CLINICAL PROTOCOL

Protocol Title:	A Phase 1/2, Open-label Study Evaluating the Efficacy, Safety, and Pharmacokinetics (PK) of Luveltamab Tazevibulin (STRO-002) in Infants and Children < 12 years of age with *CBFA2T3::GLIS2* Acute Myeloid Leukemia (AML)	
Protocol Number:	REFRaME-P1	
Investigational Product:	luveltamab tazevibulin (STRO-002)	
Indication Studied:	*CBFA2T3::GLIS2* AML in infants and children < 12 years of age	
Brief Title:	Luveltamab tazevibulin (STRO-002) in infants and children < 12 years of age with relapsed/refractory *CBFA2T3::GLIS2* AML.	
Study Phase:	1/2	
Sponsor Name and Legal Address:	Sutro Biopharma, Inc (Sutro)	
	111 Oyster Point Blvd, South San Francisco, CA 94080 Phone Number: 650-881-6500	
Regulatory Agency Identifier Numbers:	**Registry**	**Identifier Number**
	IND	163764
	EU CT	2023-506240-16-00
Collaborations	Children's Oncology Group (COG)	ADVL 2322
	Innovative Therapies for Children with Cancer Consortium (ITCC)	ITCC-114
Responsible Medical Officer:	Anne Borgman, MD	
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), ICH GCP Guidelines and applicable laws and regulations. Essential study documents will be archived in accordance with applicable regulations.	
Protocol Version and Date:	**Document Version**	**Date**
	Version 3.1 (Amendment 2.1)	30 Sep 2024
	Version 3.0 (Amendment 2)	06 Mar 2024
	Version 2.0 (Amendment 1)	28 Jul 2023
	Original (1.0) (Not approved by Agency)	20 Jun 2023

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PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Number:	REFRaME-P1
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IND	163764
EU CT	2023-506240-16-00
Date:	30 Sep 2024
Version:	Ver. 3.1, Amendment 2.1

Reviewed and Approved by:

This protocol was approved via an electronic signature in Veeva as described on the approval page appended to the document. Signatories include:

Anna Butturini MD, Executive Director, Clinical Development
Jennifer Khiem, MS, Senior Director, Regulatory Affairs
Lin Lu PhD, Senior Director Biostatistics

Medical Monitor Name and Contact Information will be provided separately.

.

PROTOCOL ACCEPTANCE FORM

Protocol Number:	REFRaME-P1
IND	163764
EU CT	2023-506240-16-00
Protocol Title	A Phase 1/2, Open-label Study Evaluating the Efficacy, Safety, and Pharmacokinetics (PK) of Luveltamab Tazevibulin (STRO-002) in Infants and Children < 12 years of age with *CBFA2T3::GLIS2* Acute Myeloid Leukemia (AML)
Date:	30 Sep 2024
Version:	Ver. 3.1, Amendment 2.1

I have carefully read this protocol and agree:

- that it contains all the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, ICH Guidelines for GCP, and all applicable regulatory requirements.
- agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements.
- will ensure that the investigational drug supplied by the Sponsor will be used only for administration to subjects included in this clinical research study.

_____ _____

Investigator's Signature **Date**

_____

Name (printed)

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AMKL	Acute megakaryoblastic leukemia
AraC	Cytarabine
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine triphosphate
AUC	Area under the curve
CAP	College of American Pathologists
CB	Cord blood
CBC	Complete blood count
CBFA2T3	*Core-binding factor alpha subunit 2, translocated to 3*
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum concentration
CNS	Central nervous system
COG	Children’s oncology group
CR	Complete remission
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete neutrophil recovery
CRp	Complete remission with incomplete platelet recovery
CRF	Case report form (eCRF, electronic case report form)
CTCAE	Common Terminology Criteria for Adverse Events
DDD	Defined daily dose
DLI	Donor lymphocyte infusion
DLT	Dose-limiting toxicity

Abbreviation or Term	Definition/Explanation
DS	Down Syndrome
EA	Expanded access
ECG	Electrocardiogram
ECHO	Echocardiogram
EDC	Electronic data capture
EFS	Event-free survival
EMD	Extramedullary disease
ENA	Extracted nucleic acids
EOT	End-of-treatment
F1Heme	FoundationOne® Heme
FDA	Food and Drug Administration
FMI	Foundation Medicine Inc.
FolRα/FOLR1	Folate receptor alpha
GCP	Good Clinical Practice
GLIS2	*GLI-similar protein 2*
GLP	Good laboratory practice
GUS	Reference (housekeeping) gene
HMBG1	High mobility group box 1
HSCT	Hematopoietic stem cell transplant
HSPC	Hematopoietic pluripotent stem cell
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent data monitoring committee
IRB/IEC	Internal review board/Independent ethics committee
IT	Intrathecal therapy
ITT	Intrathecal triple therapy
IV	Intravenous
IVRS	Interactive voice/web response system
LDT	Laboratory developed test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
MRD	Measurable residual disease

Abbreviation or Term	Definition/Explanation
MTX	Methotrexate
NGS	Next generation sequencing
NYSDOH	New York State Department of Health
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PK	Pharmacokinetic(s)
q[#]w	Every [number] weeks
QTcF	QT interval corrected using Fridericia's method
RFS	Relapse free survival
RQ-RT-PCR, RQ-PCR	Real-time quantitative reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC209	3-aminophenyl hemiasterlin warhead released from luveltamab tazevibulin
SC239	Sutro designation for unconjugated linker-hemiasterlin drug
SCT	Stem cell transplant
SoA	Schedule of assessments
SOC	Standard of care
SP8166	Anti-FOLR1 humanized IgG_1 antibody
SSC	Steering and Safety Committee
STRO-002	Anti-FOLR1 antibody–drug conjugate, luveltamab tazevibulin
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TAb	Total antibody (luveltamab tazevibulin)
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
Vss	Volume in steady state
WHO	World Health Organization

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1/2, Open-label Study Evaluating the Efficacy, Safety, and Pharmacokinetics (PK) of Luveltamab Tazevibulin (STRO-002) in Infants and Children < 12 years of age with *CBFA2T3::GLIS2* Acute Myeloid Leukemia (AML)

Brief Title: Luveltamab tazevibulin (STRO-002) in infants and children < 12 years of age with relapsed/refractory *CBFA2T3::GLIS2* AML

Regulatory Agency Identifier Number(s):

Registry	**ID**
IND	163764
EU CT	2023-506240-16-00

Rationale: This study will investigate the efficacy, safety, and PK of luveltamab tazevibulin in children with *core-binding factor alpha subunit 2, translocated to 3* (*CBFA2T3)::GLI-similar protein 2 (GLIS2)* relapsed/refractory AML, a rare and aggressive form of pediatric AML.

Study Objectives and Endpoints

Primary Objectives	Primary Endpoints
• Evaluate efficacy of luveltamab tazevibulin monotherapy	• Complete remission (CR) rate
Secondary Objectives	**Secondary Endpoints**
• Assess additional efficacy outcome measures	• Duration of CR • Response rate including complete remission with partial hematologic recovery (CRh) rate [CR + CRh] • Event-free survival (EFS) • Relapse-free survival (RFS) • Overall survival (OS)
• Evaluate safety measures	• Incidence and severity of AEs and clinical laboratory abnormalities per NCI CTCAE v5.0.
• To characterize the PK of luveltamab tazevibulin	• Concentration of luveltamab tazevibulin (ADC, TAb, and SC209) in the blood.
• Assess the immunogenic potential of luveltamab tazevibulin	• Incidence of ADAs
Exploratory Objectives	**Exploratory Endpoints**
• Evaluate other efficacy measures as applicable	• Duration of remission on combination therapy • CR + CRh on combination therapy • Proportion of subjects who proceed to transplant • Measurable residual disease (MRD)-negative response rate • Duration of MRD-negative CR
• Evaluate other safety measures as applicable	• Incidence and severity of AEs and clinical laboratory abnormalities of combination therapy per NCI CTCAE v5.0
• Evaluate potential predictive or prognostic biomarkers	• Evaluate correlation of expression of FOLR1 with efficacy

ADA = anti-drug antibodies; ADC = antibody drug conjugate; AEs = adverse events; AML = acute myeloid leukemia; CTCAE = Common Terminology Criteria for Adverse Events; FOLR1 = folate receptor alpha; NCI = National Cancer Institute; PK = pharmacokinetics; SC209 = 3-aminophenyl hemiasterlin warhead released from luveltamab tazevibulin; TAb = total antibody.

Overall Design:

This is a Phase 1/2, open-label study to evaluate the efficacy, safety, and PK of luveltamab tazevibulin in infants and children < 12 years of age with relapsed/refractory *CBFA2T3::GLIS2* AML.

This study will enroll subjects with relapsed/refractory *CBFA2T3::GLIS2* AML with ≥ 5% bone marrow involvement with leukemic blasts as determined by bone marrow morphology

(by local laboratory testing). Flow cytometry results (by local or central laboratory) will not affect subject eligibility.

The study will evaluate 2 parallel dose levels: luveltamab tazevibulin at 3.5 and 4.3 mg/kg every 2 weeks (q2w). Subjects will be randomized between the 2 dose levels at the time of enrollment to evaluate PK, safety, and efficacy across a dose range. Within a specific dose level, enrollment will employ a rolling six design (Skolnik et al, 2008). The dose limiting toxicity (DLT) evaluation period will be through Cycle 1 (28 days). Following evaluation of the safety and efficacy data on the initial enrollment of up to 3 to 6 subjects at each dose level, subsequent enrollment will be limited to the selected dose level.

All enrolled subjects will be initially assessed for eligibility during the screening period (lasting ≤ 21 days). Documentation of *CBFA2T3::GLIS2* fusion gene is required for enrollment. Results will be required prior to subjects receiving their first dose of luveltamab tazevibulin. Confirmation of FOLR1 expression on leukemia cells will be done retrospectively and will not be required for study enrollment.

All enrolled subjects will be initially assessed for eligibility during the screening period (lasting ≤ 21 days). Subjects will be monitored closely for adverse events (AEs) throughout the duration of the study and for at least 30 days after the last dose of study treatment or until initiation of another non-protocol specified systemic anti-cancer therapy, whichever occurs first. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0).

The study requires scheduled physical examinations, laboratory tests, blood draws for PK, blood draws for immunogenicity, electrocardiograms (ECGs), echocardiogram (ECHO), ophthalmic examinations, and radiographic imaging (if applicable). Clinical laboratory assessment will be performed per local laboratory. PK, immunogenicity (anti-drug antibody [ADA]), and biomarker assessments will be performed at a central laboratory. Detailed schedules of activities are provided in the Schedule of Assessments and Schedule of PK Collection (Section 1.3).

Dosing

Cycles 1 and 2 (Doses 1-4): Subjects will receive luveltamab tazevibulin monotherapy at the assigned dose level and schedule. Luveltamab tazevibulin will be infused IV over 1 hour (± 5 minutes); infusion may be slowed as clinically indicated. The starting dose levels will be Dose Levels (DL) 1a and 2a. DL1a and DL2a will be evaluated in parallel for the initial 6 to 12 subjects and 1 dose level selected for further enrollment based upon safety and preliminary anti-leukemia activity data. At Dose Level 1a, subjects will receive luveltamab tazevibulin at 3.5 mg/kg IV q2w on Days 1 and 15 of a 28-day cycle. At Dose Level 2a, subjects will receive luveltamab tazevibulin at 4.3 mg/kg IV q2w on Days 1 and 15 of a 28-day cycle (Section 1.2, Schema).

