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GT Biopharma, Inc.

GTB-3550 (CD16/IL-15/CD33) Tri-Specific Killer Engager (TriKE™) for the Treatment of High Risk Myelodysplastic Syndromes, Refractory/Relapsed Acute Myeloid Leukemia and Advanced Systemic Mastocytosis

[redacted]

IND Sponsor:
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Confidential

Key Study Personnel Contact Information

Contact Information	Role
[redacted]	Lead Center - PI
[redacted]	Multisite Program Manager
[redacted]	Lead Center – Research Nurse

Refer to the Procedures Manual for Participating Sites for a complete list of study personnel and contact information.

Revision History

Revision #	Version Date	Summary of Changes	Consent Changes
	12/28/2016	Original to CPRC	n/a
	02/16/2017	In response to CPRC stipulations: • Delete CML from inclusion and CML in blast crisis from exclusion • Add inclusion criteria for ALL	
	05/19/2017	In response to CPRC stipulations, original version to FDA • Study Schema, Page 8 – Correct to reflect that early study stopping rules only apply to the extended cohort • Synopsis, Section 5.1, Appendix 1 – further define advanced systemic mastocytosis Other edits based FDA's comments as part of the pre-IND and general edits: • Clarify dose escalation component is done as inpatient, extended component may be as an outpatient after the 1st 24 hours • Add upper age limit of 75 years • Section 8.2 add overview of correlative testing • Clarify CD33 testing for eligibility will be by flow cytometry or IHC • Clarify that dose limiting toxicity is for treatment related events occurring within 28 days of the 1st dose and that CRS toxicity uses a modified grading system based on Lee, et al. (otherwise CTCAE v4 is used) • Include toxicity profile for blinatumomab as a similar monoclonial antibody since 161533 TriKE has not be tested in humans • Updated eligibility to tighten liver function requirements based on experience with DT2219 • Other minor edits	n/a
	08/11/2017	Version submitted to FDA in Serial 001 • Updated disease-specific eligibility criteria to clearly exclude patients with good standard of care treatment options • Require both patients per dose cohort to complete the DLT evaluation period prior to dose escalation • Add pulmonary function testing to eligibility criteria • Revised DLT based on FDA guidance • Add blood pressure criterion for continuing therapy from Block 2 to Block 3 • Clarify that meeting either stopping rule criterion would stop the study. • Require that all patients be treated inpatient or on hospital-based Phase I Unit. • Add serum pregnancy test within for females of child-bearing potential • Fix discrepancy about LFT monitoring for dose adjustments • Add serum magnesium and phosphorous evaluations to the Schedule of Assessments • Added information about dose preparation and delivery	
	04/23/2018	In response to FDA request dated 8/23/2017: • Exclude diagnosis of acute lymphoblastic leukemia (ALL) • Exclude "other CD33 expressing diseases" • Update title to reflect above changes • Update eligibility to CD33 expressing malignancies, not requiring testing of CD33 status for individual patients • Require all treatment to be administered as an inpatient • Clarify during phase I 1 patient within a cohort must reach day 28 between enrollment may begin in the next 2 patient cohort • Update and clarify definition of dose limiting toxicity • Add monitoring for signs of immune activation for all phase I patients and impact plan on future dose level escalation • Add monitoring for signs of immune activation for all patients and impact plan on future enrollees	yes

Revision #	Version Date	Summary of Changes	Consent Changes
		• Eligibility for PFT's ≥ 80% per FDA • Eligibility for LVEF ≥ 45% to match transplant protocols, previously ≥ 40% • Add to exclusion criteria "eligible for standard of care transplant" • Expand management section for increased LFTs • Add management section for pulmonary toxicity • Update Section 9 to reflect CMC and product SOPs • Update appendices to match protocol changes. Other protocol revisions: • For AML patients having previous transplant, change key timeframe for eligibility from 12 months to 3 months • Update MDS eligibility and add Appendix III IPSS tables and link to calculator • TriKE dose dosing units changed to microgram/kg/day (previously mcg/m2) and change dose levels to be tested • Remove bolus test dose for phase I patients, move PK/PD sampling until after the end of each block (96 hours or earlier if infusion is ended earlier) and do for all patients (not just Phase I), updated definition of DLT to remove unable to tolerate bolus dose • Change from CTCAE v4 to CTCAE v5 • Clarify in the primary endpoint for Phase II that response is based on the "best" clinical response by Day 42 • Section 7.4 Permit retreatment for patients with clinical benefit defined as stable or better at time of 1st disease reassessment • Add additional agent administration info in Section 7.1 • Move criteria to begin Block 2 and 3 to Section 7.1 and clarify when to delay start of a new block • Define neurologic assessment in Section 7.3.4 • Revised research sample table to reflect changes in the protocol (primarily delete bolus test dose in phase I and move PK/PD sampling to end of block dosing) • Update Section 9.7 Potential Toxicities • Expand language regarding targeted toxicity and research sample collection if a patient is not continuing study treatment as planned • Update MT number to HM • Update cover page and page 3 listing [redacted] as PI and GT Biopharma as IND Sponsor • Other minor edits and clarifications Updates based on current protocol template: • Add Key abbreviations table • Section 5 patient enrollment updated • Update Section 10.1 definitions for event reporting • Other minor edits and clarifications	
	07/05/2018	In response to FDA's clinical information request dated July 3, 2018 • Synopsis and including Sections 7.2.1, 12.1 - During dose finding component require both patients reach Day 28 (end of the DLT assessment period) before enrollment of a new cohort – remove reference to time-to-event (TITE) for the continuous reassessment method (CRM) as not long applicable • Synopsis, Section 5, Appendix I - Clarify eligibility for relapsed AML in regards to transplant status • Schema, Sections 7.2.1, 10.2 - Expand general definition of DLT as emergent toxicity with the exception of those that are clearly and incontrovertibly due to extraneous causes • Schema, Section 7.2.1, 10.2 - For Grade 3 exceptions add that electrolyte disturbance must resolve, with or without intervention, to <	n/a

Revision #	Version Date	Summary of Changes	Consent Changes
		Grade 2 levels within 72 hours to not be a DLT, delete skin rash from the list of Grade 3 exceptions • Section 7.2, 12.4 - Modify the monitoring period for the early study stopping rule event for Grade 4-5 toxicity from 14 days after the start of the last treatment block to 42 days after the start of the first treatment block • Section 5.3, Appendix I – expand exclusion to include a candidate for potentially curative therapy to no previous HSCT exclusion • Section 7.1 expand criteria to continue to Block 2 and 3 to include requirements for hem, renal and liver function, adjust criteria to O2 saturation rate to match CTCAE v5 (links to management of pulmonary toxicity Section 7.3.5) • Section 7.3.5 – expand management of pulmonary toxicity • Section 9.6 – indicate the albumin used in the infusion prep is the commercially available Flexbumin 25% Other edits/clarifications • Update abbreviation table to remove TITE • Schema, Sections 7.2.1, 10.2 - Definition of DLT "add despite "support with transfusions" to definition for platelet count decreased • Section 9 - add general supportive care statement • Schema, Sections 7.2.1, 10.2 - Clarify in DLT definition that persons with increased LFT's that met criteria for further treatment in Section 7.3.3 may continue on treatment (in general a DLT in any patient = off treatment) • Section 7.4 Expand re-treatment and add new Section 8.3 Retreatment Research Related Samples • Section 7.1 – clarify a treatment delay of 1 week is permitted (previous language of up to 1 week was unclear) Other minor edits – all tracked in tracked version	
	07/09/2018	In response to FDA's 2nd request • Synopsis, Section 5.1 and Appendix I – delete AML eligibility criteria permitting enrollment of patients between 3 and 12 most post-transplant • Schema, Sections 7.2.1 and 10.2 - delete "despite support with transfusions" from the decreased platelet definition of dose limiting toxicity from synopsis Additional revision: Schema, Sections 7.2.1 and 10.2 - remove febrile neutropenia from the definition of DLT for MDS/Mast cell disorders Update Appendix I exclusion criteria #13 to match previous edit in Section 5.3	n/a
	10/15/2018	In response to the FDA's Full Clinical Hold letter received September 28, 2018 (add collection of TriKE samples pre- and post-infusion for batch analysis of drug concentration levels) • Section 7.1 – add instructions for the collection of the post-infusion TriKE sample • Section 8.2 – add drug sample collection pre- and post-infusion to table of research related testing, assessment and sample collection • Section 8.4 – indicate in #5 that the samples will be stored frozen at ≥ 80ºF in the Translational Therapy Lab until batch analysis • Section 9.6 – add a bullet point to the drug preparation instructions to collect samples of the final product before the prepared drug leaves the investigational drug services (IDS) pharmacy. In response to the FDA's clinical non-hold issues received July 12, 2018: • Sections 5.2 and 7.4, Appendix I – change eligibility threshold for renal function by eGFR from ≥40 to ≥ 60 mL/min/1.73 m^2 and change total bilirubin from ≤2.5 mg/dl to ≤ 1.5 x ULN	

Revision #	Version Date	Summary of Changes	Consent Changes
		• Section 5.3 Exclusion criteria and Appendix I - add exclusions of A family history of long QT syndrome or with a QTc interval > 480 msec at screening AND Currently taking medications known to prolong QT/QTc interval as the potential risk of QT/QTc prolongation is unknown in humans (refer to Appendix VII for a list of prohibited medications for eligibility) • Section 7.3 add a paragraph regarding the use of medications that prolong QT/QTc during the study. • Insert a new Appendix VII - Combined List of Drugs That Prolong QT/QTc. • Sections 7.1 and 7.3 – add language regarding the interactions between TriKE and the P450 system are unknown. And that the IL-15 component may affect the 3A4 and 2D6 substrates. Patients with unexpected toxicity should have a review of their con-meds to determine whether there are any potential interactions. The PI or treating physician should consider discontinuing these medications as clinically indicated. • Insert a new Appendix VI – P450 Drug Interactions • Section 8.1 Required Standard of Care – add collection of concomitant medications beginning at screen through the end of treatment visit with start and stop dates relative to TriKE infusions AND ECG at baseline per Section 5.3 exclusion criteria • Section 8.2 add antibody testing on Day 15 pre-dosing (using a portion of the red top tube already being collected at the time point In response to the continuing clinical hold: • Update Section 9 161533 TriKE Description, Supply, Preparation based on pre-clinical function/microbial testing Other edits and clarifications: • Remove [redacted] from cover page as leaving the institution • Add [redacted] as a co-I • Add re-treatment enrollment Section 6.4 and a new re-treatment eligibility checklist as Appendix II, Renumber all subsequent appendices • Section 8.2 - Reduce the intensity of research sample collection from daily during each TriKE block to prior to a block start and the 3rd day of each block with a +2 day window • Section 8.3 – limit research related sample collection to Block 1 only, while retaining baseline and Day 22 samples • Other edits and clarifications detailed in separate summary of revisions log	
1	02/11/2019	• Section 9.2 Product Manufacturing and Section 9.5 Storage and Stability – update to match current MCT process with the final product stored in a < -70º C freezer that is locked with limited access • Section 8.4 Overview of Planned Correlative – update to < -70º C freezer for research sample storage • Cover page, contact information, Replace [redacted] as PI with [redacted] (currently a co-I) as [redacted] is leaving UMN • Synopsis, Section 5.1, Appendices I and IV - Delete references to old IPSS MDS criteria (study already uses R-IPSS) • Appendix V - Add hematologic improvement criteria to MDS response criteria • Section 8.3 Re-Treatment Research samples – edit the Block 1 header to eliminate stray words	Yes – PI name/ contact info
2	07/26/2019	Updated version based on teleconference July 26, 2019 • Section 8.2 – Add daily a EKG to collect additional safety data during each of the 3 blocks of treatment at 4 hours (±15 minutes) into the each infusion start and at 4 hours (±15 minutes) after the infusion disconnection on the last day of the block • Section 10.3 – update MCC required reporting to IND Sponsor	yes

Revision #	Version Date	Summary of Changes	Consent Changes

		• Renumber references deleting references removed in July 2018 revision
		Previous edits July 10, 2019 version Based on SIV:
		• Section 5.3, Appendices 1 and 2: clarify HIV status as "known history of HIV"
		• Section 7.1 and Section 7.3.2: replace references to hypersensitivity and allergic/anaphylactic with infusion related reaction as the study switched to CTCAE v 5 in the April 2018 protocol version – makes consistent with DLT definition and Appendix VIII Targeted Toxicity Worksheet use of infusion related reaction
		• Synopsis, Section 4 and Section 10.2 Update wording on Dose Limiting Toxicities (DLT) to
		  • Resolve discrepancies in wording found in the protocol and to clarify hematologic parameters for toxicity given the baseline hematologic abnormalities inherent to AML and MDS:
		  • Updated hematologic toxicity parameters as the standard grading system does not apply to AML and MDS patients given their baseline platelets/neutrophils already meet grade 3 and 4 due to the disease process itself.
		  • Added Grade 3 Infection to the exclusions for DLT given that infection is inherent in MDS/AML as a disease related complication
		• Section 9.6, 5th bullet final product samples: delete the words "to be handed to the infusion team member along with the infusion bag and tubing" to make consistent with rest of language in bullet and Section 8.2 as left over wording from a previous revision
		• Updated Appendix I and II to new CTO format for eligibility checklists	

3	09/23/2019	Throughout protocol: Replace the product name 161533 TriKEs with GTB-3550 TriKE™ Appendices I and II: Delete Eligibility Checklists per new CTO policy and renumber remaining appendices	Update product name
4	12/18/2019	The following changes are made to the inclusion/exclusion criteria: • Synopsis and Section 5.1: Patients with AML who relapse 3 months after transplant may be included only if off immunosuppression for a minimum of 4 weeks and do not have GVHD. Rationale: Patients who relapse after transplant have no other good therapeutic options. • Section 5.2: Remove upper age limit. Rationale: Avoids exclusion of older patients who otherwise would be eligible for study participation. • Section 5.2: Redefine the pulmonary function as DLCO corrected (ml/min/mm Hg) as no more than 5 units below lower limit of normal (CTCAE v5 Grade 1 carbon monoxide diffusing capacity decreased) based on patient's height, weight, and gender as reported by the institutional pulmonary function lab. The following changes reflect moving from a single center study to multisite study • Throughout protocol: Update the study to include participating sites template language. • Update protocol to reflect external monitoring by GT Biopharma or designee for all sites. Other protocol revision: • Section 12.4 – Expand actions associated with an early stopping rule event to allow a temporary halt of enrollment while reviewing the event rather than stopping the study. Clarifications: • Section 7.1 post-infusion TriKE product collection – revise to allow sample collection either on the unit or in the institutional research lab	Yes

