Hematologic Improvement Response Criteria:

*Responses must last at least 8 weeks

Proposed Modified International Working Group Response Criteria for Hematologic Improvement Hematologic improvement*	**Response criteria (Responses must last at least 8 weeks)†**
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 × 109/L)	Absolute increase of ≥30 × 109/L for patients starting with >20 × 109/L platelets Increase from <20 × 109/L to >20 × 109/L and by at least 100%†
Neutrophil response (pretreatment, < 1.0 × 109/L)	At least 100% increase and an absolute increase >0.5 × 109/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

Source: (Cheson, et al. 2006) Abbreviations: Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement. Note: Deletions to the IWG response criteria are not shown. Note: To convert hemoglobin from g/L to g/dL, divide g/L by 10.
*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥1 week apart (modification).
†Modification to IWG response criteria (Cheson, et al. 2003) ‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth.

For each subject, response to therapy, duration of response, event-free survival, and overall survival will be calculated. The duration of response is defined as the number of

days from the date of initial response (PR or better) to the date of first documented disease progression/relapse or death, whichever occurs first. Event-free survival is defined as the number of days from the date of treatment initiation (i.e., C1D1) to the date of documented treatment failure, relapses from CR, or death from any cause, whichever occurs first, and will be calculated for all patients. In the event that neither disease progression or death is documented prior to study termination, analysis cutoff, or the start of confounding anticancer therapy, these endpoints will be censored at the date of last tumor assessment date.

In addition, relationships between anti-tumor activity, PDn markers, exploratory biomarkers, and drug exposure levels will be explored.

6.2.3. Primary Safety Endpoint

Primary safety endpoint: The overall incidence and severity of all adverse events using Common Toxicity Criteria v 4.0.

An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment. Adverse events (AEs) will be collected using the Leukemia AE guidelines.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

All “suspected adverse reactions” (as defined in 21 CFR 312.32(a)) will be captured in the case report forms. For abnormal chemical values grade 3 or 4, the apogee will be reported per course in the CRF.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

6.2.4. Serious Adverse Event Reporting (SAEs)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND office.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

Only unexpected AEs will be recorded in the Case Report Form (CRF). The Principal Investigator will sign and date the PDMS or CORE Case Report Form toxicity pages per each patient at the completion of each course. Following signature, the Case Report Form will be used as source documentation for the adverse events for attribution.

All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB. MDACC.

Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

The following SAEs are not subject to expedited reporting, but would still be included in the annual report via the SAE log.

a. Infection or cytopenias leading to hospitalization or prolongation of hospitalization Disease progression leading to death, life-threating AE, hospitalization or prolongation of hospitalization, or disability.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32

- **It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.**

6.2.5. Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 3 months from the discontinuation of dosing, the investigator should report the information to the study supporter as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information. The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes abortion and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug.

- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator.
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth.
- "Normality" of the miscarried fetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

6.2.6. SAE Reporting to Calithera

Any serious adverse events which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

All serious adverse events must be reported within 5 working days of knowledge of the event (within 24 hours for life threatening or fatal events) to Calithera Bioscience's PharmacoVigilance agent according to the Safety Data Exchange Agreement at the following:

US Toll Free Fax #: 1 (800) 727-8347

eFax forwarded to calithera@primevigilance.com

email: calithera@primevigilance.com

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to Calithera within 24 hours.

SAEs brought to the attention of the investigator at any time after cessation of telaglenastat and considered by the investigator to be related or possibly related to telaglenastat must be reported to Calithera if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged.