Based on ongoing evaluation of accumulated safety, PK, and efficacy data, the Cycle 1 starting dose level (dose and/or schedule) may be modified, based on the recommendation of the Steering and Safety Committee (SSC).

If a dose level is determined to be non-tolerable, subsequent subjects enrolled will not start or escalate to that dose level. Doses may be modified due to safety and tolerability.

At the completion of Cycle 1, bone marrow will be evaluated.

Should the subject experience ongoing Grade 4 neutropenia or thrombocytopenia, the decision on whether to proceed immediately to dose Cycle 2 is based on bone marrow evaluation.

- If a subject has no evidence of leukemia in the bone marrow but experiences an AE of Grade 4 neutropenia (absolute neutrophil count [ANC] < 500/μL) or Grade 4 thrombocytopenia (platelets < 25,000/μL), the dose will be held until counts have recovered to Grade 3.
- If a subject has evidence of leukemia in the bone marrow, they will receive another cycle of luveltamab tazevibulin, even in the presence of Grade 4 cytopenia.

After Cycle 2 response assessment, subjects in complete remission with partial hematologic recovery (CRh) will have Cycle 3 held for up to 28 days until neutrophil and platelet counts recover to meet the criteria for complete remission (CR) (ANC > 1 Gi/L and platelet count > 100 Gi/L). Repeat bone marrow will be performed if the last bone marrow was performed (≥ 14 days) prior to the peripheral count recovery. Should count recovery fail to occur by the end of the 28-day observation period, treatment may be resumed, as long as ANC > 0.50 Gi/L and platelets are > 50 Gi/L.

Cycle 3 (Doses 5 and 6): Subjects who are in CR/CRh will continue dosing at their Cycle 2 dose level until relapse, transplant or other intervening therapy, unmanageable AEs, or withdrawal from the study treatment.

If a subject does not achieve a CR/CRh prior to the start of Cycle 3, but has tolerated the original dose level, the subject may dose-escalate 1 alpha-numeric dose level. For example, if a subject is treated at Dose Level 1a (3.5 mg/kg q2w), they may escalate to Dose Level 2a (4.3 mg/kg IV q2w). Subjects that are unable to dose-escalate due to intolerability and have not achieved a CR/CRh, may discontinue study treatment or may receive luveltamab tazevibulin at 4.3 mg/kg every 4 weeks (q4w) in combination with standard AML treatment regimen until relapse, transplant or other intervening therapy, unmanageable AEs, or choose to withdraw from treatment.

Cycle 4 onwards (Subjects who dose escalated at Cycle 3) (Dose 7+): Subjects who are in CR/CRh will continue dosing at their Cycle 3 Dose Level until relapse, transplant, or other intervening therapy, unmanageable AEs, or withdrawal from study treatment. Subjects who

have not achieved a CR/CRh at the conclusion of Cycle 3 may either discontinue study treatment or may receive luveltamab tazevibulin at 4.3 mg/kg q4w (or other dose level deemed safe by SSC) in combination with standard AML treatment regimen until relapse, transplant or other intervening therapy, unmanageable AEs, or choose to withdraw from treatment.

Combination Therapy of Luveltamab Tazevibulin with Standard of Care Backbone AML Treatment

Subjects will be allowed to receive luveltamab tazevibulin at 4.3 mg/kg (or other dose level deemed safe by SSC) once per treatment cycle (q4w) in combination with standard of care (SOC) backbone AML treatment regimens detailed below, if such treatment is available at the treating center.

The subjects will be allowed to switch between any of the below listed combination regimens at Investigator discretion. Concurrent dosing of luveltamab tazevibulin and SOC backbone AML treatment therapy is allowed.

Standard of Care Backbone AML Therapies Allowed Concomitantly with Luveltamab Tazevibulin

Name	Drugs
Regimen 1	Luveltamab tazevibulin + fludarabine + intermediate dose cytarabine
Regimen 2	Luveltamab tazevibulin + intermediate dose cytarabine
Regimen 3	Luveltamab tazevibulin + azacytidine
Regimen 4	Luveltamab tazevibulin + donor lymphocyte infusion (if subject has had a prior transplant)

SOC = standard of care.

Doses for the SOC Backbone therapies include:
Regimen 1: Fludarabine + intermediate dose cytarabine:
Fludarabine 30 mg/m^2 IV over 30 minutes once per day (QD) on Days 1 to 5.
Intermediate dose cytarabine 2000 mg/m^2 IV over 1 to 3 hours QD on Days 1 to 5, given 4 hours after the start of fludarabine.
The subjects can receive up to 2 cycles of fludarabine and intermediate dose cytarabine.

Regimen 2: Intermediate dose cytarabine 2000 mg/m^2 IV over 1 to 3 hours QD on Days 1 to 5.
The subjects can receive up to 4 cycles of intermediate dose cytarabine.

Regimen 3: Azacytidine:
Subjects will be treated with either subcutaneous or IV azacytidine Days 1 to 7 of a 28-day cycle. IV azacytidine will be infused over 1 hour. The number of azacytidine cycles administered is based on clinical benefit and Investigator discretion.

Guidelines for dose is dependent on subject age:

- The recommended dose for subjects age ≥ 1 year and weighing ≥ 10 kg is 75 mg/m^2.
- For subjects less than 1 year of age or weighing less than 10 kg, azacytidine dose is 2.5 mg/kg.

Regimen 4: Donor lymphocyte infusion (DLI) (if subject has had a prior transplant) at a dose and schedule determined by the Investigator. The number of DLI cycles administered is based on clinical benefit and Investigator discretion.

Response Evaluation:

Bone marrow evaluation including flow cytometry will be performed to assess blast counts at baseline and prior to the beginning of the next cycle until Cycle 3 (on Day 28 of each cycle in dose cohorts receiving q2w dosing, and on Day 42 of each cycle in dose cohorts receiving q3w dosing). In addition to local evaluation of bone marrow aspirates and biopsies, slides, and peripheral blood smears will be sent to a central laboratory for central morphology review to confirm the response. Measurable residual disease (MRD) assessment will also be performed at a central laboratory utilizing flow cytometry. Subjects continuing monotherapy will have subsequent bone marrow evaluations at the conclusion of Cycles 4 and 6 and every other subsequent cycle, and at EOT. Additional assessments may be performed, if clinically indicated.

Determination of CR will be based on BM central morphology review and also include the evaluation of peripheral blood blasts, neutrophils, platelet counts, and EMD.

Extramedullary Disease Response Evaluation:

Subjects with clinical signs of EMD require imaging evaluation prior to enrollment or during the study. All subjects with suspected or confirmed EMD disease at baseline are required to have an imaging evaluation prior to initiation of therapy. Subjects with cutaneous disease who have biopsy confirmation do not need to have imaging. If clinically feasible, tissue biopsy should be used to determine EMD response. If tissue biopsy is not clinically appropriate, then radiographic studies including positron emission tomography scan should be used to determine EMD response. The differentiation between residual disease and residual scar tissue on radiographic studies may be difficult and the final determination of radiographic disease status should be made by the treating clinician in consultation with the local radiologist.

At screening, all subjects are required to be evaluated by lumbar puncture for the presence of CNS disease prior to initiation of therapy. Lumbar puncture will be performed based on the criteria below. Each time a lumbar puncture is performed, central nervous system (CNS) involvement will be evaluated.

- Subjects with CNS1 will receive prophylaxis therapy for CNS disease at study entry and for subsequent cycles as deemed appropriate by the Investigator.
- Subjects that begin treatment with CNS2 will receive therapy for CNS disease.

- Subjects with clinical signs of CNS leukemia that developed during luveltamab tazevibulin treatment will require lumbar puncture and imaging evaluation to confirm CNS progression.

Images and reports used to assess extramedullary response will be collected for central response adjudication.

Inclusion Criteria:

Subjects must meet the following inclusion criteria for study entry:

General Inclusion Criteria

1) Signed informed consent form and pediatric assent form, if applicable.
2) Diagnosis of relapsed or refractory AML with CBFA2T3::GLIS2 fusion. Subjects must have refractory (induction/reinduction failure) or relapsed disease with ≥ 5% bone marrow involvement with leukemic blasts as determined by morphology (by local laboratory testing). Subjects must undergo a lumbar puncture at screening to confirm (CNS) disease. Subjects with CNS1 and CNS2 are eligible (please refer to definitions below in Inclusion Criteria #3). Flow cytometry results (by central or local laboratory) will not affect subject eligibility.

   US & ROW: Eligibility requires the documentation of the *CBFA2T3::GLIS2* translocation by the Next Generation Sequencing FoundationOne® Heme assay.

   If past results from the FoundationOne Heme assay are available and meet suitable characteristics for Trial Boost, [Foundation Medicine's mechanism for transferring subject results from a prior test to a clinical trial], the past results may be reanalyzed to confirm molecular eligibility.

   EU Subjects Only: Eligibility requires the documentation of the *CBFA2T3::GLIS2* translocation performed by RQ-RT-PCR centralized testing.
3) Age < 12 years.
4) Lansky performance of ≥ 50.
5) Direct bilirubin < 1.5 × upper limit of normal (ULN). Subjects with Gilbert's disease will also require direct bilirubin < 1.5 × ULN.
6) Alanine aminotransaminase (ALT) and aspartate aminotransferase (AST) < 2.5 × ULN (unless related to leukemic involvement).
   - Subjects with hepatic EMD, ALT and AST may be ≤ 5.0 × ULN.
   - To note, for subjects with hepatic EMD who have baseline LFT > 2.5 × ULN but < 3 × ULN, DLT criteria for LFT remain. For those who start with LFT > 3 × ULN, they will not be evaluable for LFT DLT.

7) Creatinine clearance or radioisotope glomerular filtration rate ≥ 70/mL/min/1.73 m^2 OR a serum creatinine based on age/gender as follows:

	Maximum Serum Creatinine (mg/dL)	
Age	**Male**	**Female**
1 to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2

The threshold creatinine values in the table were derived from the Schwartz formula for estimating glomerular filtration rate utilizing child length and stature data published by the Centers for Disease Control and Prevention.

8) Corrected QTcF < 450 msecs.
9) Left ventricular ejection fraction > 50% by ECHO.
10) Female subjects that have experienced menarche and male subjects that have reached puberty must agree to undergo physician-approved reproductive education and discuss the side effects of the study therapy on reproduction with parent(s) and/or guardian(s).
11) Female subjects who have experienced menarche must have a negative pregnancy test within 7 days of the first dose of study drug. All subjects (male and female) who have undergone puberty and are potentially sexually active must agree to use a physical barrier (condoms) during heterosexual contact. At the discretion of the treating physician females may also use additional contraceptive methods, including hormonal contraceptives. Pregnancy prevention must continue while participating in the study, during dose interruptions, and for at least 6 months following luveltamab tazevibulin discontinuation.

Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from study entry:

1) Active CNS disease at the time of enrollment (defined as CNS3).
2) Subjects with the following constitutional conditions are not eligible: Fanconi anemia, Shwachman Diamond syndrome, subjects with constitutional trisomy 21 or with constitutional mosaicism of trisomy 21, telomere disorders, germline predispositions known, or suspected by the treating physician to increase risk of toxicity with AML therapy.
3) Clinically significant active or chronic corneal disorder, particularly corneal epitheliopathy, or any eye disorder that may predispose subject to this condition, or unable to comply with an age-appropriate ophthalmic examination.