Revision #	Version Date	Summary of Changes	Consent Changes
		• Section 7.3 – add a reminder any patient experiencing a DLT equivalent toxicity must discontinue therapy and is not eligible for retreatment Section 10.2 – clarify event monitoring begins with the 1st dose of TriKE	
5	01/30/2020	Section 5.3 – Change driving time requirement from 45 minutes to 90 minutes	No
6	02/12/2020	Section 5.2 – Change "and" to "or": Absolute lymphocyte count (ALC) ≥ 200 cells/mm³ OR absolute circulating CD56+/CD3- NK cell count >25 cells/µL within the 14 days prior to start of therapy. Rationale: More precise characterization of goal to maximize NK cells as the primary cell of interest and mechanism of action (MOA)	No
7	04/10/2020	Section 7.4 and Section 8 – add language to clarify that the standard of care procedures in Section 8.1 should be followed for patients who are enrolled for retreatment. Section 8.1 – clarified timing of procedures on the days of infusion. Consent changes – added background information to retreatment consent and updated long term specimen storage language to state that samples will be under the control of GT BioPharma.	Yes
8	05/18/2020	Study Schema, Section 7.2, and Section 10.3 –DLT assessments are protocol defined at Day 29. We recognized that our currently approved protocol has 2 different dates for assessment in the DLT section (Day 29 for non-hematologic and Day 42 for Hematologic assessment) which is incongruent. Thus, revised DLT assessments to clarify that hematological toxicity will be defined as lasting ≥ 29 days from start of cycle as all DLT assessments need to have the same timeline to be congruent with moving forward with subsequent patients at 29 days. .	No
9	08/31/2020	Section 7.1.5 and Section 7.5 – clarify that if after completing Block 1 and Block 2 patients with clear evidence of disease progression will discontinue treatment but will be fully evaluable for toxicity and efficacy Section 7.1 and Section 9.6 – Update the drug preparation instructions to match the study's Pharmacy Manual Section 12. 1 – add the definition of evaluable and when to replace a patient to complete enrollment. Other minor edits and clarifications	No
10	10/05/2020	Synopsis, Section 6.4 and Section 7.4 - clarify when re-treatment may be considered. Section 10.6 – Delete [redacted] from the list of persons who receive participating sites event reports for initial review. Section 10.7 – Clarify UMN's reporting flow to GTB and [redacted] for SAEs, remove link for MCC SAE reporting as process has changed and receiving report notification via [redacted]. Section 11.3 – Clarify that this study complies with the Masonic Cancer Data and Safety Monitoring Plan (DSMP) and add the link to the plan. Section 11.5 – add ICH compliant record retention information. Other minor edits and clarifications.	No
11	03/25/2021	Section 5.1 - updated definition of CD33-expressing myeloid malignancies to include phrase with greater than or equal to 50% CD33+ target cells in order to maximize potential patient benefit of treatment with GTB-3550 Added new eligibility for Elderly AML not fit for induction therapy can be enrolled after 2 failed inductions Section 5.2 updated ranges for hepatic function in order to limit pre-existing liver abnormalities Section 5.3 added new exclusions to reduce risk of comorbidities; concomitant active cancer, severe clinical obesity, over-the counter medication. Added new Section 6.2 Prior and Concomitant Therapy in order to document the review of the non-study medication used by the patient by both the Investigator and GT Biopharma.	No

Revision #	Version Date	Summary of Changes	Consent Changes
		Section 7.1.3 Supportive Care/Concomitant Medications added language regarding potential risk of LFT elevations. To reduce the risk of comorbidities, the use of medications known to elevate LFTs are prohibited from screening and the end of treatment visit. Section 7.2.1 DLT clarified the use of LFT results. Section 7.3.3 updated management of abnormal LFT results to enhance patient safety by stipulating a longer recovery time. Section 8.1 added INR testing to screening labs; added abdomen scan to CTs to allow for review of liver abnormalities and pre-existing conditions. Section 10.3 excluded grade 3 LFTs from DLT list Section 10.4 and section 10.5 clarified sponsor responsibility.	
12	05/07/2021	Section 7.2.1 Corrected language under Additional Dose Escalation Parameters. Rationale: This revision is to resolve an error (and inconsistency) in the written protocol. The intent of this statement was based on FDA comments to proceed more cautiously than dose doubling if we started to see signs of immune activation. Schema, Section 7.2.1 Added new dose level at 150 mcg/kg/day. Rationale, to slow down dose escalation when immune activation is possible, rather than proceeding from 100 mcg/kg/day to 200 mcg/kg/day as written, we will enroll the next cohort at 150 mcg/kg/day. Section 12.1 Updated statistics – rationale to account for new dose level Throughout protocol – updated to note that 7 dose levels are being tested Section 12.1 removed outdated reference to 2 mcg/kg/day – rationale, error correction – study never used this dose level.	Yes
13	06/01/2021	Key Study Personnel – Updated [redacted] as Lead Center PI at University of Minnesota. Synopsis, Section 7.2.1 and Section 10.3 – Updated DLT language to clarify DLT must be treatment related to GTB-3550 within 28 days as assessed on Day 29 from the first dose. Furthered clarified Grade 3 non-hematologic adverse events lasting more than 72 hours, with the exceptions noted, are DLTs. Added non-sustained Grade 3 QTc in the absence of cardiac arrhythmias (< 72 hours) is not a DLT. Added units to neutrophil and platelet count. Section 9.6 – Added language for paclitaxel non-DEHP equivalent tubing as determined by GTB can be used with GTB-3550 administration.	

Table of Contents

Key Abbreviations

ADCC	antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALC	Absolute lymphocyte count
AML	Acute myeloid (myelogenous) leukemia
CAR	chimeric antigen receptor
CI	Continuous infusion
CNS	Central nervous system
CR	Complete remission
CRi	Complete remission with incomplete hem recovery
CRM	continual reassessment method
CRp	Complete remission without platelet recovery
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Council
e-CRF	electronic case report form
FDA	Food and Drug Administration
GVHD	Graft versus host disease
HI	hematologic improvement
IND	investigational new drug
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
IV	Intravenous (into a vein)
LIMS	Laboratory Information Management System
mAB	monoclonal antibodies
MCC	Masonic Cancer Center
MDS	myelodysplastic syndrome
MDSC	myeloid derived suppressor cells
MTD	maximum tolerated dose
NK	natural killer
[redacted]	[redacted]
OS	overall survival
PFT	pulmonary function tests
PK/PD	pharmacokinetic/pharmacodynamics
PO	per os (by mouth)
SAE	serious adverse event
TriKE	Tri-Specific Killer Engager
TTL	Translational Therapy Laboratory
UMN	University of Minnesota
WPSS	WHO Based Prognostic Scoring System

Protocol Synopsis

GTB-3550 (CD16/IL-15/CD33) Tri-Specific Killer Engager (TriKE™) for the Treatment of High Risk Myelodysplastic Syndromes, Refractory/Relapsed Acute Myeloid Leukemia and Advanced Systemic Mastocytosis

Study Design:

This is a multisite Phase I/II clinical trial of GTB-3550 (CD16/IL-15/CD33) tri-specific killer cell engager (TriKE™) for the treatment of CD33-expressing high-risk myelodysplastic syndromes, refractory/relapsed acute myeloid leukemia or advanced systemic mastocytosis. Up to 10 sites may participate. The hypothesis is that GTB-3550 TriKE will induce natural killer cell function by targeting malignant cells as well as $CD33^+$ myeloid derived suppressor cells (MDSC) which contribute to tumor induced immunosuppression. Because CD16 is the most potent activating receptor on NK cells, this single agent may induce a targeted anti-$CD33^+$ tumor response.

Patients receive a single course of GTB-3550 TriKE given as 3 weekly treatment blocks. Each block consists of four consecutive 24 hour continuous infusions of GTB-3550 TriKE followed by a 72 hour break after Block #1 and #2. All treatment is given as an inpatient.

Disease response is assessed by bone marrow biopsy performed between Day 21 and Day 42 after the start of the 1st infusion. Follow-up for response and survival continues through 6 months from treatment start. Patients experiencing lack of disease progression or evidence of clinical improvement and no unacceptable side effects may be considered for a 2nd course of GTB-3550 TriKE on a compassionate basis.

The study consists of two components. The dose finding component is a modified version of a Phase I trial and the extended component is a modified Phase II trial.

Phase I Dose Finding Component:

The Phase I component uses a continual reassessment method (CRM) to determine the maximum tolerated dose (MTD) of GTB-3550 TriKE. Up to 7 doses levels will be tested. The goal of the CRM is to identify the dose level which most closely corresponds to the targeted dose limiting toxicity (DLT) rate of 20%. Patients are enrolled in cohorts of 2 beginning at Dose Level 1. A minimum of 1 week must separate each patient. Both patients within a cohort must reach Day 28 (end of the DLT assessment period) prior to enrollment of a subsequent cohort. The study statistician assigns each new cohort of 2 patients to the most appropriate dose level based on updated toxicity probabilities. As enrollment proceeds, each cohort is assigned to an increased, decreased or equivalent dose level based on prior data in the trial until the study sample reaches 30. At this time, the last dose is declared the MTD and becomes the GTB-3550 TriKE dose for the extended component.

Phase II Extended Component:

The primary goal of the extended component is to study the potential efficacy of GTB-3550 TriKE in this patient population. Efficacy is measured using rates of complete and partial remission. A Simon's MiniMax two-stage design is used in this phase. Stage 1 will enroll 13 patients, including all patients treated at the MTD defined during the dose finding component. If 3 or more of these 13 patients experience a clinical response by Day 42, the trial moves to Stage 2 and enrolls an additional 17 patients. If at least 10 of the 30 patients have a disease response, GTB-3550 TriKE will be considered for further investigation. There is no staggering of enrollment for this cohort.

Primary Objectives:

Phase I Dose Finding: To identify the maximum tolerated dose (MTD) of GTB-3550 TriKE defined as the dose level that most closely corresponds to a dose limiting toxicity rate (DLT) of 20%.

Phase II Extension: To determine preliminary efficacy as measured by the rates of "best" clinical response by Day 42 day after the start of the 1st infusion. For AML clinical response includes complete remission with or without hematologic or platelet recovery (CR, CRi or CRp) or partial response. For MDS clinical response includes complete remission, marrow CR (with incomplete peripheral blood count normalization), partial response or hematologic improvement (HI). For advanced systemic mastocytosis response is considered a decrease in mast cell burden in bone marrow or serum tryptase level by at least 30%.

Secondary Objectives:

- To evaluate the safety of GTB-3550 TriKE when administered on this schedule
- To estimate overall survival (OS) at 6 months

Correlative Objectives:

- To monitor the number, phenotype, activation status and function of NK cells, T cells, T regulatory cells and MDSCs pre- and post-therapy ([redacted])
- To evaluate the pharmacokinetics and dynamics of the TriKE reagent
- To monitor for the development of human anti-TriKE antibodies
- To monitor the occurrence of antigen negative escape variants ([redacted]) in patients without response

Eligible Diseases:

Diagnosis of one of the following CD33-expressing myeloid malignancies with greater than or equal to 50% CD33+ target cells with no good standard of care treatment options including:

High Risk Myelodysplastic Syndromes (MDS) progressive on two or more prior regimens and requiring treatment that meets **at least one** of the following:

- IPSS-R High or Very High Risk
- WHO Classification: RAEB-1 or RAEB-2
- Poor and very poor risk cytogenetic abnormality as defined by the IPSS-R cytogenetic classifications
- WHO Based Prognostic Scoring System (WPSS): High or Very High Risk

Therapy related MDS and not a candidate for induction chemotherapy or had an inadequate treatment response after induction chemotherapy

Acute Myelogenous Leukemia (AML) meeting **at least one** of the following:

- Refractory AML defined as failure to achieve remission after at least 3 induction attempts
  - Elderly AML not fit for induction therapy can be enrolled after 2 failed inductions
- Relapsed AML meeting one of the following:
- Not a candidate for hematopoietic stem cell transplant (HSCT), at least one re-induction attempt required
- Prior HSCT relapse beyond 3 months may be included only if off immunosuppression for a minimum of 4 weeks and do not have GVHD

Advanced systemic mastocytosis (defined as mast cell leukemia, aggressive systemic mastocytosis, and systemic mastocytosis associated with hematologic neoplasm) may enroll without any prior treatment, given there is no standard established therapy.

Key Inclusion Criteria:

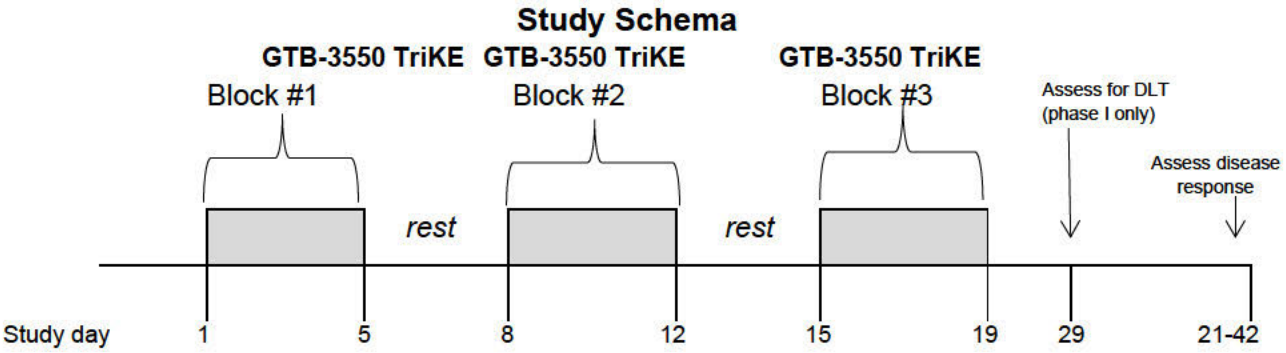
- Age ≥ 18 years of age, Karnofsky performance status ≥ 70%
- Adequate renal, hepatic, cardiac and lung function
- Absolute lymphocyte count (ALC) ≥ 200 cells/mm³ OR absolute circulating $CD56^{+}/CD3^{-}$ NK cell count >25 cells/µL within the 14 days prior to start of therapy

Enrollment: Dose Finding Component: 30 patients enrolled in cohorts of 2 testing up to 7 GTB-3550 TriKE dose levels

Extended Component:
Stage 1: enroll 13 patients at the MTD (including any from the dose finding component treated at the MTD) – If 3 or more of these 13 patients experience a clinical response by Day 42, the trial will move to Stage 2

Stage 2: enroll 17 additional patients at the MTD established during the dose finding component

If the Phase I component enrolls more than 13 patients at the MTD, the futility rule for the two stage design will be adjusted with the given number of patients enrolled at the MTD.