6.3. Secondary and Exploratory Endpoints:

6.3.1. Pharmacokinetic Analysis

PK studies will be performed on plasma to assess steady-state levels of telaglenastat over time, and drug accumulation over time. PK sampling will occur on C1D15, C2D1, and C3D1.
PK assay will be conducted at a central laboratory where the assay for telaglenastat has been validated. Details are given below and in the laboratory manual:

Intertek Pharmaceutical Services

Attn:	Sample Accessioning
Address:	10420 Wateridge Circle
	San Diego, CA 92121
Phone:	(858) 558-2599
Fax:	(858) 558-2600
Email:	sd.accessioning@intertek.com

6.3.2. Pharmacodynamic Analysis

Pharmacodynamic effects of telaglenastat will be measured in MDS CD34+ and in bone marrow stromal cells isolated before treatment and at all bone marrow study timepoints. These include measurements of intracellular metabolism; RNA expression of GLS and other metabolic genes; DNA methylation and hyddroxymethylation studies; quantitation of phenotypically defined MDS stem cells. These PD analyses will be performed in the laboratory of Dr Konopleva and Dr Amit Verma.

No formal statistical analysis of PDn endpoints will be performed. PDn data from each assay will be listed, and possible relationships between PK and PDn variables will be explored. Any biological activity will be described.

7. Regulatory and Reporting Requirements:

7.1. Informed Consent:

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The acquisition of informed consent should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

7.2. Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Calithera before recruitment of subjects into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent form. The investigator should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Calithera, in accordance with local procedures.

The investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IEC/IRB's continuance of approval must be sent to Calithera.

7.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On documents submitted to Calithera, subjects should be identified by their study number only. Documents that are not for submission to Calithera (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

7.4. Study Termination

Both Calithera and the investigator reserve the right to terminate the study according to the study contract. The investigator should notify the IEC/IRB in writing of the study's completion or early termination and send a copy of the notification to Calithera.

Subjects may be eligible for continued treatment with investigational product by extension protocol or as provided for by the local country's regulatory mechanism. However, Calithera reserves the unilateral right to determine whether to supply the investigational product, and by what mechanism, after termination of the trial and before it is available commercially.

7.5. Study Documentation and Archival

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Case report form entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data). In this study, case report forms calculating IPSS may be used as source documents for IPSS risk category assignment**.**

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Calithera and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, informed consent forms, and subject identification list

- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation and all correspondence to and from the IEC/IRB and Calithera

- Proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available. No study document should be destroyed without prior written agreement between Calithera and the investigator. Should the investigator wish to assign the study records to another party or move them to another

location, he/she must notify Calithera in writing of the new responsible person and/or the new location.

7.6. Serious Adverse Event Reporting (SAE):

See Section 6.2.4 for detailed information regarding SAE definitions.

It is the responsibility of the PI and the research teams to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to Calithera, regardless of attribution (see Section 6.2.2.3). SAE reporting will be done according to 21 CFR 312.32(c)(1)(iv) ("Sponsor must report any clinically important increase in the rate of a serious adverse reaction over that listed in the protocol or investigator brochure.").

The descriptions and grading scales found in the revised NCI Common Terminology *Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event* reporting. *(http://ctep.cancer.gov/reporting/ctc.html).*

7.7 IND Summaries:

A Toxicity Summary will be submitted to the IND Office Medical Monitor after the first six evaluable patients complete cycle one of study treatment, prior to the Dose modification or Phase II.

A Toxicity Summary will be submitted to the IND Office Medical Monitor after the first 7 evaluable patients and every 7 evaluable patients thereafter.

A Response Summary will be submitted to the IND Office Medical Monitor after 16 evaluable patients complete 6 cycles of study treatment.

8. STATISTICAL CONSIDERATIONS:

8.1. Statistical Design

This is a single institution phase Ib/II study to determine the safety, tolerability and clinical activity of telaglenastat in combination with azacitidine (AZA) for patients with advanced MDS. Up to 40 patients will be enrolled from MDACC, allowing 6 patients treated in the Phase 1b portion that are removed from study before day 28 for any reason other than toxicity and have not experienced DLT, or considered non-evaluable for DLT or response.

8.1.1 Phase Ib:

The Phase Ib part of the study is performed to assess the safety of telaglenastat in combination with AZA. We will first enroll 6 patients at dose level 0. If only 0 or 1 of 6 patients experiences a DLT, the dose level will be identified as the RP2D. If at least 2 of 6 patients experience DLTs, then the MTD has been exceeded and 6 patients will be treated at the lower dose level (i.e. dose level -1). If at least 2 of 6 patients experience DLTs in dose level -1, the combination may be considered too toxic in this indication and the study may be discontinued. The 6 patients treated at the RP2D level will be evaluated in the Phase II portion. A maximum of 12 patients will be enrolled in the Phase 1b part of the study.