4) Active or uncontrolled viral, bacterial, or fungal infection. May be receiving ongoing therapy for controlled infection.
5) Known human immunodeficiency virus, hepatitis B virus, or hepatitis C virus infection, unless on treatment and have an undetectable viral load.
6) Uncontrolled, symptomatic, intercurrent illness including but not limited to infection, congestive heart failure, cardiac arrhythmia, or social situations that would limit compliance with study requirements or in the opinion of the Investigator would pose an unacceptable risk to the subject. If the subject is in remission from a prior second malignancy, they may be considered for enrollment.
7) History of severe, immediate hypersensitivity reaction attributed to compounds of similar chemical or biologic composition to any agents used in study or in the manufacturing of the cells.
8) Subjects with a history of an allogeneic (non-autologous) hematopoietic stem cell transplant, boost infusion (any stem cell product; not including donor lymphocyte infusion [DLI]), or any organ transplant are excluded if any of the following are met:
    a) Subjects are less than 84 days post-transplant.
    b) Subjects have graft-versus-host disease (GVHD) of any severity and/or receive any immunosuppressive therapy with the exception of topical steroids for cutaneous GVHD and/or systemic steroid in doses equal or less than 10 mg of prednisone daily, which are permitted if doses were not changed in the last 14 days. Prednisone dose must be adjusted for body surface area in young children. Physiologic doses of hydrocortisone for subjects with adrenal insufficiency are allowed.
    c) Subjects who after relapse continue to receive cyclosporine, tacrolimus, or other agents to treat or prevent either GVHD post-bone marrow transplant or organ rejection post-transplant are not eligible. They must be off medications to treat or prevent either GVHD post-bone marrow transplant or organ rejection post-transplant for at least 28 days prior to enrollment. A stable steroid dose as mentioned above is allowed.
    d) Cellular therapy: less than 30 days after the completion of DLI or any type of cellular therapy (eg, modified T cells, NK cells, dendritic cells, etc.) at enrollment. After 30 days, subjects will be eligible.
9) Prior systemic chemotherapy within 21 days prior to the first luveltamab tazevibulin infusion, with the exception of:
    a) Hydroxyurea ≥ 1 day.
    b) Azacytidine/decitabine and/or venetoclax: ≥ 7 days.
    c) Antibody drug conjugate therapies: ≥ 3 half-lives.

10) Radiation therapy, including CNS, < 21 days prior to the start of luveltamab tazevibulin, with the exception of no time restriction if the volume of bone marrow treated is less than 10% and also the subject has measurable/evaluable disease outside the radiation field.

11) Prior treatment with folate receptor-targeting anti-cancer agent(s) or with ADCs that contain a tubulin inhibitor.

12) Prior treatment with an investigational anti-cancer treatment within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first luveltamab tazevibulin infusion.

    a) Note: ADC therapies washout period is ≥ 3 half-lives (see Exclusion #9).

Study Duration:

- Planned maximum treatment duration for initial therapy: 2 years
- Maximum treatment duration for post-CR from other therapy (eg, combination therapy) maintenance: 2 years
- Maximum treatment duration for post-allogeneic stem cell transplant (SCT) maintenance: 2 years
- End-of-study: 2 years from the last subject enrolled. Subjects who withdraw from the study and trial procedures will still be followed for overall survival for approximately 2 years.
- Maximum length of the trial: approximately 5 years

Milestones	**Definitions**	**Timeline**
Estimated study start	The date on which the clinical study will be open for recruitment of subjects	Q1 2024
First act of recruitment	First site open and will be the study start date, estimated to be 18 to 24 months	Q1 2024
Estimated last subject last visit	Two (2) years from last subject in	Q4 2027

Summary of Statistical Considerations

Sample Size:

Initially enroll up to 6 DLT evaluable subjects per dose level. For the selected dose regimen, enrollment will be expanded to a total of 18 subjects. Sample size of 18 subjects will provide a type I error rate of 0.025 (1-sided) and power of 80% to distinguish the target response (CR) rate of 30% and historic response rate of 5%. The historic response rate is based on the feedback of experts in this population.

Endpoints

Efficacy: Morphological complete response is the CR defined per Döhner et al, 2016. The primary endpoint is the response rate based on the central morphological complete response that occurs as a result of luveltamab tazevibulin monotherapy in subjects where central morphology review confirms eligibility. The corresponding Clopper-Pearson 95% confidence interval will be calculated. The analysis of the primary endpoint will be based upon the modified Intent-to-Treat population for the selected dose. The median duration of response will be estimated using the Kaplan-Meier method with corresponding 95% confidence interval.

Safety: Safety assessments will include physical examinations, AE assessments, clinical laboratory tests, ECGs, and ophthalmic exams. Safety data from all subjects will be summarized.

Data Monitoring/Other Committee:

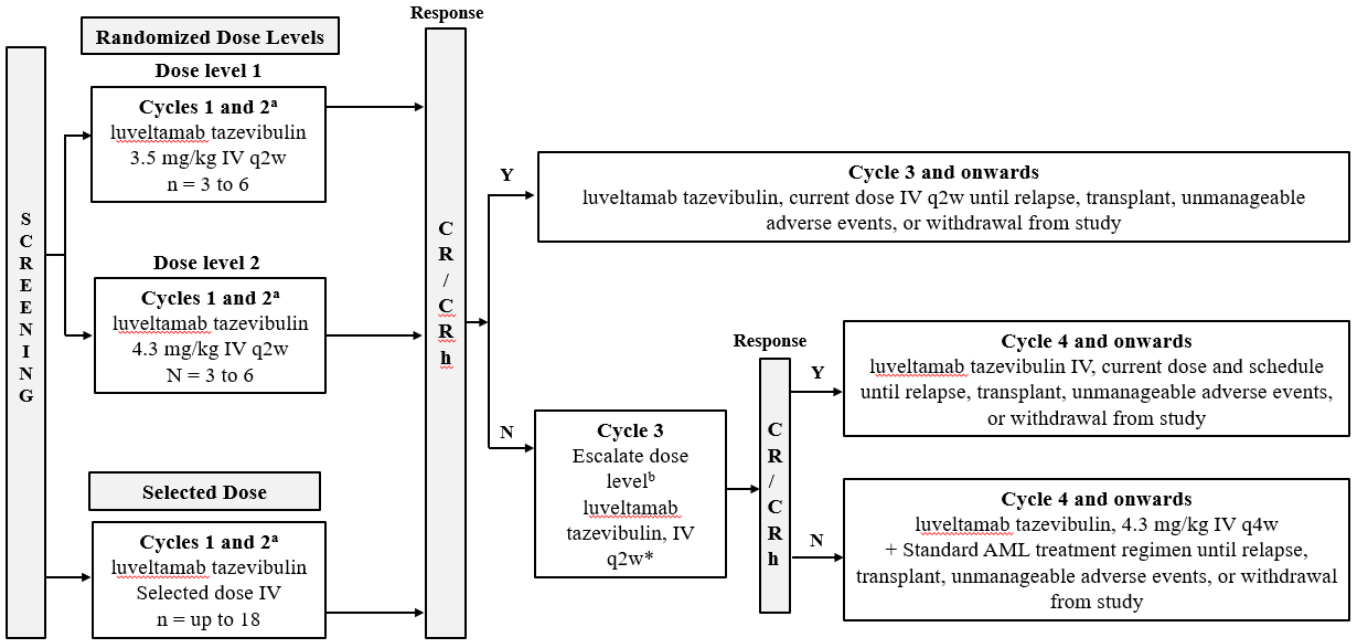
Steering and Safety Committee (SSC):
This committee will be comprised of selected members of the Sponsor clinical team and selected Investigators, members of the contract research organization who have responsibilities for managing and/or participation in the ongoing review of study subjects. The SSC may invite additional members to attend and/or participate in meetings as required (eg, pharmacokineticist).

The SSC will routinely monitor the evolving safety, efficacy, and PK data, as needed and available; and will provide recommendations to support decisions regarding the study conduct, including decisions for escalating dose escalation cohorts, identifying and confirming safety issues, modification of ongoing dosing or starting doses (eg, emerging PK data supports q4w dosing), and guidance on potential study modifications based on accumulating safety data, study conduct, and/or emerging external information.

Independent Data Monitoring Committee (IDMC):
An independent IDMC will be appointed to support the Sponsor in safeguarding the interests of study subjects, and to assess the safety and efficacy of treatment with luveltamab tazevibulin. The IDMC will be comprised of qualified clinicians and a biostatistician all independent from the Sponsor and investigational sites, selected to avoid conflict(s) of interest. The IDMC will review and assess ongoing safety data and emerging risk/benefit balance at regular intervals and on an ad-hoc basis when required. The IDMC will also provide an independent response assessment at a minimum for all subjects intended to support the filing. The IDMC's specific activities will be detailed in the IDMC charter, which will define the processes, including meeting proceedings and structure, data assessments, documentation and recordkeeping, process for IDMC recommendations, and regulatory reporting, as applicable. Additional details will be provided in the IDMC charter.

1.2 Schema

Figure 1: Schema for REFRaME-P1 Study



AML = acute myeloid leukemia; CR = complete remission; CRh = CR with partial hematologic recovery; IV=intravenous; q2w = every 2 weeks, q4w = every 4 weeks; SSC = Steering and Safety Committee. A cycle is equal to 2 doses of luveltamab tazevibulin (q2w schedule every 28 days).

* Based on evaluation of accumulated PK, safety, and efficacy data, the SSC may increase or decrease a recommended dose level.

a. Based on ongoing evaluation of accumulated safety and efficacy data following Cycle 2, the SSC will recommend, and the Sponsor will select, a dose level for subsequent enrollment.

b. Subjects unable to dose escalate due to intolerability who have not achieved a CR/CRh, may discontinue study treatment or may receive luveltamab tazevibulin at 4.3 mg/kg q4w in combination with standard AML treatment regimen until relapse, transplant or other intervening therapy, unmanageable AEs, or choose to withdraw from study.

1.3 Schedule of Assessments (SoA)

Table 1: Schedule of Assessments q2w Dosing Regimen

		Cycle 1							Cycle 2					Cycle 3			Cycle 4 and onwards				
Study Day in Dose	**Screening[a]**	**1[b]**	**2[c]**	**8**	**15**	**16[c]**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**1**	**15**	**28**	**EOT[d]**	**LTFU Q12W post EOT**
Visit Window	**≤ 21 D before C1D1**	**NA**	**NA**	**± 2D**	**± 2D**	**NA**	**± 2D**	**± 3D**	**± 2D**	**± 2D**	**± 2D**	**± 2D**	**± 3D**	**± 2D**	**± 2D**	**± 3D**	**± 2D**	**± 2D**	**± 3D**	**± 7D**	
Infusion of luveltamab tazevibulin[e]		**X**			**X**				**X**		**X**			**X**	**X**		**X**	**X**			
Prophylaxis for CNS disease[f]		**X**																			
Response Assessments																					
Bone marrow evaluation[a,g,h]	**≤ 14 D C1D1**							**X**					**X**			**X**				**X**	
EMD evaluation[i]	**X**							**X**					**X**			**X**				**X**	
General Assessments																					
Informed consent[j]	**X**																				
Eligibility review	**X**																				
Medical history[k]	**X**																				
Concomitant medication/ procedures	**X**	**X**		**X**	**X**		**X**		**X**	**X**	**X**	**X**		**X**	**X**		**X**	**X**		**X**	
Adverse events[l]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Physical examination[m]	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**	**X**		**X**	**X**		**X**	
Ophthalmic exam[n]	**X**								**X**					**X**			**X**			**X**	
Lumbar puncture[f,o]	**≤ 14 D C1D1**	**Lumbar puncture will be completed at the time of bone marrow evaluations for subjects enrolled with CNS1 or CNS2 disease and as applicable[f,o]**																		**X**	
Vital Signs[p]	**X**	**X**			**X**				**X**		**X**			**X**	**X**		**X**	**X**		**X**	
12-lead ECG[q]	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**			**X**	**X**		**X**	**X**		**X**	