Each block consists of 4 consecutive 24 hour continuous infusion (CI) of GTB-3550 TriKE at the patient's assigned CI dose with a 72 hour rest after Block #1 and #2.

Dose Finding Phase I Component:

Each patient receives GTB-3550 TriKE at the assigned CI dose for 3 sets (infusion block #1, #2, and #3) of 4 consecutive 24 hours infusions separated by a 72 hour rest.

Dose Level	GTB-3550 TriKE Dose daily continuous infusion (CI) dose (µg/kg/day)
1	5
2	10
3	25
4	50
5	100
6	150
7	200

The phase I component uses a continual reassessment method (CRM). Patients are enrolled in cohorts of 2 beginning at Dose Level 1. A minimum of 1 week must separate each patient. Both patients within each cohort must reach Day 28 (end of the DLT assessment period) prior to enrollment of a subsequent cohort. The study statistician assigns each new cohort of 2 patients to the most appropriate dose level based on updated toxicity probabilities. As enrollment proceeds, each cohort will be assigned to an increased, decreased or equivalent dose level based on prior data in the trial. Enrollment continues until the study sample reaches evaluable 30 patients. At that time the maximum tolerated dose (MTD) for the Phase II component will be identified.

Dose Limiting Toxicity (DLT) is defined as any related treatment emergent toxicity within 28 days (**as assessed on Day 29**) of the first dose of TriKE with the exception of those that are clearly and incontrovertibly due to extraneous causes for the following criteria based on CTCAE v5:

- Any Grade 4 or 5 non-hematologic events
- Grade 3 non-hematologic adverse events lasting more than 72 hours, except the following:
  - Non-sustained (< 7 days) Grade 3 liver function tests (ALT/AST, alkaline phosphatase, total or direct bilirubin) abnormalities in the absence of clinical signs of hepatic dysfunction (lethargy, confusion, anorexia, pruritus or tremors).
  - Non-sustained Grade 3 QTc prolongation (< 72 hours) in the absence of cardiac arrhythmia
  - Grade 3 electrolyte disturbances that resolve, with or without intervention, to < Grade 2 levels within 72 hours
  - Grade 3 fatigue
  - Grade 3 anorexia
  - Grade 3 fever
  - Grade 3 infection

- Hematologic Toxicity - Given that AML and MDS inherently leads to low neutrophils and platelets, standard grading cannot be used as many of these patients technically meet criteria for "grade 4" neutropenia or thrombocytopenia at baseline. Thus, the hematologic DLTs are listed below:
  - AML:
    - Grade 4 neutrophil count (<500/μL) lasting ≥ 29 days from start of cycle in absence of evidence of active leukemia
    - Grade 4 platelet count (<25,000/μL) lasting ≥ 29 days from start of cycle in the absence of active leukemia
    - Any clinically significant bleeding that is not controllable with transfusion support
  - MDS/mast cell diseases:
    - Grade 4 neutrophil count (<500/μL) lasting ≥ 29 days from start of cycle in absence of evidence of active MDS/mast cell disease
    - Grade 4 platelet count (<25,000/μL) lasting ≥ 29 days from start of cycle in the absence of active MDS/Mast cell disease
    - Any clinically significant bleeding that is not controllable with transfusion support
    - Grade 4 anemia, unexplained by the underlying disease
- Grade 3 infusion related, treatment related reaction including cytokine release syndrome which does not resolve within 72 hours despite best medical management (refer to Section 10 for modified CRS grading)
- Grade 3 or 4 Tumor Lysis Syndrome that does not resolve within 7 days with or without intervention
- Inability to complete at least one block of three 24 hour infusions due to any treatment emergent, treatment related toxicity

Maximum Tolerated Dose (MTD) is defined as the dose level that most closely corresponds to the target DLT rate of 20%.

Additional Dose Escalation Parameters (Phase I Only):
In addition to monitoring for dose limiting toxicity, patients enrolled in the Phase I component will be monitored for signs of immune activation using treatment related tachycardia and fever as clinical markers of transient bioactivity resulting from endogenous cytokine release. If detected in a single patient, subsequent dose levels will increase by 50% instead of the planned doubling (100% increase).

Extended Phase II Component:
Patients will receive three consecutive blocks of four 24 hour continuous infusions of GTB-3550 TriKE at the Phase I MTD separated by a 72 hour rest. There is no staggering of enrollment for this component.

Stage 1: Enroll a total of 13 patients (including all treated at the MTD in Phase I). If 3 or more of these patients have clinical response by Day 42 the trial will continue to Stage 2. If the Phase I component enrolls more than 13 patients at the MTD, the futility rule for the two-stage design will be adjusted with the given number of patients enrolled at the MTD.

Stage 2: Enroll an additional 17 patients. If 10 of 30 patients have a clinical response by Day 42, GTB-3550 TriKE will be considered promising for further investigation.

Monitoring for Safety (Phase II Extended):
- Grade 4-5 non-hematologic, non-relapse, non-infectious toxicity (except fever) by 42 days after the start of the first GTB-3550 TriKE treatment block
- Non-relapse, non-infectious treatment related mortality within 60 days of the 1st dose of GTB-3550 TriKE

1 Objectives

1.1 Primary Objective

Phase I Dose Finding: To identify the maximum tolerated dose (MTD) of GTB-3550 TriKE defined as the dose level that most closely corresponds to a dose limiting toxicity rate (DLT) of 20%.

Phase II Extension: To determine preliminary efficacy as measured by the rates of "best" clinical response by Day 42 after the start of the 1st infusion.

For AML clinical response includes complete remission with or without hematologic or platelet recovery (CR, CRi or CRp) or partial response. For MDS clinical response includes complete remission, marrow CR (with incomplete peripheral blood count normalization), partial response or hematologic improvement (HI). For advanced systemic mastocytosis response is considered a decrease in mast cell burden in bone marrow or serum tryptase level by at least 30%.

1.2 Secondary Objectives

- To evaluate the safety of GTB-3550 TriKE when administered on this schedule
- To estimate overall survival (OS) at 6 months

1.3 Correlative (Research) Objectives

- [redacted]
- To evaluate the pharmacokinetics and dynamics of the TriKE reagent
- [redacted]
- To monitor the occurrence of antigen negative escape variants (CD33- blasts) in patients without response

2 Background

Acute myeloid leukemia (AML) is a heterogeneous hematologic stem cell malignancy in adults with incidence rate of 3–5% per 100,000 populations. The median age at the time of diagnosis is 65–69 years.[1,2] AML is an aggressive disease and is fatal without anti-leukemic treatment. Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid neoplasms characterized by dysplastic features of erythroid/myeloid/megakaryocytic lineages, progressive bone marrow failure, a varying percentage of blast cells, and enhanced risk to evolve into acute myeloid leukemia[3]. The incidence of MDS is rising especially in states like Minnesota for unknown reasons. There are few established treatments for MDS so a drug that could be successfully employed

to treat AML and MDS would be extremely valuable. The expression of cell surface markers in MDS is complicated by its heterogeneous nature and has only been recently brought to light with the work of the First Workshop on Standardization of Flow Cytometry in MDS convened in Amsterdam bringing together experts from Europe, Japan, and the USA[4]. The workshop found that a majority of MDS cases showed an abnormally high expression of HLA-DR, CD64, and CD33. We believe that CD33 is a validated target in AML and can also target MDS cells to promote a novel targeted immunotherapy approach for these diseases.

Targeted cancer immunotherapies are currently a subject of great clinical interest and potential [5]. While a great deal of interest has recently been placed upon generation of chimeric antigen receptor (CAR) expressing T cells from monoclonal antibodies shown to target human malignancies [6], and more even more recently upon generation of CAR-expressing natural killer (NK) cells [7,8], these approaches require a personalized approach that is expensive, time consuming, and difficult to apply on a large scale. There is a clear need for targeted off-the-shelf therapies that augment the current monoclonal antibody approach. To accomplish this goal, we focus on generation of tri-specific killer engagers (TriKEs) meant to target NK cells to the tumor synapse and induce their activation at that site. Unlike full-length tri-specific antibodies, [redacted]

[redacted]

In human NK cells, [redacted]

[redacted]

[redacted] The efficacy of therapeutic mAbs in vivo, in contrast to their high ADCC efficacy in vitro, is further attenuated by the presence of physiologic serum IgG levels in plasma. In the in vivo setting, ADCC potency is diminished by saturation of CD16 receptors, thus competing for binding with the therapeutic mAb [36]. Such competition for binding of the therapeutic Fc portion of antibodies requires high serum levels of the mAb to be sustained over several months of treatment in order to achieve in vivo efficacy [37,38]. [redacted]

These attributes make them an ideal pharmaceutical platform for potentiated NK cell-based immunotherapies.

3 Summary and Rationale

The most important aspects of the humoral (antibody) response against cancer is 1) the ability of antibody to mediated antibody dependent cellular cytotoxicity (ADCC) through CD16, 2) the ability to mediate in vivo expansion of the immune population to recruit more killers to generate an anti-cancer response (the IL-15 linker) and 3) recognition of a target antigen (like CD33 being tested here). [redacted]

[redacted]

The Trispecific Killer Engager (TriKE) designated GTB-3550 was designed as a straightforward off-the-shelf product that can be used to treat CD33+ AML/MDS patients in a manner similar to the way rituximab is used to treat B cell malignancies. We believe that a major advantage of our drug as compared to chimeric antigen receptor (CAR) transduced T cells that require cell and gene therapy is the simplicity of our approach. [redacted] The MTD of exogenous IL-15 in humans following continuous IV infusion is 2 ug/kg/day for a total of 10 days (240 hours). [redacted]

4 Study Design

This is a multisite Phase I/II clinical trial of GTB-3550 (CD16/IL-15/CD33) tri-specific killer cell engager (TriKE) for the treatment of CD33-expressing high risk myelodysplastic syndromes, refractory/relapsed acute myeloid leukemia or advanced systemic mastocytosis. Up to 10 study centers may take part in this trial.

Patients receive a single course of GTB-3550 TriKE given as 3 weekly treatment blocks. Each block consists of four consecutive 24 hour continuous infusions of GTB-3550 TriKE followed by a 72 hour break after Block #1 and #2. All treatment is given as an inpatient.

Toxicities are monitored through Day 28 (as assessed on Day 29) with continued toxicity assessment through Day 60. Disease response is assessed by bone marrow biopsy performed between Day 21 and 42 after the start of the 1st infusion. Follow-up for response and survival continues through 6 months from study treatment start.

The study consists of two components. The dose finding component is a modified version of a Phase I trial and the extended component is a modified Phase II trial.

Dose Finding Component: The Phase I component uses a continual reassessment method (CRM) to determine the maximum tolerated dose (MTD) of GTB-3550 TriKE. Up to 7 doses levels will be tested. The goal of the CRM is to identify the dose level which most closely corresponds to the targeted dose limiting toxicity (DLT) rate of 20%.

Patients are enrolled in cohorts of 2 beginning at Dose Level 1. A minimum of 1 week must separate each patient. Both patients within a cohort must reach Day 28 (end of the DLT assessment period) prior to enrollment of a subsequent cohort. The study statistician assigns each new cohort of 2 patients to the most appropriate dose level based on updated toxicity probabilities. As enrollment proceeds, each cohort is assigned to an increased, decreased or equivalent dose level based on prior data in the trial until the study sample reaches 30. At this time, the last dose is declared the MTD and the GTB-3550 TriKE dose for the extended component.

Extended Component: The primary goal of the extended component is to study the potential efficacy of GTB-3550 TriKE in this patient population. Efficacy is measured using rates of complete and partial remission. A Simon's MiniMax two-stage design is used in this phase. Monitoring guidelines are in place to stop the study early for excessive toxicity.

Stage 1 enrolls 13 patients, including all patients treated at the MTD defined during the dose finding component. If 3 or more of these 13 patients have a clinical response to GTB-3550 TriKE, the trial moves to Stage 2 and enrolls an additional 17 patients. If the Phase I component enrolls more than 13 patients at the MTD, the futility rule for the two-stage design will be adjusted with the given number of patients enrolled at the MTD.

If at least 10 of the 30 patients have a clinical response, GTB-3550 TriKE will be considered for further investigation.

Patients experiencing clinical benefit (defined as stable or better) at the time of the 1st disease reassessment may be considered for a 2nd course of GTB-3550 TriKE on a compassionate basis provided they experienced no side effects equivalent to a DLT and continue to meet relevant study inclusion/exclusion criteria. Refer to Section 7.4 for additional information.

5 Patient Selection

Study entry is open to adult patients 18 years of age and older regardless of gender, race, or ethnic background. While there will be every effort to seek out and include women and minority patients, the patient population is expected to be no different than that of other high risk malignancies studies at the University Of Minnesota and other participating institutions.

A potential participant must meet all of the inclusion and exclusion criteria to be considered eligible for study participation.

5.1 Eligible Diseases

Diagnosis of one of the following CD33-expressing myeloid malignancies with greater than or equal to 50% CD33+ target cells with no good standard of care treatment options including:

High Risk Myelodysplastic Syndromes (MDS) progressive on two or more prior regimens and requiring treatment that meets **at least one** of the following:

- IPSS-R High or Very High Risks
- WHO Classification: RAEB-1 or RAEB-2
- Poor and very-poor risk cytogenetic abnormality as defined by the IPSS-R cytogenetic classifications
- WHO Based Prognostic Scoring System (WPSS): High or Very High Risk

Therapy related MDS and not a candidate for induction chemotherapy or had an inadequate treatment response after induction chemotherapy.