A Toxicity Summary will be submitted to the IND Office Medical Monitor after the first six evaluable patients complete cycle one of study treatment, prior to the Dose modification or Phase II.

8.1.2. Phase II:

The Simon minimax two-stage design will be employed for the Phase II portion.(15) We assume a target response rate of 60% and a response rate of 40% or lower will be considered not desirable. Response is defined as complete remission (CR), partial remission (PR), marrow CR (mCR), or Hematologic Improvement (HI) by modified IWG criteria for MDS patients. For example a 29% CR/PR rate was reported in the azacitidine arm in the randomized AZA-001 trial, and a 23% CR/PR rate and 60% ORR (including 37% HI) was seen in the azacitidine arm of the CALGB 9221 trial. To implement the Simon's two-stage design, the assessment window for response (CR+PR+mCR+HI) is defined as response occurring within the first 6 cycles of treatment. With a type I error rate of 10% and 80% power, we will enroll 16 patients in the first stage. If 6 or fewer patients achieve response, enrollment will be halted. If 7 or more out of the first 16 patients achieve response, accrual will continue until a total of 28 patients have been enrolled. If 15 or more out of these 28 patients achieve response, the treatment will be considered efficacious and worthy of further investigation. Under this Simon's minimax two-stage design, the probability of early termination is 53% and the expected sample size is 22 if the true response rate is 40%.

A Toxicity Summary will be submitted to the IND Office Medical Monitor after the first 7 evaluable patients and every 7 evaluable patients thereafter.

A Response Summary will be submitted to the IND Office Medical Monitor after 15 evaluable patients complete 6 cycles of study treatment.

8.1.3. Toxicity:
The method of Thall, Simon and Estey will be used for toxicity monitoring for the Phase II part of this study.(16) For monitoring purposes, toxicity is defined as DLT which occurs during the first cycle. Denote the probability of toxicity by P_T. We assume as a priori, P_T ~ beta (0.6, 1.4). Our stopping rule is to stop the trial if Pr(P_T > 0.30 | data)>0.90. That is, we will stop the trial for new patient enrollment if at any time during the study; we determine that there is more than 90% chance that the toxicity rate is more than 30%. This toxicity stopping rule will be applied in cohort size of 7, starting from the 7th patient. Stopping boundaries corresponding to this stopping rule are listed in Table 1. The operating characteristics are summarized in Table 2. The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M. D. Anderson Cancer Center (MDACC) was used to generate the toxicity stopping boundaries and the operating characteristics table.

Table 1. Early stopping boundaries for toxicity monitoring

# of patients (in cohort size of 7, starting from the 7th patient)	Stop the trial if there are this many patients with toxicities:
7	4-7
14	7-14
21	10-21

Table 2. Operating characteristics for toxicity monitoring

True toxicity rate	Prob(stop the trial early)	Average sample size
0.10	0.0028	27.94
0.20	0.0398	27.22
0.30	0.1817	24.69
0.40	0.4639	19.91
0.50	0.7697	14.37

8.2 Analysis Populations:

8.2.1. Safety Population

All patients who receive at least 1 dose of telaglenastat will be included in the analysis of safety regardless of the duration of treatment. Patients who experience adverse events during the Screening period but who do not start on study treatment due to reasons that include, but are not limited to ineligibility/screen failure, death or withdrawal of consent, will not be included in the safety population.

8.2.2. DLT-evaluable:

Unless doses are missed in Cycle 1 due to DLT(s), a patient must receive at least 85% of the planned doses of telaglenastat and at least $\geq$ 5 doses of azacitidine to be considered evaluable for DLTs. If a patient received fewer doses of telaglenastat or AZA in the first 28 days of treatment for reasons other than a DLT, the patient will be considered non-evaluable for DLT and replaced.