		Cycle 1							Cycle 2					Cycle 3			Cycle 4 and onwards				
Study Day in Dose	**Screening[a]**	**1[b]**	**2[c]**	**8**	**15**	**16[c]**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**1**	**15**	**28**	**EOT[d]**	**LTFU Q12W post EOT**
Visit Window	**≤ 21 D before C1D1**	**NA**	**NA**	**± 2D**	**± 2D**	**NA**	**± 2D**	**± 3D**	**± 2D**	**± 2D**	**± 2D**	**± 2D**	**± 3D**	**± 2D**	**± 2D**	**± 3D**	**± 2D**	**± 2D**	**± 3D**	**± 7D**	
ECHO	**X**																			**X**	
Lansky performance	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**	**X**		**X**	**X**		**X**	
Survival status[r]																					**X**
Hematology[s]	**≤ 14 D C1D1**	**X**		**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Serum chemistry[t]	**≤ 14 D C1D1**	**X**		**X**	**X**		**X**		**X**	**X**	**X**	**X**		**X**	**X**		**X**	**X**		**X**	
Amylase and lipase[u]	**X**																			**X**	
Thyroid tests[v]	**X**																**X**	**X**		**X**	
CPK[w]	**X**				**X**				**X**		**X**			**X**	**X**		**X**	**X**		**X**	
Urinalysis[x]	**X**	**X**																		**X**	
Immunogenicity (ADA)[y]		**X**							**X**					**X**			**X**			**X**	
PK[c,z]		**See Table 5 for PK assessment timepoints and visit windows[y]**																			

Abbreviations: ADA = anti-drug antibodies; AE = adverse events; CPK = creatine phosphokinase; CSF = cerebrospinal fluid; CT = Computed Tomography; D = day; Dem = demographics; DLT = dose limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; EOT = end-of-treatment; EMD = extramedullary disease, H = hour; IHC = immunohistochemistry, LTFU = long-term follow-up; m = month; MRI = magnetic resonance imaging, NA = not applicable; NGS = next generation sequencing; PK = pharmacokinetics; PT = prothrombin time; Q12W = every 12 weeks; SAE = serious adverse event; TSH = thyroid stimulating hormone.

Footnotes:

Please note – Additional tests and assessments may be performed any time at the discretion of the Investigator and results should be recorded in the source and eCRF, if applicable.

a. Screening assessments should be performed within 21 days before first administration of study drug, unless otherwise noted. Screening assessment of *CBFA2T3::GLIS2* fusion gene may be completed within 21 days before the first administration of study drug; see eligibility criteria and Section 6.10.4 for details. Screening bone marrow evaluations must be performed within 14 days of initiation of study drug. **EU subjects only**: Bone marrow samples collected at baseline will be stored at a central laboratory for future retrospective NGS testing at Foundation Medicine. Screening hematology and chemistry laboratories must be obtained within 14 days of initiation of study drug. FOLR1 expression at screening is not required for subjects to enroll in the study.

b. Assessments which must occur on Cycle 1 Day 1 (C1D1) include treatment with luveltamab tazevibulin, hematology and chemistry labs, AE and concomitant medication assessment, physical exam, vital signs, Lansky performance, PK and ADA. C1D1 labs may be collected up to 36 hours prior to dosing and confirmed to meet eligibility requirements to qualify for treatment. All other required C1D1 assessments may be performed within 3 days before C1D1.

c. Please see Table 5 for PK collections as applicable. All other assessments can be collected any time during the day of the visit.

d. An EOT safety visit will occur at 30 (± 7) days from the last dose of study drug and should be scheduled prior to starting a new therapy. All AEs that occur within 30 days of the last treatment dose should be recorded.

e. Luveltamab tazevibulin dosage will depend on the current dose and response to treatment. Both intra-subject and inter-subject dose level adjustments based on ongoing efficacy, safety, and PK data will be permitted.

f. Standard of care intrathecal cytarabine or Triple IT (methotrexate, hydrocortisone, and cytarabine) may be administered at any point during the study for either prophylaxis or treatment of CNS leukemia.

g. Local bone marrow evaluation post-screening will be performed by both aspirate and biopsy to assess blast counts on Day 28 (± 3days) of each cycle. In addition to local evaluation, bone marrow samples and peripheral blood smears will be sent to a central laboratory for central review. Flow cytometry will be evaluated at a central laboratory. Subjects continuing monotherapy will have subsequent bone marrow evaluations at the conclusion of Cycle 4 (ie, C4D28) and Cycle 6 (ie, C6D28) and every other subsequent cycle and at EOT. Additional tests may be performed at the Investigator's discretion. Samples will be analyzed for biomarkers related to AML, FOLR1, and *CBFA2T3::GLIS2*, please see Section 8.8 for biomarker testing. When bone marrow biopsies and ophthalmic exams occur on the same cycle, planned anesthesia for the bone marrow biopsies should be coordinated with the planned anesthesia for ophthalmic examinations (if required). Subjects who remain on study drug greater than 1 year may have bone marrow evaluations at the discretion of the treating physician, but not less than twice annually.

h. Immediate treatment decisions will be based on local assessment of bone marrow aspirate and biopsy morphology.

i. EMD evaluation - Subjects with marrow disease only and no clinical signs of extramedullary disease do not require imaging evaluation prior to enrollment or during the study. All subjects with suspected or confirmed EMD disease are required to have an imaging evaluation prior to initiation of therapy, on Day 28 (± 3days) of each cycle and at the conclusion of Cycle 4 and Cycle 6 and every other subsequent cycle and at EOT. Additional tests may be performed at the Investigator's discretion. All subjects will require a lumbar puncture at screening to test for CNS disease.

j. ICF can be signed ≤ 21 days prior to first dose. However, no study assessments may be performed until after the subject/parent/guardian has signed the ICF.

k. Signs and symptoms occurring between screening visit and first dose of luveltamab tazevibulin should be recorded as Medical History, unless they are a result of a screening procedure, then they will be recorded as an AE/SAE

l. AEs and SAEs will only be reported for 30 days following the last dose of luveltamab tazevibulin. SAEs that occur > 30 days after the last dose of study drug will only be reported if assessed as related to study drug by the Investigator.

m. Height will be recorded at screening visit only. Weight will be recorded at each D1 visit for dosage calculations. Physical exams should include asking the parent/legal guardian if the subject has experienced any ocular problems/discomfort have occurred and check for signs and symptoms of peripheral neuropathy. Symptom-directed physical exams will be done during the treatment phase (after C1D1) and at the EOT visit.

n. Ophthalmic exams must be performed by an ophthalmologist, optometrist, or other qualified professional at Screening, pre-dose Cycle 2 and 3 and every 2 cycles thereafter, and at EOT. Additional tests may be performed at the Investigator's discretion. Anesthesia is not required for ophthalmic examinations, however, if anesthesia is needed, when bone marrow biopsies and ophthalmic exams occur on the same cycle, planned anesthesia for the bone marrow biopsies should be coordinated with the planned anesthesia for ophthalmic examinations (if required).

o. All subjects will require a lumbar puncture at screening to test for CNS disease which must be performed within 14 days of initiation of study drug and will receive prophylaxis therapy for CNS disease at study entry. Subjects with CNS1 disease will not need to be evaluated again until EOT, unless they show clinical signs and symptoms. See Section 10.6 for CNS prophylaxis and therapy in subjects with CNS2 disease. Subjects with clinical signs of CNS leukemia that developed during luveltamab tazevibulin treatment will require lumbar puncture and imaging evaluation. CNS involvement will be evaluated any time a lumbar puncture is completed.

p. Vital signs should be collected prior to infusion of luveltamab tazevibulin.

q. ECG assessments will be performed in triplicate using the ECG machine provided by the site unless notified by the Sponsor to use central ECGs or in cases where the local ECG machine is not available and/or working. Corrected QTcF must be < 450 msec during Screening and prior to the C1D1 dose for subject to meet eligibility requirements. ECGs should be performed prior to PK draw when able. Cycle 1 Day 2 and Cycle 1 Day 16 ECG collections must be completed within a ± 4-hour window.

r. Subjects who withdraw from the study will continue to be followed for overall survival unless consent for follow up is withdrawn.

s. Complete blood count (CBC) including hemoglobin, platelet count, white blood cells, and differential with absolute neutrophil count, and blast count. CBCs are obtained in screening (≤ 14 days prior to first dose), pre-dose on dosing days and every week up to Cycle 3. Cycle 3 onwards, assessments should be collected, pre-dose on dosing days. Additional tests may be performed at the Investigator's discretion. Coagulation profile consisting of prothrombin time (INR), partial thromboplastin time, and fibrinogen will be collected pre-dose on Day 1 of Cycle 1 and at EOT and may be performed at the Investigator's discretion. A peripheral blood smear will also be collected on Day 28 that will be sent to a central laboratory for central review.

t. For serum chemistry labs please refer to Section 10.3, Table 18. Serum chemistry labs are obtained in Screening (≤ 14 days prior to first dose), pre-dose on dosing days and every week up to Cycle 3. Cycle 3 onwards, assessments should be collected, pre-dose on dosing days. Additional tests may be performed, per Investigator's discretion and results should be recorded in the source and eCRF. Labs for Tumor Lysis syndrome should be monitored per institutional guidelines.

u. Amylase, lipase, T3 and T4 are obtained in screening (≤ 21 days prior to first dose) and at EOT. Additional tests may be performed per Investigator's discretion and results should be recorded in the source and eCRF.

v. TSH is obtained in Screening (≤ 21 days prior to first dose) and at EOT. TSH is obtained at Cycle 4 (pre-dose) and every 3 subsequent cycles. If TSH is abnormal at EOT, T3 and T4 should be repeated. Additional tests may be performed per Investigator's discretion and results should be recorded in the source and eCRF.

w. CPK is obtained in Screening (≤ 21 days prior to first dose), pre-dose on dosing days of each cycle beginning at C1D15 up to Cycle 3. Cycle 4 onwards, assessments should be collected every other cycle. Additional tests may be performed, per Investigator's discretion and results should be recorded in the source and eCRF.

x. Urinalysis is obtained in screening (≤ 21 days prior to first dose), Day 1, and at EOT. Day 1 labs must qualify or subject will not be treated until resolution to level that qualifies for eligibility. Additional tests may be performed, per Investigator's discretion and, when available, results should be recorded in the source and eCRF.

y. Blood samples for ADA assessment will be obtained pre-dose, within 2 hours before luveltamab tazevibulin infusion, on Day 1 of Cycle 1 and 2, pre-dose on Day 1 of Cycles 3 through 5, and pre-dose on Day 1 every 6 cycles (ie, every 6 months) thereafter, and at the EOT visit following last dose of luveltamab tazevibulin. Blood samples for ADA analysis should be collected at the requested time.

z. PK samples will be analyzed by central laboratory as shown in Table 5. Cycle 1 Day 2 and Cycle 1 Day 16 PK collections must be completed within a ± 4-hour window. An aliquot of the PK sample may be allocated for biomarker analyses.