Refractory or Relapsed Acute Myelogenous Leukemia (AML) meeting **at least one** of the following:

- Refractory AML defined as failure to achieve remission after at least 3 induction attempts
    - Elderly AML not fit for induction therapy can be enrolled after 2 failed inductions
- Relapsed AML
    - Not a candidate for hematopoietic stem cell transplant (HSCT), at least one re-induction attempt required
    - Prior HSCT relapse beyond 3 months may be included only if off immunosuppression for a minimum of 4 weeks and do not have GVHD

Notes:

1) For hypomethylating agents (i.e. decitabine, azacititdine) to count as an induction/re-induction attempt, the patient must have completed a minimum of 3 monthly cycles
2) For targeting agents (i.e. sorafenib) to count as an induction/re-induction attempt, the patient must have completed a minimum of 1 month without attaining CR

Advanced systemic mastocytosis (defined as mast cell leukemia, aggressive systemic mastocytosis, and systemic mastocytosis associated with hematologic neoplasm) may enroll without any prior treatment, given there is no standard established therapy.

5.2 Age, Performance Status, Organ Function, Contraception Use

- At least 18 years of age
- Karnofsky score ≥ 70% (Appendix I)
- Adequate organ function within 14 days (30 days for cardiac and pulmonary) of study enrollment defined as:
  - Renal: an estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2
  - Hepatic: AST, ALT, alkaline phosphatase and total bilirubin within normal range
  - Pulmonary function: DLCO corrected (ml/min/mm Hg) defined as no more than 5 units below lower limit of normal (CTCAE v5 Grade 1 carbon monoxide diffusing capacity decreased) based on patient's height, weight, and gender as reported by the institutional pulmonary function lab.
  - Cardiac: Absence of decompensated congestive heart failure, or uncontrolled arrhythmia; left ventricular ejection fraction ≥ 45% by echocardiogram, MUGA or cardiac MRI.
- Absolute lymphocyte count (ALC) ≥ 200 cells/mm^3 OR absolute circulating $CD56^+/CD3^-$ NK cell count >25 cells/µl within the 14 days prior to start of therapy
- Sexually active females of childbearing potential and males with partners of child-bearing potential must agree to use adequate birth control during study treatment
- Participant provides voluntary written consent signed before performance of any study-related procedure not part of normal medical care

5.3 Exclusion Criteria

- New or progressive pulmonary infiltrates on screening chest x-ray or chest CT scan unless cleared for study by Pulmonary. Infiltrates attributed to infection must be stable/improving with associated clinical improvement after 1 week of appropriate therapy (4 weeks for presumed or documented fungal infections).
- Uncontrolled bacterial, fungal or viral infections, known history of HIV
- Active Hepatitis B or Hepatitis C (virus detectable by PCR) - chronic asymptomatic viral hepatitis is allowed
- Other concurrent active cancer within the last year (excluding non-melanoma skin cancers)
- Severely clinically obese patients, BMI >38

- Currently taking any over-the-counter [OTC], vitamin, mineral, or dietary supplement within 14 days prior to study drug administration on Day 1 and during study conduct that may confound study safety goals (e.g. St. John's wort). Questions should be discussed with GT Biopharma.
- Pregnant or breast feeding. The effect of GTB-3550 TriKE on the fetus is unknown. Females of childbearing potential must have a blood test within 7 days prior to enrollment to rule out pregnancy - must be repeated if not within 7 days of treatment initiation
- History of central nervous system malignancy or symptoms of active CNS disease
- A family history of long QT syndrome or with a QTc interval > 480 msec at screening
- Currently taking medications known to prolong QT/QTc interval as the potential risk of QT/QTc prolongation is unknown in humans (refer to Appendix V for a list of prohibited medications for eligibility)
- A candidate for potentially curative therapy, including hematopoietic cell transplant
- Unwilling to remain within a 90 minute drive of the study center through at least Day 29

6 Patient Screening and Study Enrollment

Written consent must be obtained prior to the performance of any research related tests or procedures. Consent is usually obtained before final eligibility is determined.

6.1 Consent and Study Screening in [redacted]

Any patient who has been consented is to be entered in [redacted] by the Study Coordinator or designee. If a patient is consented but is not enrolled in the study treatment, the patient's record is updated in [redacted] as a screen failure and reason for exclusion recorded.

6.2 Prior and Concomitant Therapy:

All non-study medications, including prescription, OTC, or herbal therapies, used by the patient will be documented (i) for the 14 days prior to screening (prior medications), (ii) during screening, and (iii) throughout the study (concomitant medications). The Investigator in communication with the Sponsor will review and determine if prior/concomitant medication(s) affect the patient's eligibility to participate or continue to participate in the study.

Administering medications known to elevate Liver Function Tests (LFTs) during the treatment interval and the week before should be avoided. Azole antifungal

agents frequently increase liver function tested in >10% of subjects. For 1 week prior to and concurrent with GTB-3550 administration, patients should be treated with micafungin if medically indicated.

6.3 Study Enrollment and GTB-3550 TriKE Dose Level

To be eligible for this study, the patient must sign the treatment consent and meet each inclusion criteria and none of the exclusion criteria listed on the eligibility checklist based on the eligibility assessment documented in the patient's medical record.

To complete enrollment in [redacted], the Study Coordinator or designee records the GTB-3550 TriKE dose level assignment.

6.4 Inability to Begin Study Treatment

If a patient is enrolled to the study, and is later found not able begin the study treatment, for whatever reason, the patient will be taken off study and treated at the physician's discretion. The Study Coordinator or designee will update [redacted] of the patient's non-treatment status. The patient will be replaced to fulfill enrollment requirements.

6.5 Re-Treatment Enrollment onto 2015LS167R

Any patient, in the judgement of the Principal Investigator, who experiences lack of disease progression or evidence of clinical improvement after completion of the 1st treatment course may be considered for retreatment per Section 7.4. To be eligible for re-treatment the patient must sign the re-treatment consent and meet each inclusion criteria and none of the exclusion criteria listed on the eligibility checklist based on the eligibility assessment documented in the patient's medical record. Any qualifying patient who has signed the re-treatment consent is entered onto the re-treatment protocol ([redacted]) in [redacted] by the Study Coordinator or designee.

7 Treatment Plan

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (i.e. acetaminophen, diphenhydramine, G-CSF, antimicrobials, etc.).

7.1 GTB-3550 TriKE Administration

Patients receive a single course of GTB-3550 TriKE at their assigned dose as 3 weekly treatment blocks. Each block consists of four consecutive 24 hour

continuous infusions (over approximately 96 hours) of GTB-3550 TriKE followed by a 72 hour break after Block #1 and #2. All treatment is given as an inpatient.

The assigned dose will be calculated on a weight obtained within 5 days prior to or on day of the 1st dose. The dose is not be recalculated for subsequent treatment blocks.

The institutional Investigational Pharmacy will prepare each 24 hour bag for infusion per Section 9.6 based on the patient's assigned GTB-3550 TriKE dose. Each assigned dose will be administered as a 100 mL infusion over 24 hours period at 4.17 mL/hour rate. Note: actual bag volume is 130 ml to allow for the product sample collection before and after infusion.

Pre-meds:
Pre-meds: 30 minutes prior to each infusion, patients will receive acetaminophen 325 mg PO and diphenhydramine 25mg PO/IV. Repeat prn.

IV Fluid Management:
IV fluids should be administered at a minimum rate of 50 cc/hour additional fluids given based on the clinical status of the patient.

Infusion Related Reactions:
If Grade 2 infusion related reaction occurs, interrupt the infusion and treat symptomatically with antihistamines, NSAIDS, narcotics, IV fluids as medically appropriate. Any patient experiencing a second Grade 2 infusion related reaction after restarting, despite pre-medication or a Grade 3 or 4 infusion related reaction will be permanently discontinued from GTB-3550 TriKE.

Administration of glucocorticoids is prohibited during the TriKE treatment period as the use of systemic steroid medications may result in loss of therapeutic effects of the study drug. They should be avoided except in the event of a severe toxicity.

Any Grade 3 or 4 infusion related reaction will result in permanent discontinuation of study drug with appropriate medical intervention.

Post-Infusion TriKE Sample Collection (Week 1 infusions only):
Upon completion of each infusion during Week 1 only, the nursing staff will disconnect the infusion bag and tubing from the patient. Prior to discarding the bag and tubing, two pre-labeled 1.8 ml cryo-vial (containing wording "Post-Infusion" as well as dose and date when bag was prepared) will be filled with a minimum of 1 ml of drug each. This may be done on the unit or the bag/tubing transferred to the institutional research lab and samples collected there. Regardless, the vials or

infusion bag/tubing must be refrigerated while awaiting transfer to the research lab. The research lab will freeze samples for later batch shipping to UMN TTL (if applicable) and testing. Refer to Section 8.2 for additional details.

7.1.1 Monitoring Requirements During TriKE Infusions

Monitoring during the 1st infusion of each continuous infusion (CI) block:
Vital signs including blood pressure, pulse, temperature, respirations, and pulse oximetry will be measured as follows:

- prior to the infusion start
- every 15 minutes (±10 minutes) during the 1st hour
- every 30 minutes (±10 minutes) during the 2nd hour
- every 60 minutes (±10 minutes) for the next 2 hours
- then every 4 hours (±20 minutes) for the remainder of the infusion

Monitoring during the infusion 2, 3, and 4 of each CI block:
Vital signs including blood pressure, pulse, temperature, respirations, and pulse oximetry will be measured as follows:

- every 15 minutes (±10 minutes) during the 1st hour
- then every 4 hours (±20 minutes) for the remainder of the infusion

Targeted toxicities (Appendix VI) and unexpected adverse events will be collected at the time points listed in Section 10.2.

7.1.2 Monitoring for Signs of Immune Activation (Phase I Patients):

In addition to monitoring as above, patients enrolled in Phase I will be monitored for clinical signs of immune activation:

- treatment related tachycardia defined as a heart rate of >30 BPM than baseline heart rate measured each cycle pre-infusion and persists for 4 hours
- fever defined as Grade 2 (>39.0 - 40.0 degrees C [102.3 - 104.0 degrees F]) and persists for 4 hours

If a patient meets either of the above criteria, no dose adjustment will be made unless a dose limiting toxicity (DLT) occurs. Refer to Section 7.2.1 for impact on subsequent dose level escalation.

7.1.3 Supportive Care/Concomitant Medications

Supportive measures may include acetaminophen for fevers, meperidine for chills, anti-emetics for nausea and vomiting, normal saline or furosemide to maintain fluid balance/blood pressure/pulmonary function, and electrolyte replacement. Use of G-CSF is permitted as clinically indicated. Refer to Section 7.3 for management of selected toxicities.

Administration of glucocorticoids is prohibited during the TriKE treatment period as the use of systemic steroid medications may result in loss of therapeutic effects of the study drug. They should be avoided except in the event of a severe toxicity.

The potential risk of QT/QTc prolongation is unknown in humans receiving TriKE. Persons with a family history of long QT syndrome, with a QTc interval > 480 msec at screening, or taking concurrent medications known to prolong QT/QTc interval are not eligible for this study. The use of medications known to prolong QT/QTc interval (refer to Appendix V) are prohibited between screening and the end of treatment visit if at all possible.

The interactions between TriKE and the P450 system are unknown. The IL-15 component may affect substrates of CYP3A4 and CYP2D6 substrates. See Appendix IV for a list of drugs which may be affected. Patients with unexpected toxicity should have a review of their con-meds to determine whether there are any potential interactions. The PI or treating physician should consider discontinuing these medications as clinically indicated.

All concomitant medications, with a start and stop date must be documented relative to administration of GTB-3550 TriKE.

7.1.4 Dose Modifications

No individual patient dose modifications are permitted other than as described in Section 7.3.3 for elevated liver enzymes.

7.1.5 Criteria to Continue with GTB-3550 TriKE Block #2 and #3

A dose limiting toxicity (for any patient, not just dose finding) during the previous block's infusions (defined in Section 7.2.1) will disqualify a patient from receiving further therapy.

Disease based treatment decisions: If after completing Block #1 and Block #2, the patient has clear evidence of disease progression they will be discontinued from study treatment and further treatment with study drug is to be discontinued. Such patients remain fully evaluable for efficacy and toxicity.

To begin a new block, on the day of the planned treatment the patient must:

- not currently meet any disease specific hematologic dose limiting toxicity as defined in Section 7.2.1.
- have an estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2
- have a total bilirubin of ≤1.5 times the ULN

- have AST and ALT ≤ 3 x upper limit of normal, and alkaline phosphatase levels ≤ 2.5 x upper limit of normal
- be afebrile (defined as a temperature of ≤ 101ºF)
- have room air 0_2 saturation ≥ 88%
- have a blood pressure ≥ 100/65 mm/Hg
- have no signs or symptoms of infection

If the above criteria is not met, treatment must be delayed for appropriate supportive care and clinical assessment. The study drug may begin the following day, if the above criteria are met and, in the opinion of the clinical provider it is safe to proceed. Otherwise delay 1 week from the planned start and reassess at that time.

Patients unable to begin treatment after a 1 week delay will be permanently discontinued from treatment and followed per Section 7.6.

The start of Block #2 or Block #3 may be delayed for up to 1 week (i.e. start 1 week later than planned) to allow for the resolution of any treatment or non-treatment issues (i.e. URI, UTI, etc.) or for holiday/scheduling issues.

7.2 GTB-3550 TriKE Dose Levels

7.2.1 Dose Finding Component (Phase I)

The 1st two patients will be assigned dose level 1. The study statistician (UMN biostatistician Todd DeFor or designee) will assign each new cohort of 2 patients to the most appropriate dose level based on updated toxicity probabilities. Both patients within a dose cohort must reach Day 28 (end of the DLT assessment period) prior to enrollment of a subsequent cohort. Enrollment continues until 30 evaluable patients are accrued.