8.2.3. Efficacy Evaluable Population

All patients who complete at least one post-baseline disease status assessment or who discontinue study medication early due to study drug-related toxicity will be considered evaluable for efficacy. Patients who discontinue and have not received at least 85% of the telaglenastat doses and at least 5 doses of azacitidine within the first cycle of treatment will be considered non-evaluable for response and may be replaced.

8.3. Analysis Plan:

During Phase II portion, if 6 or fewer patients out of the first 16 patients achieve response, enrollment will be halted. If 7 or more out of the first 16 patients achieve response, accrual will continue until a total of 28 patients have been enrolled. If 15 or more out of these 28 patients achieve response, the treatment will be considered efficacious and worthy of further investigation. The rates of response (CR+PR+mCR+HI) to therapy will be estimated along with the 95% confidence interval. The Kaplan-Meier method will be used to estimate the probabilities of event-free survival (EFS), overall survival (OS) and duration of response. Log-rank tests will be used to compare among subgroups of patients in terms of EFS, OS or duration of response. Anti-tumor activity, PDn markers, exploratory biomarkers and drug exposure levels will be summarized graphically and with descriptive statistics. Safety data will be summarized using frequency and percentage, by category and severity.

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APPENDIX A: CYP2C9 Substrates with a narrow therapeutic index*

- S-Warfarin (anticoagulant)
- Phenytoin (antiepileptic)

*Narrow therapeutic index is defined as "CYP *substrates with narrow therapeutic range* refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes)."

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Other CYP2C9 Substrates

- NSAIDs (analgesic, antipyretic, anti-inflammatory)
  - celecoxib
  - lornoxicam
  - diclofenac
  - ibuprofen
  - naproxen
  - ketoprofen
  - piroxicam
  - meloxicam
  - suprofen
- fluvastatin (statin)
- sulfonylureas (antidiabetic)
  - glipizide
  - glibenclamide
  - glimepiride
  - tolbutamide
  - glyburide
- irbesartanlosartan
- sildenafil (in erectile dysfunction)
- terbinafine (antifungal)
- amitriptyline (tricyclic antidepressant)
- fluoxetine (SSRI antidepressant)
- nateglinide (antidiabetic)
- rosiglitazone (antidiabetic)
- tamoxifen (SERM)
- torasemide (loop diuretic)ketamine

APPENDIX B: PK Collection of Specimens

Approximately 2ml of blood will be collected via peripheral venipuncture into an EDTA tube (lavender top). This blood sample will be used to measure concentrations of telaglenastat (CB-839) of each pharmacokinetic blood collection. The time of collection must be noted in the source documents and eCRFs.

For collecting specimens, the following protocol should be followed:

- Label a 3.0 mL K2EDTA vacutainer tube.
- Label 2 cryovials.
- Prepare an ice bucket.
- Draw blood into the 3.0 mL vacutainer tube. Ensure that tube is filled with a minimum of 2 mL of blood.
- Samples should be thoroughly mixed by completely and gently inverting the tube 8 times. If a complete 2 mL volume of blood was not obtained, please discard sample and re-collect with a fresh vacutainer.
- The whole blood samples should be placed on ice immediately after collection. Try not to wet the label.
- Plasma should be prepared within 30 minutes of collection by centrifuging the blood samples at 2000 x g for 10 minutes at 4˚C.
- Split the resultant plasma into two aliquots of approximately equal amounts (at least 0.3 mL) and transfer into the two labeled cryovials.
- Place each of the three samples immediately into the cryobox and store at -70˚C until shipment.

Note: PK assay will be conducted at a central laboratory where the assay for CB-839 has been validated. Details are given below and in the laboratory manual:

Pharmacokinetic analysis will be carried out by central lab

Intertek Pharmaceutical Services
Attn: Sample Accessioning
Address: 10420 Wateridge Circle
San Diego, CA 92121
Phone: (858) 558-2599
Fax: (858) 558-2600
Email: sd.accessioning@intertek.com

All plasma samples will be analyzed for telaglenastat (CB-839) by using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method of appropriate specificity and sensitivity according to Good Laboratory Practices (GLPs).