Table 2: Schedule of Assessments q3w Dosing Regimen (to be used only for Dose Modifications)

		Cycle 1									Cycle 2							Cycle 3			Cycle 4 and onwards				
Study Day in Dose	**S[a]**	**1[b]**	**2[c]**	**8**	**15**	**22**	**23[c]**	**29**	**36**	**42**	**1**	**8**	**15**	**22**	**29**	**36**	**42**	**1**	**22**	**42**	**1**	**22**	**42**	**EOT[d]**	**LT/ FU**
Visit Window	**≤ 21 days before C1D1**	**NA**	**NA**	**± 2 D**	**± 2 D**	**± 2 D**	**NA**	**± 2D**	**± 2D**	**± 3D**	**± 2 D**	**± 2 D**	**± 2 D**	**± 2 D**	**± 2 D**	**± 2 D**	**± 3 D**	**± 2 D**	**± 2 D**	**± 3 D**	**± 2 D**	**± 2 D**	**± 3 D**	**± 7 D**	
Infusion of luveltamab tazevibulin[e]		**X**				**X**					**X**			**X**				**X**	**X**		**X**	**X**			
Prophylaxis for CNS disease[f]		**X**																							
Response Assessments																									
Bone marrow evaluation[a,g,h]	**≤ 14D C1D1**									**X**							**X**			**X**			**X**	**X**	
EMD evaluation[i]	**X**									**X**							**X**			**X**			**X**	**X**	
General Assessments																									
Informed consent[j]	**X**																								
Eligibility review	**X**																								
Medical history[k]	**X**																								
Concomitant medication/ procedures	**X**	**X**		**X**	**X**	**X**		**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		**X**	**X**		**X**	
Adverse Events[l]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Physical examination[m]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		**X**	**X**		**X**	
Ophthalmic exam[n]	**X**										**X**							**X**			**X**			**X**	

		Cycle 1									Cycle 2							Cycle 3			Cycle 4 and onwards				
Study Day in Dose	**S[a]**	**1[b]**	**2[c]**	**8**	**15**	**22**	**23[c]**	**29**	**36**	**42**	**1**	**8**	**15**	**22**	**29**	**36**	**42**	**1**	**22**	**42**	**1**	**22**	**42**	**EOT[d]**	**LT/ FU**
Visit Window	**≤ 21 days before C1D1**	**NA**	**NA**	**± 2 D**	**± 2 D**	**± 2 D**	**NA**	**± 2D**	**± 2D**	**± 3D**	**± 2 D**	**± 2 D**	**± 2 D**	**± 2 D**	**± 2 D**	**± 2 D**	**± 3 D**	**± 2 D**	**± 2 D**	**± 3 D**	**± 2 D**	**± 2 D**	**± 3 D**	**± 7 D**	
Lumbar puncture[f,o]	**≤ 14D C1D1**	**Lumbar puncture will be completed at the time of bone marrow evaluations as applicable[f,o]**																						**X**	
Vital signs[p]	**X**	**X**				**X**					**X**			**X**				**X**	**X**		**X**	**X**		**X**	
12-lead ECG[q]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**			**X**	**X**			**X**	**X**		**X**	**X**		**X**	
ECHO	**X**																							**X**	
Lansky performance	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		**X**	**X**		**X**	
Survival status[r]																									**X**
Hematology[s]	**≤ 14D C1D1**	**X**		**X**	**X**	**X**		**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		**X**	**X**		**X**	
Serum chemistry[t]	**≤ 14D C1D1**	**X**		**X**	**X**	**X**		**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Amylase and lipase[u]	**X**																				**X**			**X**	
Thyroid tests[v]	**X**																				**X**	**X**		**X**	
CPK[w]	**X**					**X**					**X**			**X**				**X**	**X**		**X**	**X**		**X**	
Urinalysis[x]	**X**	**X**																						**X**	
Immunogen (ADA)[y]		**X**				**X**					**X**			**X**				**X**			**X**			**X**	
PK[z]		**See Table 6 for PK assessment timepoints and visit windows[w]**																							

Abbreviations: ADA = anti-drug antibodies; AE = adverse events; CPK = creatine phosphokinase; CT = computed tomography; D = day; Dem = demographics; DLT = dose limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; EOT = End of Treatment; EMD = Extramedullary disease, H = hour; IHC = immunohistochemistry, Immunogen = immunogenicity; LTFU = long-term follow-up; m = month; MRI = magnetic resonance imaging, N/A = not applicable; NGS = next generation sequencing; PK = pharmacokinetics; PT = prothrombin time; Q12W = every 12 weeks; SAE = serious adverse event; TSH = thyroid stimulating hormone.

Footnotes:

Please note – Additional tests and assessments may be performed any time at the discretion of the Investigator and results should be recorded in the source and eCRF, if applicable.

a. Screening assessments should be performed within 21 days before first administration of study drug, unless otherwise noted. Screening assessment of *CBFA2T3::GLIS2* fusion gene may be completed within 21 days before the first administration of study drug; see eligibility criteria and Section 6.10.4 for details. Screening bone marrow evaluations must be performed within 14 days of initiation of study drug. **EU subjects only**: Bone marrow samples collected at baseline will be stored at a central laboratory for future retrospective NGS testing at Foundation Medicine. Screening hematology and chemistry laboratories must be obtained within 14 days of initiation of study drug. FOLR1 expression at screening is not required for subjects to enroll in the study. C1D1 labs may be collected up to 48 hours prior to dosing and must still meet eligibility criteria, or subject will not be considered eligible until resolution to level that qualifies for eligibility.

b. Assessments which must occur on Cycle 1 Day 1 (C1D1) include treatment with luveltamab tazevibulin, hematology and chemistry labs, AE and concomitant medication assessment, physical exam, vital signs, Lansky performance, PK and ADA. C1D1 labs may be collected up to 36 hours prior to dosing and confirmed to meet eligibility requirements to qualify for treatment. All other required C1D1 assessments may be performed within 3 days before C1D1.

c. Please see Table 6 for PK collections as applicable. All other assessments can be collected any time during the day of the visit.

d. An EOT safety visit will occur at 30 (±7) days from the last dose of study drug and should be scheduled prior to starting a new therapy. All AEs that occur within 30 days of the last treatment dose should be recorded.

e. Luveltamab tazevibulin dosage will depend on the current dose and response to treatment. Both intra-subject and inter-subject dose level adjustments based on ongoing efficacy, safety, and PK data will be permitted.

f. Standard of care intrathecal cytarabine or Triple IT (methotrexate, hydrocortisone and cytarabine) may be administered at any point during the study for either prophylaxis or treatment of CNS leukemia.

g. Local bone marrow evaluation post-screening will be performed by both aspirate and biopsy to assess blast counts on Day 42 (± 3days) of each cycle. In addition to local evaluation, bone marrow samples and peripheral blood smears will be sent to a central laboratory for central review. Flow cytometry will be evaluated at a central laboratory. Subjects continuing monotherapy will have subsequent bone marrow evaluations at the conclusion of Cycle 4 (ie, C4D42) and Cycle 6 (ie, C6D42) and every other subsequent cycle, and at EOT. Additional tests may be performed at the Investigator's discretion. Samples will be analyzed for biomarkers related to AML, FOLR1, and *CBFA2T3::GLIS2*, please see Section 8.8 for biomarker testing. When bone marrow biopsies and ophthalmic exams occur on the same cycle, planned anesthesia for the bone marrow biopsies should be coordinated with the planned anesthesia for ophthalmic examinations (if required). Subjects who remain on study drug greater than 1 year may have bone marrow evaluations at the discretion of the treating physician, but not less than twice annually.

h. Immediate treatment decisions will be based on local assessment of bone marrow aspirate and biopsy morphology.

i. EMD evaluation: Subjects with marrow disease only and no clinical signs of extramedullary disease do not require imaging evaluation prior to enrollment or during the study. All subjects with suspected or confirmed EMD disease are required to have an imaging evaluation prior to initiation of therapy, on Day 42 (± 3days) of each cycle and at the conclusion of Cycle 4 and Cycle 6 and every other subsequent cycle and at EOT. Additional tests may be performed at the Investigator's discretion. All subjects will require a lumbar puncture at screening to test for CNS disease.

j. ICF can be signed ≤ 21 days prior to first dose. However, no study assessments may be performed until after the subject/parent/guardian has signed the ICF.

k. Signs and symptoms occurring between screening visit and first dose of luveltamab tazevibulin should be recorded as Medical History, unless they are a result of a screening procedure, then they will be recorded as an AE/SAE.

l. AEs and SAEs will only be reported for 30 days following the last dose of luveltamab tazevibulin. SAEs that occur > 30 days after the last dose of study drug will only be reported if assessed as related to study drug by the Investigator.

m. Height will be recorded at screening visit only. Weight will be recorded at each D1 visit for dosage calculations. Physical exams should include asking the parent/legal guardian if subject has experienced any ocular problems/discomfort have occurred and check for signs and symptoms of peripheral neuropathy. Symptom-directed physical exams will be done during the treatment phase (after C1D1) and at the EOT visit.

n. Ophthalmic exams must be performed by an ophthalmologist, optometrist, or other qualified professional at Screening, pre-dose Cycle 2 and 3 and every 2 cycles thereafter and at EOT. Additional tests may be performed at the Investigator's discretion. Anesthesia is not required for ophthalmic examinations, however, when bone marrow biopsies and ophthalmic exams occur on the same cycle, planned anesthesia for the bone marrow biopsies should be coordinated with the planned anesthesia for ophthalmic examinations (if required).

o. All subjects will require a lumbar puncture at Screening to test for CNS disease which must be performed within 14 days of initiation of study drug and will receive prophylaxis therapy for CNS disease at study entry. Subjects with CNS1 disease will not need to be evaluated again until EOT, unless they show clinical signs and symptoms. See Section 10.6 for CNS prophylaxis and therapy in subjects with CNS2 disease. Subjects with clinical signs of CNS leukemia that developed during luveltamab tazevibulin treatment will require lumbar puncture and imaging evaluation. CNS involvement will be evaluated any time a lumbar puncture is completed.

p. Vital signs should be collected prior to infusion of luveltamab tazevibulin.

q. ECG assessments will be performed in triplicate using the ECG machine provided by the site unless notified by the Sponsor to use central ECGs or in cases where the local ECG machine is not available and/or working. Corrected QTcF must be < 450 msec during screening and prior to C1D1 dose for subject to meet eligibility requirements. ECG should be performed prior to PK draw when able. Cycle 1 Day 2 and Cycle 1 Day 23 ECG collections must be completed within a ± 4-hour window.

r. Subjects who withdraw from the study will continue to be followed for overall survival.

s. Complete blood count (CBC) including hemoglobin, platelet count, white blood cells, and differential with absolute neutrophil count, and blast count. CBCs are obtained in Screening (≤ 14 days prior to first dose), pre-dose on dosing days and every week up to Cycle 3. Cycle 3 onwards, assessments should be collected, pre-dose on dosing days. Additional tests may be performed at the Investigator's discretion. Coagulation profile consisting of prothrombin time (INR), partial thromboplastin time, and fibrinogen will be collected pre-dose on Day 1 of Cycle 1 and at EOT and may be performed at the Investigator's discretion. A peripheral blood smear will also be collected on Day 42 which will be sent to a central laboratory for central review.

t. For serum chemistry labs please refer to Section 10.3, Table 18. Serum chemistry labs are obtained in screening (≤ 14 days prior to first dose), pre-dose on dosing days and every week up to Cycle 3. Cycle 3 onwards, assessments should be collected pre-dose on dosing days. Additional tests may be performed, per Investigator's discretion and results should be recorded in the source and eCRF. Labs for Tumor Lysis syndrome should be monitored per institutional guidelines.

u. Amylase, lipase, T3 and T4 are obtained in screening (≤ 21 days prior to first dose), and at EOT. Additional tests may be performed, per Investigator's discretion and results should be recorded in the source and eCRF.

v. TSH is obtained in Screening (≤ 21 days prior to first dose), and at EOT. TSH is obtained at Cycle 4 (pre-dose) and every 3 subsequent cycles. If TSH is abnormal at EOT, T3 and T4 should be repeated. Additional tests may be performed, per Investigator's discretion and results should be recorded in the source and eCRF.

w. CPK is obtained in Screening (≤ 21 days prior to first dose), pre dose on dosing days of each cycle beginning at C1D22 up to Cycle 3. Cycle 4 onwards, assessments should be collected every other cycle. Additional tests may be performed, per Investigator's discretion and results should be recorded in the source and eCRF.

x. Urinalysis is obtained in Screening (≤ 21 days prior to first dose), Day 1, and at end of treatment. Day 1 labs must qualify or subject will not be treated until resolution to level that qualifies for eligibility. Additional tests may be performed per Investigator's discretion and when available, results should be recorded in the source and eCRF.

y. Blood samples for ADA assessment will be obtained pre-dose, within 2 hours before luveltamab tazevibulin infusion, on Day 1 and Day 22 of Cycle 1 and 2, pre-dose on Day 1 of Cycles 3 through 5, and pre-dose on Day 1 every 6 months thereafter, and at the EOT visit following last dose of luveltamab tazevibulin. Blood samples for ADA analysis should be collected at the requested time.

z. PK samples will be analyzed by central laboratory as shown in Table 6. Cycle 1 Day 2 and Cycle 1 Day 23 PK collections must be completed within a ± 4-hour window. An aliquot of the PK sample may be allocated for biomarker analyses.