Dose Level	GTB-3550 TriKE Dose daily continuous infusion (CI) dose (µg/kg/day)
1	5
2	10
3	25
4	50
5	100
6	150
7	200

Dose Limiting Toxicity (DLT) is defined as any of the following related treatment emergent toxicity with the exception of those that are clearly and incontrovertibly due to extraneous causes within 28 days (**as assessed on Day 29**) of the first dose of TriKE for the following criteria based on CTCAE v5:

- Any Grade 4 or 5 non-hematologic events
- Grade 3 non-hematologic adverse events lasting more than 72 hours, except the following:
  - Non-sustained (< 7 days) Grade 3 liver function tests (ALT/AST, alkaline phosphatase, total or direct bilirubin) abnormalities in the absence of clinical signs of hepatic dysfunction (lethargy, confusion, anorexia, pruritus or tremors).
  - Non-sustained Grade 3 QTc prolongation (< 72 hours) in the absence of cardiac arrhythmia
  - Grade 3 electrolyte disturbances that resolve, with or without intervention, to < Grade 2 levels within 72 hours
  - Grade 3 fatigue
  - Grade 3 anorexia
  - Grade 3 fever
  - Grade 3 infection
- Hematologic Toxicity - Given that AML and MDS inherently leads to low neutrophils and platelets, standard grading cannot be used as many of these patients technically meet criteria for “Grade 4” neutropenia or thrombocytopenia at baseline. Thus, the hematologic DLTs are listed below:
  - AML
    - Grade 4 neutrophil count (< 500/μL) lasting ≥ 29 days from start of cycle in absence of evidence of active leukemia
    - Grade 4 platelet count (< 25,000/uL) lasting ≥ 29 days from start of cycle in absence of evidence of active leukemia

  Any clinically significant bleeding that is not controllable with transfusion support
  - MDS/mast cell diseases:
    - Grade 4 neutrophil count (<500/μL) lasting ≥ 29 days from start of cycle in absence of evidence of active MDS/mast cell disease
    - Grade 4 platelet count (<25,000/μL) lasting ≥ 29 days from start of cycle in the absence of active MDS/Mast cell disease
    - Any clinically significant bleeding that is not controllable with transfusion support
    - Grade 4 anemia, unexplained by the underlying disease

- Grade 3 infusion related, treatment related reaction including cytokine release syndrome which does not resolve within 72 hours despite best medical management (refer to Section 10 for modified CRS grading)
- Grade 3 or 4 Tumor Lysis Syndrome that does not resolve within 7 days with or without intervention
- Inability to complete at least one block of three 24 hour infusions due to any treatment emergent, treatment related toxicity.

Maximum Tolerated Dose (MTD) is defined as the dose level that most closely corresponds to the target DLT rate of 20%.

Additional Dose Escalation Parameters (Phase I Only):
In addition to monitoring for dose limiting toxicity, patients enrolled in the Phase I component will be monitored for signs of immune activation using treatment related tachycardia and fever as clinical markers of transient bioactivity. Refer to Section 7.1.2 Monitoring for Signs of Immune Activation (Phase I patients) for the definition of tachycardia and fever thresholds.

If detected in a single patient (fever or tachycardia lasting > 4 hours OR meets criteria for any DLT) subsequent dose levels will increase by 50% instead of the planned doubling (100% increase). For example, if signs of immune activation occurred at Dose Level 4 (50 µg/kg/day), Dose Level 5 would be adjusted to 75 µg/kg/day rather than 100 µmg/kg/day and Dose Level 6 would be 115 µg/kg/day (75 x 1.5 rounded up to the nearest 5) rather than 200 µg/kg/day.

7.2.2 Extended Component (Phase II)

The treatment schedule is identical to the dose finding component. The extended component uses a Simon's MiniMax two-stage design for continued enrollment using the maximum tolerated dose (MTD) established during Phase I with monitoring guidelines to stop the study early for excessive toxicity.

In Stage 1, a total of 13 patients (including all treated at the MTD in part 1) will be enrolled. If 3 or more of these have clinical response the trial will continue to Stage 2. If the phase I component enrolls more than 13 patients at the MTD, the two-stage design will be adjusted with the given number of patients enrolled at the MTD.

In Stage 2, an additional 17 patients will be enrolled for a total of 30 patients treated at the MTD.

7.3 Management of Selected GTB-3550 TriKE Toxicities

Throughout the study, the investigator may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care. Supportive care may include antibiotics, anti-fungals, analgesics, transfusions, and G-CSF/cytokines.

Note: Any patient experiencing a DLT equivalent toxicity must discontinue treatment per Section 7.5 and is not eligible for retreatment.

Please refer to Section 9.7 for potential toxicities.

7.3.1 Tumor Lysis Syndrome

Tumor lysis syndrome is a possible risk associated with therapy of active leukemia. All patients (except those with known allergy) will begin on prophylactic allopurinol 300 mg po before the 1st dose of GTB-3550 TriKE and continue daily as clinically indicated.

7.3.2 Infusion Related Reaction

Patients will be monitored for the occurrence of hypotension, dyspnea and angioedema during the infusion. The infusion will be stopped and the reaction treated per Section 7.1. A Grade 3 or Grade 4 infusion related reaction will result in permanent discontinuation of the infusion.

7.3.3 Increase in Liver Function Tests

Liver function tests will be monitored three times weekly during each CI block and at Day 22, 29, and 60 visits.

Elevated liver function tests (ALT, AST and/or total bilirubin) guidelines based on CTCAE v 5 grading:

Grade 1 or 2: continue therapy per protocol
Grade 3: discontinue treatment for the current block after completion of the currently hung infusion bag, if applicable. Missed doses are not made up.

At the time of next scheduled treatment, if LFTs return to Grade 0 in two weeks or less, initiate the next block of treatment; however, reduce the TriKE dosing by 1 dose level.

Grade 4 or recurrence of a Grade 3: permanently discontinue therapy

7.3.4 Neurotoxicity

A neurological assessment including basic motor (gait), coordination (steadiness) and cognitive function (alert and oriented) should be performed daily during each CI block. Any abnormalities should be followed up with a detailed neurologic exam and appropriate clinical care.

7.3.5 Pulmonary Toxicity

Patients will be monitored for clinical signs and symptoms of pulmonary toxicity through routine daily patient assessments and via the Targeted Toxicities Worksheet (Appendix VI). O_2 saturation levels will be checked per routine in-patient assessments (minimum of once every nursing shift).

Any new hypoxia will be evaluated with a chest x-ray or other imaging as clinically indicated.

Grade 3 hypoxia (decreased oxygen saturation at rest [e.g., pulse oximeter < 88%]) or higher is a dose limiting toxicity. In this situation, discontinue treatment for per Section 7.5 after completion of the currently hung infusion bag, if applicable.

7.3.6 Cytokine Release Syndrome (CRS) or CRS-Like Symptoms

While CRS is a clearly defined syndrome in T cell therapy, it is not known to occur to the full extent in NK cell therapies. However, we have seen immune activation syndromes with other IL-15 products that include fever, and rash. If symptoms occur, CRP, IL-6 and ferritin levels will be assessed. If indicated by the presence of medically significant symptoms and/or high IL-6 levels or any symptoms requiring intervention, steroids are the first line of treatment.

Patients will be monitored for clinical signs and symptoms of CRS through routine daily patient assessments and via the Targeted Toxicities Worksheet (Appendix VI). Refer to Section 10 for the revised CRS grading system that will be used for this study.

7.4 Opportunity for Re-Treatment

If a patient completes the planned 3 blocks of TriKEs treatment per protocol with lack of disease progression or evidence of a clinical improvement, re-treatment may be an option after discussion with the institutional PI or designee. The patient must continue to fulfill the relevant eligibility criteria in Section 5 and have had no toxicity equivalent to a DLT with the 1st treatment course. Participants would sign a re-treatment consent and be enrolled onto the retreatment protocol CPRC

#2015LS167R, while continuing to be followed for the main study's endpoints as planned.

Eligible patients will receive TriKE at the same or a lower dose level and on the same schedule as initially treated. Treatment must begin within 2 to 4 weeks after completion of the 1st course. Treatment guidelines will be followed per Section 7. Re-treatment patient events will not apply toward dose limiting toxicities (DLTs) or early stopping rule events. Tests and evaluations (with a limited research related sample collection plan) during and after treatment would follow those in Section 8.1 and Section 8.3. This includes frequent assessments for toxicity and survival follow-up through 6 months from the 1st dose of the re-treatment.

Such situations are considered compassionate and would not be included in the statistical analysis.

7.5 Duration of Study Treatment

Patients will receive one treatment course consisting of three sets (blocks) of four consecutive 24 hour continuous infusions GTB-3550 TriKE unless:

- the patient experiences the equivalent of a dose limiting toxicity (see Section 7.2.1 for definition),
- the patient is unable to start Block #2 or #3 within 1 week of the planned date,
- the patient refuses further treatment,
- **Disease based treatment decisions:** If after completing Block #1 and Block #2, the patient has clear evidence of disease progression they will be discontinued from study treatment and further treatment with study drug is to be discontinued.
- In the opinion of the treating investigator, continuing treatment is not in the best interest of the patient.

For patients discontinuing prior to completing 3 blocks, post-treatment activities at Day 22 and Day 29 are shifted earlier to maintain the timing (i.e. 1 and 2 weeks from the start of the final block).

7.6 Duration of Study Participation

Direct study participation ends with the end of treatment visit at Day +60 (±1 week) or earlier, if a new treatment is started. For patients not receiving all 3 blocks, the end of treatment visit occurs approximately 6 weeks (±1 week) from the start of the last block.

Further treatment, independent of the study, will be at the treating physician's discretion.

Follow-up will continue for overall survival continues on all evaluable patients through 6 months from the 1st treatment by record review or other means.

8 Schedule of Patient Activities

Scheduled evaluations after screening may be performed ±1 day from the targeted date through Day 29; unless otherwise noted. A disease reassessment will occur between Days 21 and 42. A ±7 day window is permitted for the end of treatment (EOT) visit. If a patient discontinues treatment before receiving all 3 blocks, subsequent time points are adjusted to maintain timing (i.e. Day 22 is moved to 1 week after the start of the last block).

In addition, targeted days may be altered as clinically appropriate. Follow-up visits are per standard of care with disease status and survival status abstracted from the medical record.

8.1 Required Standard of Care

Standard of care procedures should be followed for all enrolled patients, including those who are enrolled for retreatment.

Activity	Screening within 30 days of enrollment (within 14 days if for eligibility)	Day 1, Day 8, and Day 15 (start of treatment block)	Daily during infusions (i.e. Day 2-5, 9 12, 16-19)	Day 22	Day 29	Anytime between Day 21 through Day 42	End of Treatment Visit Day 60 (±7 days)	FU for overall survival (through Month 6)
consent	X							
baseline assessment	X							
medical history	X	X		X	X		X	
concomitant meds[7]	X	X	X	X	X		X	
physical exam	X	X		X	X		X	
vital signs including pulse oximetry	X	X	per Section 7.1.1	X	X		X	
neurologic assessment		X[2]	X					
provider assessment			X					
survival status							X[5]	X
assessment of toxicity		X	X	X	X		X	
Karnofsky PS	X				X		X	
height	X							
weight		X (- 5 days)						
CBC/diff/plt	X	X	X	X	X		X	
basic metabolic panel			X					
comprehensive metabolic panel[3], magnesium and phosphorus	X	X		X	X		X	
ALT, AST, total bili, albumin[4]			2 times					
hepatitis B and C screening	X							
INR[8]	X							
eGFR	X							
Serum pregnancy test for FOCBP within 7 days of treatment start	X							
Disease assessment	X					X		
BM biopsy[1]	X					X		
Electrocardiogram	X							
Echocardiogram, cardiac MRI or MUGA	X							
Chest/abdomen CT	X							
assessment of response						X		X[6]

1 - sample to TTL per Section 8.2 at time of each SOC bone marrow biopsy

2 - Neurological assessment daily including basic motor (gait), coordination (steadiness) and cognitive function (alert and oriented) - any abnormalities should be followed up with a detailed neurologic exam.

3 - Albumin, alkaline phosphatase, ALT, AST, bilirubin (total), calcium, chloride, CO2, creatinine, glucose, potassium, protein (total), sodium, urea nitrogen

4 - perform LFTs and albumin twice more during infusion week (in addition to Day of infusion start CMP) = three times during infusion week

5 - survival status at Day 60 for early study stopping rule for expansion component only
6 - until relapse/progression or start of a new therapy, then survival only
7 - document all concomitant medications, including start and stop dates, relative to administration of GTB-3550 TriKE
8- Measure and report prior to commencement of GTB-3550 therapy for information only and not as criteria for inclusion.

8.2 Research Related Testing, Assessments, and Sample Collections

Sample collections and other procedures after the end of the infusions will coincide with outpatient clinic visits which may not occur on the targeted day.

	Screen/ Baseline	Pre Dose 1 each Block (Day 1, 8, 15)	Daily during infusions (i.e. Day 2-5, 9-12, 16-19)	PK/PD sampling at end of each infusion block	Day 22	Day 29	Day of SOC Disease Reassessment (Day 21 – Day 42)
Toxicity Assessment		Refer to Section 10.2 for details					
Assessment for dose limiting toxicity		By Day 29 – report as DLT for Phase I only; however any patient experiencing a DLT is not eligible to continue treatment per Section 7.5					
Assessment for stopping rules		Expansion component only through Day 42 for non-hematologic, non-relapse, non-infectious toxicity (except fever), Day 60 for TRM,					
Monitoring for signs of immune activation		Pre and during TriKE infusions – all patients					
CRP, ferritin[4]	X	X	X (Day 5 only)				
Pulmonary Function Testing	X						
EKG		X (At 4 hours (±15 min) into the infusion)	X (at 4 hours (±15 min) into each daily infusion and at 4 hours (±15 min) after disconnect at block end)				
T Cell Subset Extended Profile[4]	X						
5 - 10 ml green top tubes and 1- 10 ml red top tube	X	X	X (Day 3, 10, and 17, only)[5]		X	X	X[3]
antibody testing (sample obtained from the 10 ml red top collected in previous row)	X[2]	X (Day 15 only)			X	X	X[3]
5 ml red top for each PK/PD time point		X	X	X[1]			
30 ml or as much as able to obtain of heparinized bone marrow aspirate at time of SOC bm bx	X[3]						X[6]
Pre- and Post-TriKE drug product concentrations levels samples – each drug bag during Week 1 only							
TriKE pre-infusion sample - 2 ml of drug split between two pre-labeled 1.8 ml cryo-vials		Each drug bag during Week 1 only per Section 9.6 – collected after drug preparation is complete and before bag sent to floor, – keep refrigerated until pick-up					
TriKE post-infusion sample collection ~2 ml of drug split between two pre-labeled 1.8 ml cryo-vials		Each drug bag during Week 1 only – per Section 7.1 after infusion end and prior to discarding bag and tubing - keep refrigerated until samples are collected					

1. PK/PD time points in association with the end of each infusion block (i.e. Day 5, 12, and 19 or at the discontinuation of the block's infusions, if prior to 96 hours) - 1 hour post (±5 min), 2 hours post (±10 min), 3 hours post (±10 min), 4 hours post (±10 min) and optional 10 hours (±30 min)
2. Antibody testing will not be performed in real time nor affect a patient's initial eligibility or ongoing treatment
3. Baseline sample if feasible (repeat marrow is not required solely for research sample)

4. To Institution's clinical lab, charge to research
5. A +2 day window is permitted for this time point (Day 3 (window of days 3- 5), Day 10 (window of days 10-12) and Day 17 (window of days 17-19)
6. At time of post-treatment bone marrow biopsy or at Day 60 (End of Treatment visit)

For UMN patients: All samples unless otherwise noted go to Masonic Cancer Center Translational Therapy Laboratory (TTL) - Call [redacted] for sample pick-up.