Table 3: Schedule of Assessments for Maintenance (q4w) Dosing Regimen

Cycles[a]		Cycles 1[a] and 2	Cycle 3 onwards		
Study Day in Dose/Cycle	S[b]	1[c]	1	EOT[d]	LTFU Q12W post EOT
Visit Window	≤ 21D C1D1	N/A	± 2D	± 7D	
Infusion of luveltamab tazevibulin[e]		X	X		
Prophylaxis for CNS disease[f]		X			
Response Assessments					
Bone marrow evaluation[b,g,h]	X				
EMD evaluation[i]	X				
General Assessments					
Concomitant medication/ procedures	X	X	X	X	
Adverse events[j]	X	X	X	X	X
Physical examination[k]	X	X	X	X	
Ophthalmic exam[l]	X	X	X	X	
Lumbar puncture[f]	≤ 14D C1D1	Lumbar puncture will be completed at the time of bone marrow evaluations as applicable[e,l]			
Vital signs[m]	X	X	X	X	
12-lead ECG[n]	X	X	X	X	
Lansky performance	X	X	X	X	
Survival status[o]					X
Laboratory Assessments					
Hematology[p]	X	X	X	X	
Serum chemistry[q]	X	X	X	X	
Immunogenicity (ADA)[r]		X	X	X	
PK[s]		X	X	X	

Abbreviations: ADA = anti-drug antibodies; AE = adverse events; D = day; ECG = electrocardiogram; eCRF = electronic case report form; EMD = extramedullary disease; EOT = End of Treatment; H = hour; IHC = immunohistochemistry, LTFU = long-term follow-up; m = month; PK = pharmacokinetics; Q12W = every 12 weeks; SAE = serious adverse event.

Footnotes:

Please note – Additional tests and assessments may be performed any time at the discretion of the Investigator and results should be recorded in the source and eCRF, if applicable.

a. The number of cycles restart after subjects begin maintenance treatment.

b. Subject will be required to qualify for maintenance therapy. Screening bone marrow evaluations must be performed within 14 days of initiation of study drug. Screening hematology and chemistry laboratories must be obtained within 14 days of initiation of study drug. FOLR1 expression at screening is not required for subjects to enroll in the study. C1D1 screening labs must still qualify, or subject will not be until resolution to level that qualifies for eligibility.

c. Assessments which must occur on Cycle 1 Day 1 (C1D1) include treatment with luveltamab tazevibulin, hematology and chemistry labs, AE and concomitant medication assessment, physical exam, vital signs, Lansky performance, PK and ADA. C1D1 labs may be collected up to 36 hours prior to dosing and confirmed to meet eligibility requirements to qualify for treatment. All other required C1D1 assessments may be performed within 3 days before C1D1.

d. An EOT safety visit will occur at 30 (±7) days from the last dose of study drug and should be scheduled prior to starting a new therapy. All AEs that occur within 30 days of the last treatment dose should be recorded.

e. Luveltamab tazevibulin will be administered on a q4w schedule at selected dose for up to 13 cycles (52 weeks). Dose and schedule modifications or extension of treatment duration beyond 13 cycles may be requested by the Investigator and will require discussion with the Sponsor and/or Steering and Safety committee (SSC).

f. Standard of care intrathecal cytarabine or Triple IT (methotrexate, hydrocortisone and cytarabine) may be administered at any point during maintenance treatment for either prophylaxis or treatment of CNS leukemia.

g. Local bone marrow evaluation post-screening will be performed by both aspirate and biopsy to assess blast counts every 12 weeks. In addition to local evaluation, bone marrow samples and peripheral blood smears will be sent to a central laboratory for central review. Flow cytometry will be evaluated at a central laboratory. Samples will be analyzed for biomarkers related to AML, FOLR1, and *CBFA2T3::GLIS2*, please see Section 8.8 for biomarker testing. Additional and more frequent tests may be performed at the Investigator's discretion, per local guidelines. When bone marrow biopsies and ophthalmic exams occur on the same cycle, planned anesthesia for the bone marrow biopsies should be coordinated with the planned anesthesia for ophthalmic examinations (if required).

h. Immediate treatment decisions will be based on local assessment of bone marrow aspirate and biopsy morphology.

i. EMD evaluation: All subjects with suspected or confirmed EMD disease are required to have an imaging evaluation prior to initiation of therapy, every 12 weeks and at EOT. Additional tests may be performed at the Investigator's discretion. All subjects will require a lumbar puncture at screening to test for CNS disease.

j. AEs and SAEs will only be reported for 30 days following the last dose of luveltamab tazevibulin. SAEs that occur > 30 days after the last dose of study drug will only be reported if assessed as related to study drug by the Investigator.

k. Weight will be recorded at each D1 visit for dosage calculations. Physical exams should include asking the parent/legal guardian if subject has experienced any ocular problems/discomfort have occurred and check for signs and symptoms of peripheral neuropathy. Symptom-directed physical exams will be done during the treatment phase (after C1D1) and at the EOT visit.

l. Ophthalmic exams must be performed by an ophthalmologist, optometrist, or other qualified professional at Cycle 1, and Cycle 3, then every 3 cycles after, and EOT. Additional tests may be performed at the Investigator's discretion. Anesthesia is not required for ophthalmic examinations, however, if anesthesia is needed, when bone marrow biopsies and ophthalmic exams occur on the same cycle, planned anesthesia for the bone marrow biopsies should be coordinated with the planned anesthesia for ophthalmic examinations (if required).

m. Vital signs should be collected prior to infusion of luveltamab tazevibulin.

n. All ECGs will be performed in triplicate using the ECG machine provided by the site unless notified by the Sponsor to use central ECGs or in cases where the local ECG machine is not available and/or working. Corrected QTcF must be < 450 msec during screening and prior to C1D1 dose for subject to meet eligibility requirements. ECG should be performed prior to PK draw when able**..**

o. Subjects who withdraw from the study will continue to be followed for overall survival.

p. Complete blood count (CBC) including hemoglobin, platelet count, white blood cells, and differential with absolute neutrophil count, and blast count. CBCs are obtained pre-dose on every cycle. Additional tests may be performed at the Investigator's discretion.

q. For serum chemistry labs please refer to Section 10.3, Table 18. Samples will be collected locally and pre-dose on every cycle. Additional tests may be performed, per Investigator's discretion and results should be recorded in the source and eCRF. Labs for Tumor Lysis syndrome should be monitored per institutional.

r. Blood samples for ADA assessment will be obtained pre-dose, within 2 hours before luveltamab tazevibulin infusion, on Day 1 of Cycle 1 and 2, pre-dose on Day 1 of Cycles 3 through 5, and pre-dose on Day 1 every 6 cycles (ie, every 6 months) thereafter, and at the EOT visit following last dose of luveltamab tazevibulin.. Blood samples for ADA analysis should be collected at the requested time.

s. PK samples will be analyzed by central laboratory as shown in Table 7. An aliquot of the PK sample may be allocated for biomarker analyses.

Table 4: Schedule of Assessments for Luveltamab Tazevibulin (4.2 mg/kg q4w) plus Standard of Care Dosing Regimen (Subjects Who do not Achieve a CR/CRh or Target Reduction in Leukemic Burden by Cycle 4)

Cycle	Cycle 1[a]	Cycle 2	Cycle ≥ 3		
Study Day in Dose/Cycle	1[b]	1	1	EOT[c]	LTFU Q12W post EOT
Visit Window	N/A		± 2D	± 7D	
Infusion of luveltamab tazevibulin[d]	X	X	X		
Standard of care chemotherapy[e]	X	X	X		
Prophylaxis for CNS disease[f]	X	X			
Response Assessments					
Bone marrow evaluation[g,h]	Evaluations will be performed in line with SOC chemotherapy regimen[g]				
EMD evaluation[h,i]	Evaluations will be performed in line with SOC chemotherapy regimen[g]				
General Assessments					
Concomitant medication/ procedures	X	X	X	X	
Adverse events[j]	X	X	X	X	X
Physical examination[k]	X	X	X	X	
Ophthalmic exam[l]	X		X	X	
Lumbar puncture[f,m]	X	Lumbar puncture will be completed at the time of bone marrow evaluations as applicable[e,l]			
Vital signs[n]	X	X	X	X	
12-lead ECG[o]	X	X	X	X	
Lansky performance	X	X	X	X	
Survival status[p]					X
Laboratory Assessments					
Hematology[q]	X	X	X	X	
Serum chemistry[r]	X	X	X	X	
Immunogenicity (ADA)[s]	X	X	X	X	

Abbreviations: ADA = anti-drug antibodies; AE = adverse events; D = day; ECG = electrocardiogram; eCRF = electronic case report form; EMD = extramedullary disease; EOT = End of Treatment; H = hour; IHC = immunohistochemistry, LTFU = long-term follow-up; m = month; PK = pharmacokinetics; Q12W = every 12 weeks; SAE = serious adverse event; SOC = standard of care.

Footnotes:

Please note – Additional tests and assessments may be performed any time at the discretion of the Investigator and results should be recorded in the source and eCRF, if applicable.

a. The number of cycles restart after subjects begin luveltamab tazevibulin treatment plus standard of care dosing regimen.

b. Assessments which must occur on Cycle 1 Day 1 (C1D1) include treatment with luveltamab tazevibulin, hematology and chemistry labs, AE and concomitant medication assessment, physical exam, vital signs, Lansky performance, PK and ADA. C1D1 labs may be collected up to 36 hours prior to dosing and confirmed to meet eligibility requirements to qualify for treatment. All other required C1D1 assessments may be performed within 3 days before C1D1.

c. An EOT safety visit will occur at 30 (±7) days from the last dose of study drug and should be scheduled prior to starting a new therapy. All AEs that occur within 30 days of the last treatment dose should be recorded.

d. Luveltamab tazevibulin in combination with standard of care backbone therapies will be administered on a q4w schedule of a 28-day cycle. Concomitant dosing of luveltamab tazevibulin and SOC backbone therapies is allowed. The starting dose and schedule will be 4.3 mg/kg IV q4w for up to 13 cycles (52 weeks). Dose and schedule modifications or extension of treatment duration beyond 13 cycles may be requested by the Investigator and will require discussion with the Sponsor and/or Steering and Safety committee (SSC).

e. Anytime a subject begins a new permutation of a chemotherapy regimen, assessment schedule must restart at Cycle 1. Standard of care backbone therapies could include the following:

   Regimen 1: luveltamab tazevibulin + fludarabine + intermediate dose cytarabine; 30 mg/m^2 IV over 30 minutes QD (Days 1 to 5); intermediate dose cytarabine 2000 mg/m^2 IV over 1 to 3 hours QD on Days 1 to 5, given 4 hours after the start of fludarabine; subjects can receive up to 2 cycles of fludarabine and intermediate dose cytarabine.