For non-University of Minnesota sites:

- The 5 green top and 1 red top samples are shipped the day of collection (Monday-Thursday) for next day delivery to the Masonic Cancer Center's Translational Therapy Lab (MCC TTL).
- PK/PD samples are stored frozen and batched shipped to MCC TTL at the end of the patient's treatment.
- TriKE pre and post infusion samples (Week 1 only) are stored frozen and batch shipped to MCC TTL during Week 2.
- Bone marrow aspirate is collected at the time of standard of care bone marrow prior to treatment start and at the time of the post-treatment bone marrow biopsy. Ship day of collection to MCC TTL.

Refer to the Laboratory Manual for additional details.

It is recognized that with novel therapies as used in this study, the timing of protocol directed research samples may miss important patient specific events. For this reason, additional sets of research samples may be drawn at up to 3 time points that are not specified above.

Note: if a patient is not abiding by the standard of care study calendar (Section 8.1), collection of the research related samples (and targeted toxicities) may be altered or discontinued on an individual patient basis, as appropriate.

8.3 Re-Treatment Research Related Testing, Assessments, and Sample Collections

All standard of care procedures described in Section 8.1 are also required for retreatment. Sample collections and other procedures after the end of the infusions will coincide with outpatient clinic visits (and may not occur on the targeted day).

	Screen/ Baseline	Block 1 only		Pre and during TriKE infusions	Day 22 or 1 week after the start of the last block	Day of SOC Disease Reassessment (Day 21 – Day 42)
		Pre Dose 1	Day 5			
Toxicity Assessment				Refer to Section 10.2 for details		
Monitoring for signs of immune activation				Pre and during TriKE infusions – all patients		
CRP, ferritin[1]	X	X	X			
Pulmonary Function Testing	X					
T Cell Subset Extended Profile[1]	X					
5 - 10 ml green top tubes and 1- 10 ml red top tube		X			X	
antibody testing 5 ml red top tube (sample obtained from the 10 ml red top collected in previous row)	X[2]				X	
30 ml or as much as able to obtain of heparinized bone marrow aspirate at time of SOC bm bx	X[3]					X

1- To Institutional Lab, but charge to research
2- Antibody testing will not be performed in real time nor affect a patient's initial eligibility or ongoing treatment
3- May be same sample as reassessment from 1st treatment course

For UMN patients, all samples unless otherwise noted go to Masonic Cancer Center Translational Therapy Laboratory (TTL) - Call [redacted] for sample pick-up.

For non-University of Minnesota sites, refer to Section 8.2 for shipping information.

All "rules" of sample collection found in Section 8.2 also apply to the re-treatment research samples (i.e., windows, missed samples, extra samples).

8.4 Overview of Planned Correlative Studies

A number of correlative studies are performed to understand the safety and ability of the GTB-3550 TriKE to activate the immune response. Immune monitoring is a critical component of the GTB-3550 TriKE clinical trial to understand the drug pharmacokinetic/pharmacodynamic (PK/PD), its in vivo functional activity and clinical tolerance.

1. PK sampling to determine TriKE levels and secondary cytokines. In association with each TriKE treatment block, TriKE concentrations will be determined at multiple time points by standard IL-15 ELISA to detect the IL-15 linker in the TriKE as we have already validated. Samples will also be contract tested for IFNα, IL-6, IL-10 and TNF (and other inflammatory cytokines determined informative). This will allow us to determine drug PK/PD and immediate secondary cytokine responses in vivo.
2. Determine the absolute number and proportion of NK cells, T cells and their subsets. We have designed multi-color flow cytometry panels to look at basic lymphocytes in whole blood as well as in more detail on ficolled mononuclear cells to determine lymphocyte (and subset) proliferation as measured by Ki-67, inhibitory cells [Treg and CD33+ myeloid-derived suppressor cells] and a number of established NK cell subsets defining adaptive or conventional NK cells.
3. NK cell function induced by GTB-3550 TriKE. CD107A degranulation and cytokine production against K562 (to measure natural cytotoxicity) and CD33+ HL60 targets (± exogenous TriKE) will be performed.
4. [redacted]
5. Pre- and Post- TriKE drug product concentrations levels samples will be stored in TTL frozen at < -70ºC for future batch testing.

The marrow will be used in the research lab to study CD33 expression and targeting by allogeneic and autologous lymphocytes.

9 GTB-3550 TriKE Description, Supply, Preparation, and Potential Toxicities

9.1 Product Description

[redacted]

9.2 Product Manufacturing

[redacted]

9.3 Product Formulation

[redacted]

9.4 How Supplied

[redacted]

9.5 Study Site Storage and Product Stability

[redacted]

9.6 Preparation and Administration

[redacted]

- [redacted]

[redacted]

9.7 Potential Toxicities

Although blinatumomab, a bi-specific T cell engager (BiTE), is conceptually similar to our NK cell GTB-3550 TriKE, there are important differences. Blinatumomab's toxicity is presumed related to the anti-CD3 moiety that acts as a potent stimulus for CD3+ T cells. The TriKE is different since the anti-CD16 moiety does not deliver a proliferative stimulus and in fact, we do not expect that promotion of an immune synapse alone will lead to toxicity much like natural engagement of CD16 by FDA-approved monoclonal antibodies such as trastuzumab or rituximab. Instead, we expect the toxicities of GTB-3550 TriKE may be similar to those seen with blinatumomab and/or IL-15. Other than the intramural center at the NCI in Washington DC, we probably have the most experience administering IL-15 to patients as a single agent and in combination with chemotherapy and NK cells.

[redacted] Most of the side effects of IL-15 are related to immune activation including fevers, chills and some degree of immune activation. We have a prospective plan to monitor patients for these immune side effects to characterize the safety profile of the TriKE. In addition, we will use fever and tachycardia as validated clinical markers to measure early signs of immune activation to modify our dose escalation plan if needed.

10 Event Monitoring, Documentation and Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events version 5 (CTCAE v5). A copy of the CTCAE can be downloaded from the CTEP home page at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

An exception to the use of CTCAE will be for the assessment of cytokine release syndrome (CRS). Individual adverse events which are associated with CRS will be graded per CTCAE; however the ultimate assessment will be made using a revised grading system for CRS as presented by Lee et al[43].

CRS Revised Grading System (replaces CTCAE v4 CRS grading)	
Grade	**Toxicity Description**
Grade 1	Symptoms are not life threatening and require symptomatic treatment only, e.g., fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Symptoms require and respond to moderate intervention - Oxygen requirement < 40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
Grade 3	Grade 3 Symptoms require and respond to aggressive intervention - Oxygen requirement ≥40% or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening symptoms - Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

Grades 2-4 refer to CTCAE v4.0 grading.

10.1 Definitions

The following definitions are based on the Code of Federal Regulations Title 21 Part 312.32 (21CFR312.32(a)).

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Life-Threatening Adverse Event Or Life-Threatening Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an

adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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

- Death
- A life-threatening adverse event
- 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
- An important medical event

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious 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

If either the IND sponsor or the investigator believes the event is life-threatening or serious, the event must be evaluated by the sponsor for expedited reporting (21CRF 312.32(a)).

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Expedited (Rapid) Reporting: Certain events may require rapid notification to entities providing patient safety oversight (e.g. IRB) as detailed in Section 10.5.

The categories for AE attribution to study treatment are as follows:

- Definite – clearly related
- Probable – likely related
- Possible – may be related
- Unlikely – doubtfully related
- Unrelated – clearly not related

The following definitions are from the Masonic Cancer Center's Standard Operating Procedure (SOP) Deviation Reporting:

Major Deviation: A deviation or violation that impacts the risks and benefits of the research; may impact subject safety, affect the integrity of research data and/or affect a subject's willingness to participate in the research. Deviations that place a subject at risk, but do not result in harm are considered to be major deviations.

Minor Deviation: A deviation or violation that does not impact subject safety, compromise the integrity of research data and/or affect a subject's willingness to participate in the research.

10.2 Event Documentation

Event monitoring and documentation begins with the 1st dose of TriKEs.

For the purposes of this study, selected expected adverse events will be assessed using the Targeted Toxicity Worksheet (Appendix VI) and any unexpected events will be collected at the following time points in relation to the GTB-3550 TriKE infusions through Day 29:

- Prior to the infusion start of each 24 hour infusion (i.e. Day 1, 2, 3, 4, and Day 8, 9, 10, 11, and Day 15, 16, 17, 18)
- At the end of the final infusion of each block (i.e. Day 5, Day 12, Day 19)
- Day 22
- Day 29

At each time point, the worst grade of the targeted toxicity since the last assessment or the previous 24 hours (whichever is shorter) will be recorded in addition to any unexpected toxicities felt at least possibly related the study treatment.

If a patient discontinues study therapy early or otherwise does not receive treatment as planned, the targeted toxicity assessment time points may be adjusted or eliminated; however, patients must be assessed for a minimum of 28 days from the 1st dose of study drug.

If a patient is not abiding by the standard of care study calendar (Section 8.1), collection of the corresponding targeted events (and research related samples) also may be altered or discontinued on an individual patient basis, as appropriate.

Monitoring for adverse events will end after the last targeted assessment; however, the investigator is obligated, upon knowledge of, to report any event meeting the criteria in Section 10.5.

10.3 Dose Limiting Toxicity Documentation and Reporting (Phase I Dose Finding)

The following events count toward dose limiting toxicity (DLT) during the Phase I dose finding component and must be reported the UMN Multisite Program Manager per Section 10.6.

Note: DLT events are only reported for patients enrolled in the Phase I portion of the trial; however, any patient experiencing a DLT is not eligible to continue treatment per Section 7.5.

A DLT is defined as a related treatment emergent toxicity that occurs within 28 days after the 1st TriKE dose with the exception of those that are clearly and incontrovertibly due to extraneous causes:

- Any Grade 4 or 5 non-hematologic events
- Grade 3 non-hematologic adverse events lasting more than 72 hours, **except** the following:
  - Non-sustained (< 7 days) Grade 3 liver function tests (ALT/AST, alkaline phosphatase, total or direct bilirubin) abnormalities in the absence of clinical signs of hepatic dysfunction (lethargy, confusion, anorexia, pruritus or tremors).
  - Non-sustained Grade 3 QTc prolongation (< 72 hours) in the absence of cardiac arrhythmia
  - Grade 3 electrolyte disturbances that resolve, with or without intervention, to < Grade 2 levels within 72 hours
  - Grade 3 fatigue
  - Grade 3 anorexia
  - Grade 3 fever
  - Grade 3 infection
- Hematologic Toxicity - Given that AML and MDS inherently leads to low neutrophils and platelets, standard grading cannot be used as many of these patients technically meet criteria for “grade 4” neutropenia or thrombocytopenia at baseline. Thus, the hematologic DLTs are listed below:
  - AML
    - Grade 4 neutrophil count (< 500/μL) lasting ≥ 29 days from start of cycle in absence of evidence of active leukemia

- Grade 4 platelet count (< 25,000/μL) lasting ≥ 29 days from start of cycle in absence of evidence of active leukemia
- Any clinically significant bleeding that is not controllable with transfusion support

- MDS/mast cell diseases:
  - Grade 4 neutrophil count (<500/μL) lasting ≥ 29 days from start of cycle in absence of evidence of active MDS/mast cell disease
  - Grade 4 platelet count (<25,000/μL) lasting ≥ 29 days from start of cycle in the absence of active MDS/Mast cell disease
  - Any clinically significant bleeding that is not controllable with transfusion support
  - Grade 4 anemia, unexplained by the underlying disease

- Grade 3 infusion related, treatment related reaction including cytokine release syndrome which does not resolve within 72 hours despite best medical management (refer to Section 10 for modified CRS grading)
- Grade 3 or 4 Tumor Lysis Syndrome that does not resolve within 7 days with or without intervention
- Inability to complete at least one block of three 24 hour infusions due to any treatment emergent, treatment related toxicity.

10.4 Early Study Stopping Rules - Event Documentation and Reporting (Phase II Dose Expansion)

Early study stopping rules for the Phase II dose expansion component patients are:

- Grade 4-5 non-hematologic, non-relapse, non-infectious toxicity (except fever) by 42 days after the start of the first GTB-3550 TriKE treatment block
- Non-relapse, non-infectious treatment related mortality (TRM) within 60 days of starting GTB-3550 TriKE treatment

Meeting either stopping rule criterion temporarily will halt study enrollment until the event is fully evaluated and the Principal Investigator and GT Biopharma make a decision regarding the continuation of the trial. Any patients currently receiving treatment may continue after discussion with the study PI and GT Biopharma.

Events that count toward dose limiting toxicity and early stopping rules do not necessarily constitute a serious adverse event requiring expedited reporting and should be reported as such only if they meet the criteria for expedited reporting as defined in Section 10.6.

10.5 Documentation of Death and Reporting Requirements

Deaths during treatment and the follow-up period, including death due to disease, will be recorded as an SAE and reported per Section 10.6. Deaths due to disease should be recorded as a Grade 5 Neoplasm.

In addition, even after the follow-up period ends, the death date must be documented in the patient follow-up tab in [redacted] upon knowledge using the comment field in survival status section to record the cause.