   Regimen 2: luveltamab tazevibulin + intermediate dose cytarabine; 2000 mg/m^2 IV over 1 to 3 hours QD on Days 1 to 5; subjects can receive up to 4 cycles of intermediate dose cytarabine.

   Regimen 3: luveltamab tazevibulin + azacytidine; subjects will be treated with either SC or IV azacytidine on Days 1 to 7 of a 28-day cycle. IV azacytidine will be infused over 1 hour. The number of azacytidine cycles administered is based on clinical benefit and Investigator discretion.

   Regimen 4: luveltamab tazevibulin + donor lymphocyte infusion (if subject has had a prior transplant) at a dose and schedule determined by the Investigator. The number of DLI cycles administered is based on clinical benefit and Investigator discretion.

f. Standard of care intrathecal (IT) MTX/cytarabine and hydrocortisone may be administered at any point during the study for either prophylaxis or treatment of CNS leukemia.

g. Local bone marrow evaluation will be performed by biopsy to assess blast counts every 12 weeks and if needed, in line with SOC (see footnote g below). Bone marrow evaluation on aspirates may also be performed. In addition to local evaluation, bone marrow samples and peripheral blood smears will be sent to a central laboratory for central review. Flow cytometry will be evaluated at a central laboratory. Samples will be analyzed for biomarkers related to AML, FOLR1, and *CBFA2T3::GLIS2*, please see Section 8.8 for biomarker testing. Additional and more frequent tests may be performed at the Investigator's discretion, per local guidelines. When bone marrow biopsies and ophthalmic exams occur on the same cycle, planned anesthesia for the bone marrow biopsies should be coordinated with the planned anesthesia for ophthalmic examinations (if required).

h. Bone marrow/EMD evaluations to be done at completion of each cycle of intermediate dose chemotherapy (fludarabine + intermediate dose cytarabine or intermediate dose cytarabine) and if subject switches from 1 intermediate dose regimen to another intermediate dose regimen or switches to azacytidine regimen or receives DLI. For subjects receiving azacytidine or DLI, evaluation every 12 weeks is required. A peripheral blood smear will also be collected anytime a bone marrow evaluation is performed and will be sent to a central laboratory for central review.

i. EMD evaluation: All subjects with suspected or confirmed EMD disease are required to have an imaging evaluation prior to initiation of therapy, and in line with SOC chemotherapy regimens, and at EOT. Additional tests may be performed at the Investigator's discretion.

j. AEs and SAEs will only be reported for 30 days following the last dose of luveltamab tazevibulin. SAEs that occur > 30 days after the last dose of study drug will only be reported if assessed as related to study drug by the Investigator.

k. Weight will be recorded at each D1 visit for dosage calculations. Physical exams should include asking the parent/legal guardian if the subject has experienced any ocular problems/discomfort have occurred and check for signs and symptoms of peripheral neuropathy. Symptom-directed physical exams will be done during the treatment phase (after C1D1) and at the EOT visit.

l. Ophthalmic exams must be performed by an ophthalmologist, optometrist, or other qualified professional at Cycle 1, and Cycle 3, then every 3 cycles after, and EOT. Additional tests may be performed at the Investigator's discretion. Anesthesia is not required for ophthalmic examinations, however, if anesthesia is needed, when bone marrow biopsies and ophthalmic exams occur on the same cycle, planned anesthesia for the bone marrow biopsies should be coordinated with the planned anesthesia for ophthalmic examinations (if required).

m. Lumbar puncture in subjects receiving luveltamab tazevibulin in combination with SOC chemotherapy is at the discretion of the Investigator.

n. Vital signs should be collected prior to infusion of luveltamab tazevibulin.

o. All ECGs will be done in triplicate using the ECG machine provided by the site unless notified by the Sponsor to use central ECGs or in cases where the local ECG machine is not available and/or working. Corrected QTcF must be < 450 msec during screening and prior to C1D1 dose for subject to meet eligibility requirements. ECG should be performed prior to PK draw when able and if applicable.

p. Subjects who withdraw from the study will continue to be followed for overall survival.

q. Complete blood count (CBC) including hemoglobin, platelet count, white blood cells, and differential with absolute neutrophil count, and blast count. CBCs are obtained pre-dose on every cycle. Additional tests may be performed at the Investigator's discretion.

r. For serum chemistry labs please refer to Section 10.3, Table 18. Samples will be collected locally and pre-dose on every cycle. Additional tests may be performed, per Investigator's discretion and results should be recorded in the source and eCRF. Labs for Tumor Lysis syndrome should be monitored per institutional guidelines.

s. Blood samples for ADA assessment will be obtained pre-dose, within 2 hours before luveltamab tazevibulin infusion, on Day 1 of Cycle 1 and 2, pre-dose on Day 1 of Cycles 3 through 5, and pre-dose on Day 1 every 6 cycles (ie, every 6 months) thereafter, and at the EOT visit following last dose of luveltamab tazevibulin. Blood samples for ADA analysis should be collected at the requested time.

Table 5: Luveltamab Tazevibulin Pharmacokinetic Collection Schedule for q2w

Study Day	**Pharmacokinetic Timepoints[a,b,d]**
Cycle 1[c]	
Day 1	Predose (-1 hour)
	5 to 10 minutes after end of infusion (EOI)
Day 2	24 hours (± 4 hr) after EOI
Day 8	Anytime[e]
Day 15	Predose (-1 hour)
	5 to 10 minutes after EOI
Day 16	24 hours (± 4 hr) after EOI
Day 22	Anytime[e]
Cycle 2 onwards	
Day 1	Predose (-1 hour)
	5 to 10 minutes after EOI
Day 15	Predose (-1 hour)
	5 to 10 minutes after EOI
End of Treatment	Anytime[e]

a. Pharmacokinetic analysis will be performed by the central laboratory. An aliquot of the PK sample may be allocated for biomarker analyses.

b. Table 5 is only for the PK assessments for q2w dosing schedule and does not apply to maintenance therapy.

c. Cycle 1 pharmacokinetic timepoints apply to the first cycle with a modified dose, including initiation of combination therapy.

d. In case of an overdose, an unscheduled plasma sample would be collected for PK analysis as scheduled or within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

e. Collection can occur any time on the day of visit.

Table 6: Luveltamab Tazevibulin Pharmacokinetic Collection Schedule for q3w

Study Day	**Pharmacokinetic Timepoints[a,c]**
Cycle 1[b]	**-**
Day 1	Predose (-1 hour)
	5 to 10 minutes after end of infusion (EOI)
Day 2	24 hours (± 4 hr) after EOI
Day 8	Anytime[d]
Day 15	Anytime[d]
Day 22	Predose (-1 hour)
	5 to 10 minutes after EOI
Day 23	24 hours (± 4 hr) after EOI
Day 29	Anytime[d]
Cycle 2 onwards	
Day 1	Predose (-1 hour)
	5 to 10 minutes after EOI
Day 22	Predose (-1 hour)
	5 to 10 minutes after EOI
End of Treatment	Anytime[d]

a. Pharmacokinetic analysis will be performed by the central laboratory. An aliquot of the PK sample may be allocated for biomarker analyses.

b. Cycle 1 pharmacokinetic time points apply to the first cycle with a modified dose, including initiation of combination therapy.

c. In case of an overdose, an unscheduled plasma sample would be collected for PK analysis as scheduled or within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

d. Collection can occur any time on the day of visit.

Table 7: Luveltamab Tazevibulin Pharmacokinetic Collection Schedule for Q4W Maintenance Dosing Only

Study Day	**Pharmacokinetic Timepoints[a,b,c]**
Cycles 1 and 2	
Day 1	Predose (-1 hour)
	5 min (± 2 min) at end of infusion
Cycles 3 through 5	
Day 1	Predose (-1 hour)
Every Odd Cycle (eg, 7, 9, etc.)	
Day 1	Predose (-1 hour)
End of Treatment	Anytime[d]

a. Pharmacokinetic analysis will be performed by the central laboratory. An aliquot of the PK sample may be allocated for biomarker analyses.

b. Cycle 1 pharmacokinetic timepoints apply to the first cycle with a modified dose, including initiation of combination therapy.

c. In case of an overdose, an unscheduled plasma sample would be collected for PK analysis as scheduled or within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

d. Collection can occur any time on the day of visit.

2.0 INTRODUCTION

2.1 Study Rationale

Pediatric acute myeloid leukemia (AML) with *core binding factor (CBF)A2T3::GLI-similar protein 2 (GLIS2)* is an ultrarare, serious and life-threatening disease with poor outcomes to standard of care (SOC) and no effective alternative treatment options. The recent discovery that folate receptor alpha (FOLR1 also referred to as FolRα) was uniquely expressed in *CBFA2T3::GLIS2* AML provides the potential to develop and study therapeutics that specifically recognize this target. Due to the dismal prognosis, US physicians have requested access to luveltamab tazevibulin through expanded access to evaluate subjects with the *CBFA2T3::GLIS2* fusion under single-subject Investigational New Drug (INDs) Applications. Data from these subjects has demonstrated encouraging preliminary efficacy with monotherapy treatment with luveltamab tazevibulin, which warrants further investigation in a clinical trial setting. This study will investigate the efficacy, safety, and PK of luveltamab tazevibulin in children with *CBFA2T3::GLIS2* AML.

2.2 Background

2.2.1 Folate Receptor Alpha (FOLR1; FolRα)

FOLR1 is a glycosylphosphatidylinositol linked cell-surface glycoprotein that has high affinity for folates. Its physiologic role in normal and cancerous tissues has not yet been fully elucidated,

although it is believed to support the increased requirement for folate to maintain DNA synthesis in rapidly dividing cancer cells. High levels of FOLR1 have been found in multiple cancer types including epithelial ovarian cancer, endometrial adenocarcinoma, mesothelioma, non-small cell lung cancer, and triple-negative breast cancer (Cheung et al, 2016; Scaranti et al, 2020). In normal tissue, the highest FOLR1 expression is detected in the plasma membranes of epithelial cells of fallopian tube (mucosa), kidney (tubules), and placenta (villous and extravillous trophoblasts), and in the cytoplasm of multiple tissues and in the extracellular compartment of select tissues (Cheung et al, 2016).

FOLR1 expression has recently been identified in a rare, serious and life-threatening pediatric AML which harbors the *CBFA2T3::GLIS2* fusion gene. Presence of the *CBFA2T3::GLIS2* fusion gene, leads to up-regulation of FOLR1 in leukemic cells making it a promising therapeutic candidate for luveltamab tazevibulin (Le et al, 2022; Tang et al, 2022; Le et al, 2021).