10.6 Participating Sites Event Reporting Table

Event Type	Reporting Timeframe	Form to Use	Email to
Any event meeting the definition of serious	Within 24 hours of knowledge	Paper SAE Report Form	Masonic Cancer Center (MCC) Multisite Program Manager [redacted]
Dose Limiting Toxicity Event	Within 24 hours of knowledge	DLT Event Form	
Stopping Rule Event	Within 24 hours of knowledge	Stopping Rule Event Form	
Major Deviations, as defined in Section 10.1.	Within 5 working days of knowledge	Record in Deviations Tab, generate report and have PI sign	
Minor Deviations, as defined in Section 10.1.	Reporting not applicable	Record in Deviations Tab – signed report not required	Not applicable

Participating Sites are responsible for reporting to Local institutional IRB or other entities per institutional policies and guidelines.

The Multisite Program Manager will forward all reports to GT Biopharma and [redacted] within 3 business hours.

GT Biopharma/[redacted] is responsible for submission of IND safety reports to the FDA per federal regulations.

10.7 UMN Required Reporting: UMN IRB, GT Biopharma, [redacted], and Masonic Cancer Center's SAE Coordinator

Entity Reported To:	Criteria for reporting	Timeframe	Form to Use	Report to
U OF MN IRB	Information that indicates a new or increased risk, or safety issue. Unexpected Death per UMN requirements.	5 business days	Ethos Reportable New Information (RNI)	Via [redacted] with copy GT Biopharma*
	Clinical deviations per current IRB reporting requirements (UMN patients only)		[redacted] Deviation Report and [redacted]	
GT Biopharma and [redacted]*	Any event meeting the definition of serious regardless of attribution	Within 24 hours of knowledge	CTO SAE Report Form	GT Biopharma and [redacted]
	Events that count toward dose limiting toxicity during the dose finding component or an early study stopping rule during the expanded component	At time of reporting	Appropriate form	

*GT Biopharma/[redacted] is responsible for submission of IND safety reports to the FDA per federal regulations.

11 Study Data Collection and Monitoring

11.1 Data Management

This study will collect regulatory and clinical data using [redacted]

The [redacted] database resides on dedicated secure and PHI compliant hardware consisting of 3 physical servers: dev, DR, and production. All the data servers are managed by the [redacted] All relevant [redacted] procedures related for PHI compliant servers (as required by the Center of Excellence for HIPAA Data) apply to [redacted] databases.

The integrated data will be stored in PHI compliant servers managed by [redacted] with access given to those authorized users in the Clinical and Translation Science Institute Informatics team (CTSI BPIC and MCC CISS).

[redacted]

Key study personnel are trained on the use of [redacted] and will comply with protocol specific instructions embedded within the [redacted].

11.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRF) developed [redacted] based on its library of standardized forms. The e-CRFs will be approved by the lead center PI and the UMN biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into [redacted] at time of study entry, completing e-CRF based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

11.3 Data and Safety Monitoring

The study will be in compliance with the [redacted]

The site PI will comply with at least twice yearly monitoring of the project by their site's internal monitoring staff. Monitoring reports are forwarded to the U of MN Multisite Program Manager who will forward to the reports to GT Biopharma [redacted] Refer to the Procedures Manual for Participating Sites for additional information.

All sites must permit study-related monitoring, audits, and inspections by the IND Sponsor (GT Biopharma and/or their designee), IRB, government regulatory bodies, and compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

11.4 UMN Led Teleconferences – Participating Sites, GT Biopharma [redacted]

Regular teleconferences will be held to facilitate communication between the participating sites and IND sponsor/representative regarding the study's progress, including patient updates, a summary of safety reports, dose level/patient slot availability, case report form completion, and other issues for discussion. The Masonic Cancer Center Multisite Program Manager is responsible for arranging these teleconferences and preparing the agenda. Meetings occur every 2 weeks; however, they may be scheduled more or less frequently at the discretion of the lead institution. Participation of a minimum of one representative from each participating clinical site is expected. Attendance by [redacted] GT Biopharma is agenda driven.

These teleconferences are in addition to other previously described site interactions including centralized patient registration, institutional and MCC required reporting of safety related issues, and case report form completion in the study's central database [redacted]

11.5 Record Retention

The investigator will retain essential documents (e.g. study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence) 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 have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period

however if required by the applicable regulatory requirements or by an agreement with the sponsor.

It is the responsibility of the sponsor (GT Biopharma) to inform the investigator/institution as to when these documents no longer need to be retained.

12 Statistical Considerations

12.1 Study Design and Endpoints

This is a multisite Phase I/II study of GTB-3550 trispecific killer cell engager (TriKE) for the treatment of high risk MDS and relapsed AML. Once the MTD is identified, the objective will be to confirm safety and obtain preliminary estimates of efficacy as measured by the objective response, the **primary trial endpoint** as assessed between Day 21 and Day 42. For AML clinical response includes complete remission with or without hematologic or platelet recovery (CR, CRi or CRp) or partial response. For MDS clinical response includes complete remission, marrow CR (with incomplete peripheral blood count normalization), partial response or hematologic improvement (HI). For advanced systemic mastocytosis response is considered a decrease in mast cell burden in bone marrow or serum tryptase level by at least 30%.

All patients completing Block #1 will be evaluable for DLTs and toxicities. Patients who discontinue therapy prior to completion of both Block #1 and Block #2 will be replaced. Patients completing Block #1 and Block #2, but come off treatment for disease progression, will still be evaluable for efficacy and will not be replaced. If needed a subgroup of patients receiving all 3 blocks will also be evaluated for response as a secondary population. We expect that the number of patients coming off therapy after only completing block #1 will be minimal.

Secondary trial endpoints will include toxicity through Day 29 and overall survival (OS) at 6 months from 1st dose of study drug.

Phase I component: Estimating the MTD of GTB-3550 TriKE:
The first phase is a dose finding study with the aim of establishing the MTD of GTB-3550 TriKE when given as a block of four 24 hour infusions with a 72 hour break for 3 consecutive weekly courses in patients with CD33-expressing high risk myelodysplastic syndromes, refractory/relapsed acute myeloid leukemia or advanced systemic mastocytosis. The MTD will be identified using the continual reassessment method (CRM)[44].

The MTD will be defined as the dose that most closely corresponds to a dose limiting toxicity (DLT) rate of 20%. Dose limiting toxicity (DLT) is defined Section 7.2.1. Determination of the target rate of 20% was based on clinical input and acceptability.

Seven dose levels of GTB-3550 TriKE will be tested (5.0 µg/kg, 10.0 µg/kg, 25.0 µg/kg; 50.0 µg/kg, 100.0 µg/kg, 150 µg/kg, and 200 µg/kg daily dose). The CRM uses a Bayesian framework that combines experience from patients in the earlier part of the trial with clinicians' initial best probability estimates of DLT at each dose. We are using a one parameter power model for the probability of DLT, where the probability at each dose *i*, is modeled as $F(d, \alpha)=d_i^{exp(\alpha)}$ where α is distributed a priori as a normal random variable with mean 0 and variance 0.5. The variance of the prior distribution, 0.5, was determined through simulations to balance accuracy and patient safety.

Revision 5/5/2021: Seven dose levels of GTB-3550 TriKE are now being tested per 7.2.1 (5.0 µg/kg, 10.0 µg/kg, 25.0 µg/kg, 50.0 µg/kg, 100.0 µg/kg, 150.0 µg/kg and 200 µg/kg daily dose) using an expected "true" probability of 17% for DLTs at 150.0 µg/kg (median probability between 100 and 200 µg/kg daily dose) and the same target DLT rate of 20%.

The prior mean for the probability of DLT for the six doses (i.e. the power model skeleton) are 3%, 5%, 7%, 10%, 14% and 20%, respectively. As the study progresses, updated probabilities of DLT are computed before each new cohort of patients is enrolled and both patients of each cohort have reached Day 28 (end of the DLT assessment period) prior to enrollment of a subsequent cohort. Each subsequent cohort will be assigned to the most appropriate dose based on these updated probabilities. Eventually the final dose (within our proposed sample of 30 patients) will be identified as the dose most closely associated with a DLT rate of 20%. To promote patient safety: 1) we will enroll cohorts of 2 patients starting at the 1st dose; and 2) dose levels will not be skipped when escalating.

[redacted]

Phase II Extension: Studying the efficacy of GTB-3550 TriKE for the endpoint of objective response:

After completion of the dose finding trial, the final dose will be carried forward into an uncontrolled two-stage Phase II extension trial to confirm safety and make a preliminary determination of the activity level. For advanced MDS/AML, the lack of

defined effective alternative therapies precludes a control regimen for comparisons at this stage of testing. If the Phase I trial enrolls fewer than 14 patients at the MTD, we will employ a Simon's Minimax two-stage design[45] with the possibility to discontinue after the 1st stage if the response rate is low.

- Stage 1: Enroll a total of 13 patients (including all treated at the MTD in Phase I). If 3 or more of these respond, the trial will continue to stage 2.
- Stage 2: Enroll an additional 17 patients. If 10 of 30 patients respond, GTB-3550 TriKE will be considered promising for further investigation.

If the Phase I trial enrolls more than 13 patients at the MTD, we will adjust the futility rule above for the two-stage design with the given number of patients enrolled at the MTD.

12.2 Statistical Analysis

Response will be estimated with simple proportions and descriptive plots. The secondary endpoint of OS will be estimated with Kaplan-Meier curves. Safety measures will be described with frequencies and proportions.

The change in number, phenotype and function of NK cells from baseline to the end of treatment will be correlated with clinical response using appropriate regression analyses such as Cox or Logistic regression. Assessment of serum TriKE levels will be determined using descriptive statistics.

12.3 Sample Size Justification

Trial Size Determination: [redacted]. Assuming a target DLT probability of 20%, an effect size or odds ratio of 1.7 and a commonly used accuracy index of 0.5, the initial sample size is 27. We conservatively rounded to 30 patients. [redacted] Operating characteristics for various 'true' probabilities are listed in Table 1.

Table 1. [redacted]

If fewer than 14 patients are enrolled at the MTD, the Phase II extension trial using the Simon's two-stage design will require 30 patients to test the null hypothesis that the response rate is <20% versus the alternative that the response rate is ≥40% after assuming 80% power and a significance level of 0.05.

If the Phase I trial enrolls more than 13 patients at the MTD, we will adjust the futility rule of the two-stage design while maintaining the constraints of 80% power, a significance level of 0.05 and using a maximum of 30 patients. We will choose the rule that minimizes the expected sample size given a true response rate equivalent to the null hypothesis. We expect that approximately 44 patients will be required due to use of patients from the Phase I trial in the Phase II extension but the sample size may be as high as 57. Enrollment is expected to be 1-2 patients per month.

12.4 Monitoring Guidelines (Study Stopping Rule Events)

During the CRM, the trial will stop if the posterior probability that the lowest dose is more toxic than the target is greater than 90%.

After the MTD has been established stopping rules will also be employed to monitor excess toxicity outside of the Phase I trial[47].

Meeting either stopping rule criteria temporarily will halt enrollment per Section 10.4.

(1) **Grade 4-5 non-hematologic, non-relapse, non-infectious toxicity (except fever) by 42 days after the start of the first GTB-3550 TriKE treatment block:** We will construct a boundary such that the probability of early stopping is at most 10% if the toxicity rate is equal to 10%. Assuming 27 additional patients are enrolled after phase I, the upper stopping boundary for toxicity would be 2/3, 3/8, 4/13, 5/20, 6/26 or 7 events.
(2) **Non-relapse, non-infectious treatment related mortality** within 60 days of starting GTB-3550 TriKE treatment: Assuming the same parameters as in (1), the upper stopping boundary for TRM will be 2/3, 3/8, 4/13, 5/20, 6/26 or 7 events. If the true rates of both toxicity and TRM are 30%, the probability of early stopping will be 88% for each guideline.

13 Conduct of the Study

13.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

13.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

13.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

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Appendix I - Karnofsky Performance Status

Karnofsky Performance Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

Appendix II - Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndromes and Risk Assessment Calculator Link

Developed by the International Working Group for the Prognosis of MDS (IWG-PM) under the aegis of the MDS Foundation, Inc.
https://www.mds-foundation.org/ipss-r-calculator/

IPSS-R Cytogenetic Risk Groups*,**

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

IPSS-R Prognostic Score Values*

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	≤2		>2-<5%		5-10%	>10%	
Hemoglobin	≥10		8-<10	<8			
Platelets	≥100	50-<100	<50				
ANC	≥0.8	<0.8					

IPSS-R Prognostic Risk Categories/Scores*

RISK CATEGORY	RISK SCORE
Very Low	≤1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

*Greenberg, Tuechler, Schanz et al, Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndrome, Blood 120: 2454, 2012

**Schanz J et al, J Clin Oncology 2012; 30:820.

Appendix III - Response Criteria

Acute Leukemias:

- **Morphologic complete remission (CR)**: ANC ≥ 1,000/mcl, platelet count ≥ 100,000/mcl, < 5% bone marrow blasts, no Auer rods, no evidence of extramedullary disease. (No requirements for marrow cellularity, hemoglobin concentration).
- **Morphologic complete remission with incomplete platelet recovery (CRp):** Same as CR platelet count < 100,000/mcl.
- **Morphologic complete remission with incomplete blood count recovery (CRi)**: Same as CR but ANC may be < 1,000/mcl and/or platelet count < 100,000/mcl.
- **Partial remission (PR):** ANC ≥ 1,000/mcl, platelet count > 100,000/mcl, and at least a 50% decrease in the percentage of marrow aspirate blasts to 5-25%, or marrow blasts < 5% with persistent Auer rods.

Myelodysplastic Syndromes (MDS):

Category	Response criteria (responses must last at least 4 wk)
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 x 10^9/L • Neutrophils ≥ 1.0 x 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 weeks
Cytogenetic response	Complete • Disappearance of the chromosomal abnormality without appearance of new ones Partial • At least 50% reduction of the chromosomal abnormality
Hematologic Improvement	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. Platelet response (pretreatment,< 100 X 109/L): Absolute increase of < 30 X 109/L for patients starting with 20 X 109/L platelets Increase from less than 20 X 109/L to greater than 20 X 109/L and by at least 100% Neutrophil response (pretreatment,< 1.0 X 109/L) At least 100% increase and an absolute increase0.5109/L

MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.
*Dysplastic changes should consider the normal range of dysplastic changes (modification).
†Modification to IWG response criteria.
‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Ref: Cheson BD, Greenberg DL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006 108: 419-425.

Appendix IV - P450 Drug Interactions

Flockhart Table ™

For complete table: http://medicine.iupui.edu/clinpharm/ddis/clinical-table
accessed July 25, 2018
P450 Drug Interactions select substrates

Abbreviated "Clinically Relevant" Table

SUBSTRATES	
2D6	3A4,5,7

Beta Blockers:
carvedilol
S-metoprolol
propafenone
timolol

Antidepressants:
amitriptyline
clomipramine
desipramine
duloxetine
fluoxetine
imipramine
paroxetine

Antipsychotics:
haloperidol
risperidone
thioridazine

Others:
aripiprazole
atomoxetine
codeine
dextromethorphan
doxepine
flecainide
mexiletine
ondansetron
oxycodone
risperidone
tamoxifen
TAMOXIFEN GUIDE
tramadol
venlafaxine

Macrolide antibiotics:
clarithromycin
erythromycin (not 3A5)
NOT azithromycin
telithromycin

Anti-arrhythmics:
quinidine→3-OH(not 3A5)

Benzodiazepines:
alprazolam
diazepam→3OH
midazolam
triazolam

Immune Modulators:
cyclosporine
tacrolimus (FK506)
sirolimus

HIV Antivirals:
indinavir
ritonavir
saquinavir
nevirapine

Prokinetics:
cisapride

Antihistamines:
astemizole
chlorpheniramine

Calcium Channel Blockers:
amlodipine
diltiazem
felodipine

SUBSTRATES	
2D6	3A4,5,7

nifedipine
nisoldipine
nitrendipine
verapamil

HMG CoA Reductase Inhibitors:
atorvastatin
lovastatin
NOT pravastatin
NOT rosuvastatin
simvastatin

PDE-5 Inhibitors:
sildenafil
tadalafil
vardenafil

Others:
alfentanyl
aripiprazole
boceprevir
buspirone
carbamazepine
gleevec
haloperidol
pimozide
quinine
tamoxifen
telaprevir
trazodone
vincristine

INHIBITORS

■ A Strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
■ A Moderate inhibitor is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
■ A Weak inhibitor is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

2D6	3A4,5,7
■ bupropion	**HIV Antivirals:**
■ fluoxetine	■ indinavir
■ paroxetine	■ nelfinavir
■ quinidine,	■ ritonavir
	■ clarithromycin
	■ itraconazole
■ duloxetine	■ ketoconazole
	■ nefazodone
■ amiodarone	
■ cimetidine	■ erythromycin
	■ grapefruit juice
aripiprazole	■ verapamil$_2$
diphenhydramine	
chlorpheniramine	■ suboxone
clomipramine	■ diltiazem
doxepin	
haloperidol	■ cimetidine
methadone	
ritonavir	amiodarone
terbinafine	NOT azithromycin
	fluvoxamine
	troleandomycin
	voriconazole

INHIBITORS

■ A Strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
■ A Moderate inhibitor is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
■ A Weak inhibitor is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

2D6	3A4,5,7
■ bupropion ■ fluoxetine ■ paroxetine ■ quinidine[1]	**HIV Antivirals:** ■ indinavir ■ nelfinavir ■ ritonavir
■ duloxetine	■ clarithromycin ■ itraconazole ■ ketoconazole ■ nefazodone
■ amiodarone ■ cimetidine	■ erythromycin ■ grapefruit juice ■ verapamil[2]
aripiprazole diphenhydramine chlorpheniramine clomipramine doxepin haloperidol methadone ritonavir terbinafine	■ suboxone ■ diltiazem ■ cimetidine amiodarone NOT azithromycin fluvoxamine troleandomycin voriconazole

INDUCERS	
2D6	3A4,5,7
	carbamazepine efavirenz nevirapine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's Wort troglitazone

Metabolizer Phenotypes:
PM = Poor
IM = Intermediate
EM = Extensive
UM = Ultrarapid

Appendix V - Combined List of Drugs That Prolong QT/QTc

CredibleMeds Filtered QTDrug List

The last revision date: May 20, 2018

See Note below for safe use of this Table

Highlighted Drugs are those frequently used in cancer patient care.

The drug list below contains drugs from the categories: Known Risk of TdP And Avoid in congenital long QT

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Aclarubicin (Only on Non US Market)	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Anti-cancer	Cancer	Risk of TdP And Avoid in congenital long QT	injection
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic	Arrhythmia	Risk of TdP And Avoid in congenital long QT	oral, injection
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor	Thrombocythemia	Risk of TdP And Avoid in congenital long QT	oral
Arsenic trioxide	Trisenox	Anti-cancer	Cancer (leukemia)	Risk of TdP And Avoid in congenital long QT	injection
Astemizole (Removed from Market)	Hismanal	Antihistamine	Allergic rhinitis	Risk of TdP And Avoid in congenital long QT	oral
Azithromycin	Zithromax, Zmax	Antibiotic	Bacterial infection	Risk of TdP And Avoid in congenital long QT	oral, injection
Bepridil (Removed from Market)	Vascor	Antianginal	Angina Pectoris (heart pain)	Risk of TdP And Avoid in congenital long QT	oral
Chloroquine	Aralen	Antimalarial	Malaria	Risk of TdP And Avoid in congenital long QT	oral
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic	Schizophrenia, nausea, many others	Risk of TdP And Avoid in congenital long QT	oral, injection, suppository
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor	Intermittent claudication	Risk of TdP And Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic	Bacterial infection	Risk of TdP And Avoid in congenital long QT	oral, injection
Cisapride (Removed from Market)	Propulsid	GI stimulant	Increase GI motility	Risk of TdP And Avoid in congenital long QT	oral
Citalopram	Celexa, Cipramil	Antidepressant, SSRI	Depression	Risk of TdP And Avoid in congenital long QT	oral
Clarithromycin	Biaxin, Prevpac	Antibiotic	Bacterial infection	Risk of TdP And Avoid in congenital long QT	oral, inhaled
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)	Risk of TdP And Avoid in congenital long QT	oral, nasal
Disopyramide	Norpace	Antiarrhythmic	Arrhythmia	Risk of TdP And Avoid in congenital long QT	oral, injection
Dofetilide	Tikosyn	Antiarrhythmic	Arrhythmia	Risk of TdP And Avoid in congenital long QT	oral
Domperidone (Only on Non US Market)	Motilium, Motillium, Motinorm Costi, Nomit	Antiemetic	Nausea, vomiting	Risk of TdP And Avoid in congenital long QT	oral, injection, suppository
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)	Risk of TdP And Avoid in congenital long QT	oral
Dronedarone	Multaq	Antiarrhythmic	Arrhythmia	Risk of TdP And Avoid in congenital long QT	oral
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic/ Antiemetic	Anesthesia (adjunct), nausea	Risk of TdP And Avoid in congenital long QT	injection
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic	Bacterial infection, increase GI motility	Risk of TdP And Avoid in congenital long QT	oral, injection

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E (India), Exodus (Brazil), Esto (Israel), Seroplex, Elicea, Lexamil, Lexam, Entact (Greece), Losita (Bangladesh), Reposil (Chile), Animaxen (Colombia), Esitalo (Australia), Lexamil (South Africa)	Antidepressant, SSRI	Depression (major), anxiety disorders	Risk of TdP And Avoid in congenital long QT	oral
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic	Arrhythmia	Risk of TdP And Avoid in congenital long QT	oral
Fluconazole	Diflucan, Trican	Antifungal	Fungal infection	Risk of TdP And Avoid in congenital long QT	oral, injection
Gatifloxacin (Removed from Market)	Tequin	Antibiotic	Bacterial infection	Risk of TdP And Avoid in congenital long QT	oral, injection
Grepafloxacin (Removed from Market)	Raxar	Antibiotic	Bacterial infection	Risk of TdP And Avoid in congenital long QT	oral
Halofantrine (Only on Non US Market)	Halfan	Antimalarial	Malaria	Risk of TdP And Avoid in congenital long QT	oral
Haloperidol	Haldol (US & UK), Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol (Germany), Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation	Risk of TdP And Avoid in congenital long QT	oral, injection
Ibogaine (Only on Non US Market)	None	Psychedelic	Narcotic addiction, unproven	Risk of TdP And Avoid in congenital long QT	oral
Ibutilide	Corvert	Antiarrhythmic	Arrhythmia	Risk of TdP And Avoid in congenital long QT	injection
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection	Risk of TdP And Avoid in congenital long QT	oral, injection
Levomepromazine (methotrimeprazine) (Only on Non US Market)	Nosinan, Nozinan, Levoprome	Antipsychotic	Schizophrenia	Risk of TdP And Avoid in congenital long QT	oral, injection

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Levomethadyl acetate (Removed from Market)	Orlaam	Opiate	Narcotic dependence	Risk of TdP And Avoid in congenital long QT	oral
Levosulpiride (Only on Non US Market)	Lesuride, Levazeo, Enliva (with rabeprazole)	Antipsychotic	Schizophrenia	Risk of TdP And Avoid in congenital long QT	oral, injection
Mesoridazine (Removed from Market)	Serentil	Antipsychotic	Schizophrenia	Risk of TdP And Avoid in congenital long QT	oral
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opiate	Narcotic dependence, pain	Risk of TdP And Avoid in congenital long QT	oral, injection
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection	Risk of TdP And Avoid in congenital long QT	oral, injection
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting	Risk of TdP And Avoid in congenital long QT	oral, injection, suppository
Oxaliplatin	Eloxatin	Anti-cancer	Cancer	Risk of TdP And Avoid in congenital long QT	injection
Papaverine HCl (Intra-coronary)	none	Vasodilator, Coronary	Diagnostic adjunct	Risk of TdP And Avoid in congenital long QT	injection
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis pneumonia)	Risk of TdP And Avoid in congenital long QT	injection, inhaled
Pimozide	Orap	Antipsychotic	Tourette's Disorder	Risk of TdP And Avoid in congenital long QT	oral
Probucol (Removed from Market)	Lorelco	Antilipemic	Hypercholesterolemia	Risk of TdP And Avoid in congenital long QT	oral
Procainamide	Pronestyl, Procan	Antiarrhythmic	Arrhythmia	Risk of TdP And Avoid in congenital long QT	injection
Propofol	Diprivan, Propoven	Anesthetic, general	Anesthesia	Risk of TdP And Avoid in congenital long QT	injection
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Arrhythmia	Risk of TdP And Avoid in congenital long QT	oral, injection
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid,	Antibiotic	Bacterial infection	Risk of TdP And Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
	Tirabicin, Coroxin				
Sevoflurane	Ultane, Sojourn	Anesthetic, general	Anesthesia	Risk of TdP And Avoid in congenital long QT	inhaled
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic	Arrhythmia	Risk of TdP And Avoid in congenital long QT	oral
Sparfloxacin (Removed from Market)	Zagam	Antibiotic	Bacterial infection	Risk of TdP And Avoid in congenital long QT	oral
Sulpiride (Only on Non US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical	Schizophrenia	Risk of TdP And Avoid in congenital long QT	oral, inhaled
Sultopride (Only on Non US Market)	Barnetil, Barnotil, Topral	Antipsychotic, atypical	Schizophrenia	Risk of TdP And Avoid in congenital long QT	oral, injection
Terfenadine (Removed from Market)	Seldane	Antihistamine	Allergic rhinitis	Risk of TdP And Avoid in congenital long QT	oral
Terlipressin (Only on Non US Market)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss and others	Vasoconstrictor	Septic shock	Risk of TdP And Avoid in congenital long QT	injection
Terodiline (Only on Non US Market)	Micturin, Mictrol (not bethanechol)	Muscle relaxant	Bladder spasm	Risk of TdP And Avoid in congenital long QT	oral
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia	Risk of TdP And Avoid in congenital long QT	oral
Vandetanib	Caprelsa	Anti-cancer-	Cancer (thyroid)	Risk of TdP And Avoid in congenital long QT	oral

Note: Medicines on this list are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list. The list changes regularly and we recommend checking the website at crediblemeds.org for the most up-to-date information. There may be many additional brand names that are not listed on this form.

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Appendix VI - Targeted Expected Toxicities Worksheet

HM2015-39 CTCAE v5 Refer to Section 10.2 for time points

Patient Initials: _____ **Date of Assessment:** _____ **Assessment Time Point:** _____

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Infusion related reaction	None	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interrup ion indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interrup ion of infusion); recurrence of symptoms following initial improvement; hospitalizatio indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated
Dyspnea	None or no change	Shortness of breath wi h moderate exertion	Shortness of breath wi h minimal exer ion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Hypoxia	None		Decreased O_2 saturation with exercise (e.g., pulse oximeter < 88%) intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter < 88% or PaO_2 ≤ 55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Fever*	None	38.0 - 39.0◦ C (100.4 -102.2◦ F)	> 39.0 - 40 0◦C (102.3 - 104.0◦F)	> 40.0 ◦ C (>104.0◦ F) for ≤ 24 hrs	> 40.0 ◦ C (>104.0◦ F) for > 24 hrs
Tachycardia*	None	Asymptomatic, interven ion not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated
Chills	None	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	
Hypertension	None	Pre-hypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent ≥ 24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated.	Stage 2 hypertension (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated.	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated.
Hypotension	None	Asymptomatic, interven ion not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated
Edema	None	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limi ing instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	
Pneumonitis	None	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g. intuba ion or tracheotomy)
Headache	None	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	
Confusion (Altered Mental Status)	None	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Rash	None	Covering < 10% body surface area (BSA)	Covering 10-30% body surface area (BSA)	>30% body surface area (BSA)	Generalized exfoliative, ulcera ive, or bullous dermatitis
Gait Disturbance	None	Mild change in gait (eg, wide-based, limping or hobbling)	Moderate change in gait (eg, wide-based, limping or hobbling); assistance device indicated; limi ing instrumental ADL	Disabling; limiting self care ADL	
Ataxia (Incoordination)	None	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	

*refer to Section 7.1.2 - Monitoring for Signs of Immune Activation if present in a Phase I patient

Person Completing Form: _____ ADL = activities of daily living