2.2.2 Luveltamab Tazevibulin Mechanism of Action

Luveltamab tazevibulin is a novel, antibody-drug conjugate (ADC) targeting FOLR1. Luveltamab tazevibulin is comprised of a humanized aglycosylated IgG1 antibody (SP8166) conjugated with a cleavable 3-aminophenyl hemiasterlin drug-linker (SC239) at 4 specific sites. The antibody is conjugated covalently with the drug linker at the non-natural amino acid *para*-azidomethyl-L-phenylalanine residue at positions 180 and 404 on the heavy chains. The resultant ADC, luveltamab tazevibulin, is well-defined with a predominant species having a drug-to-antibody ratio of 4. Previous studies have shown that luveltamab tazevibulin binding to FOLR1 results in internalization of the complex and subsequent cleavage of SC239, releasing the active tubulin-targeting 3-aminophenyl hemiasterlin warhead, SC209, which targets microtubules and inhibits mitosis, resulting in potent cytotoxic activity.

Notably luveltamab tazevibulin can induce immunogenic cell death, as shown when FOLR1-positive KB cells and FOLR1 very low A549 cells were incubated with naked antibody (SP8166), luveltamab tazevibulin, control ADC (anti-GFP-SC239), or SC209 for 3 days and changes in immunogenic cell death markers (calreticulin expression, adenosine triphosphate [ATP] and high mobility group box 1 [HMGB1] release) were assessed.

SC209 induced calreticulin expression on all 3 cells tested, while the control anti-GFP-SC239 ADC or the unconjugated antibody (SP8166) did not. Luveltamab tazevibulin induced calreticulin expression only on FOLR1-positive KB cells, but not on FOLR1 very low A549 cells, which indicated that this effect was dependent on FOLR1 expression on the cell surface. A similar effect was observed for other immunogenic cell death markers such as ATP and HMBG1 release.

A possible consequence of its ability of triggering immunogeneic cell death, may be that luveltamab tazevibulin is synergistic when used with checkpoint inhibitors. In vivo studies were conducted in the immune-competent MC38 tumor model that was engineered to express

hFOLR1 to evaluate the single agent and combination efficacy of luveltamab tazevibulin with the anti-programmed death-ligand 1(PD-L1) checkpoint inhibitor avelumab (Bavencio®). Avelumab (Bavencio®) is a humanized anti-PD-L1 monoclonal IgG1 antibody that acts by blocking PD-L1 on the surface of certain immune cells thereby restoring anti-tumor immune responses and thus inhibiting tumor growth.

Animals bearing established MC38-hFOLR1 tumors were treated with luveltamab tazevibulin, various doses of avelumab (5 to 20 mg/kg, intraperitoneal; single or q3d × 3) and the combination of both. Luveltamab tazevibulin in combination with all doses of avelumab markedly enhanced anti-tumor activity as evidenced by tumor regression and prolonged median survival compared to single agents alone. Furthermore, combination treatment demonstrated curative effects or complete remission (eg, no palpable tumors) based on significantly prolonged survival of healthy animals with normal body weight gain and no tumor re-growth in approximately 50% of animals (within each combination treatment group) for up to 95 days post-treatment which is > 2-fold longer median survival than single agents.

Figure 2: Mechanism of Action of Luveltamab Tazevibulin

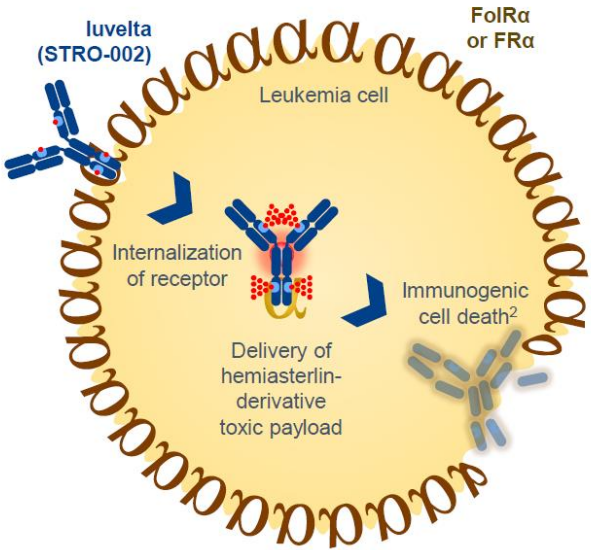


Figure Legend: Luveltamab tazevibulin is an antibody drug conjugate-targeting FOLR1 which was designed using site-specific conjugation and a cell-free synthesis platform to induce cytotoxic and immunogenic cell death. The antibody portion of the drug recognizes folate receptor alpha (FOLR1) on the cell surface and delivers the hemiasterilin payload into the leukemia cell.

2.2.3 Luveltamab Tazevibulin Nonclinical Studies

In vitro and in vivo toxicology studies included cross-reactivity with human tissues, single-dose, and repeat-dose toxicokinetic studies of luveltamab tazevibulin have been performed to characterize the nonclinical safety.

No luveltamab tazevibulin-related morbidity was noted during the dosing phase and all animals survived to their scheduled interim and recovery (4 weeks) sacrifices for anatomic pathology evaluation. The main toxicity findings consisted of dose-related, minimal to marked, and cyclical neutropenia (without bone marrow histopathology correlates); and minimal to mild lymphoid tissue hypocellularity. These findings were reversible or showed evidence of reversibility and were considered antigen-independent (attributed to the anti-proliferative effects of the 3-aminophenyl hemiasterlin component of luveltamab tazevibulin). More information can be found in the Investigator's Brochure.

2.2.4 Luveltamab Tazevibulin Clinical Studies in Adults with Ovarian Cancer

2.2.4.1 Luveltamab Tazevibulin Monotherapy Clinical Study: STRO-002-GM1

STRO-002-GM1 is a first-in-human Phase 1, open-label, multicenter, dose escalation study with a modified 3 + 3 design followed by dose expansion with 4 dose expansion cohorts. The study is designed to assess the safety, establish a recommended Phase 2 dose, and assess preliminary efficacy for luveltamab tazevibulin as a single agent in subjects with advanced epithelial ovarian cancer or endometrial cancer. The population for dose escalation and the ovarian cancer dose expansion cohorts are subjects with relapsed/refractory ovarian cancer. The population for the second dose expansion cohort (endometrial cancer dose expansion cohort) is relapsed/refractory endometrial cancer.

The dose escalation phase of STRO 002-GM1 completed enrollment and has evaluated a total of 9 dose levels (0.5 to 6.4 mg/kg). A dose limiting toxicity (DLT) of bone pain (Grade 3) was observed in the first subject dosed at 6.4 mg/kg. Luveltamab tazevibulin doses between 0.5 to 6.0 mg/kg were administered IV q3w, as single agent. A maximum tolerated dose was not found during dose escalation, and while DLTs were not commonly observed in the 6.0 mg/kg cohort, dose reductions were frequent and therefore further exploration focused on lower dose levels. Clinical activity was observed at doses from 2.9 to 6.0 mg/kg.

In the ovarian cancer dose expansion cohorts of STRO-002-GM1, subjects have received 3.5, 4.3, or 5.2 mg/kg q3w doses of luveltamab tazevibulin. A higher response rate and earlier onset of response was observed at the 5.2 mg/kg dose compared to the 4.3 mg/kg dose. Additionally, the safety profile of luveltamab tazevibulin was manageable (Oaknin et al, 2023).

2.2.4.2 Pharmacokinetics, Pharmacodynamics, and Exposure in Adults: STRO-002-GM1

An interim PK analysis of dose and plasma concentration-time data (total ADC, total antibody [TAb] and SC209) from the STRO-002-GM1 study as of 12 Jul 2022 were available for Cycle 1 dosing in 86 subjects, for Cycle 2 in 35 subjects, and for Cycle 4 in 51 subjects.

After IV administration of luveltamab tazevibulin, maximum plasma concentrations of ADC and TAb were achieved within 1 hour of the end of infusion. Peak concentrations of SC209 occurred at a median time of 16 to 24 hours after the start of infusion. Concentrations of all analytes

declined in a biphasic pattern exhibiting a log linear terminal phase, with ADC and TAb terminal $t_{1/2}$ ranging from 50 to 60 hours.

2.2.4.3 Luveltamab Tazevibulin Safety Analysis in Adults: STRO-002-GM1

As of 08 Nov 2022, treatment-emergent adverse events (TEAEs) reported at an incidence of ≥ 25% in adults with ovarian and endometrial cancer (STRO-002-GM1), included neutropenia (66.4%), nausea (64.5%), fatigue (59.1%), arthralgia (53.6%), constipation (48.2%), decreased appetite (45.5%), neuropathy (40.9%), abdominal pain (39.1%), anemia (38.2%), aspartate aminotransferase (AST) increased (36.4%), vomiting (31.8%), diarrhea (28.2%), alanine aminotransferase (ALT) increased (27.3%), platelet count decreased (27.3%), pyrexia (25.5%), and myalgia (25.5%).

In STRO-002-GM1, ≥ Grade 3 TEAEs in ≥ 10% of subjects at luveltamab tazevibulin doses of 4.3 mg/kg included neutropenia (67.6%), white blood cell (WBC) count decreased (21.6%), arthralgia (21.6%), fatigue (13.5%), and hyponatremia (13.5%). At the 5.2 mg/kg dose, ≥ Grade 3 TEAEs (≥ 10%) included neutropenia (56.9%), anemia (17.6%), and WBC count decreased (15.7%).

The most common adverse events (AEs) of interest identified for luveltamab tazevibulin were neutropenia, peripheral neuropathy, ocular AEs, and interstitial pneumonitis. Neutropenia was the most frequently observed TEAE leading to a dose reduction and most frequently observed TEAE (66.4%) in STRO-002-GM1. Peripheral neuropathy was the second most frequent AE leading to a dose delay or dose reduction and was also frequently observed (40.9%). Ocular AEs and pneumonitis are of interest because they are a reported class effect of other FOLR1-targeting ADCs. However, these were not frequently observed with STRO-002 in subjects with gynecologic malignancies.

Clinical data are being collected on STR0-002 anti-drug antibody (ADA) in STRO-002-GM1. Blood specimens were collected per protocol for determination of ADA at pre-dose and scheduled times post-dose during the study. As of 03 Jul 2023, 41 out of 123 subjects had at least one positive post-dose ADA titer. To date, it could not be determined whether the observation of ADA positivity affected the luveltamab tazevibulin concentration-time profile, as too few subjects were positive in Cycle 1 or 2, when PK analysis was conducted. Addition of later PK time assessments were added to the STRO 002 GM1 study (Cycle 4 instead of Cycle 2), in order to further quantify potential luveltamab tazevibulin ADA development and assess any effect on drug exposure. Further assessments are being conducted in the luveltamab tazevibulin clinical studies.

2.2.4.4 Luveltamab Tazevibulin Clinical Study as Combination Therapy: STRO-002-GM2

STRO-002-GM2 is a Phase 1, open-label, multicenter, dose escalation/de-escalation study with a standard 3 + 3 design followed by dose expansion. The study is designed to assess the safety,

establish recommended Phase 2 dose, and assess preliminary efficacy for luveltamab tazevibulin combined with bevacizumab in subjects with advanced ovarian cancer that is refractory or has relapsed after standard available therapy. The dose levels of luveltamab tazevibulin for dose escalation are 3.5, 4.3, and 5.2 mg/kg. As of 08 Nov 2022, 8 subjects have been treated with luveltamab tazevibulin combined with bevacizumab. A total of 87.5% of subjects experienced at least 1 TEAE. TEAEs ≥ Grade 3 were experienced by 37.5% of subjects. TEAEs leading to dose delay in both luveltamab tazevibulin and bevacizumab were neutropenia, abdominal pain, and enterocolitis infectious. Serious adverse events (SAEs) were reported for 3 subjects and included abdominal pain, gastrointestinal hemorrhage, vomiting, enterocolitis infectious, and hyponatremia.

2.2.5 Disease Background, Non-clinical Efficacy and Clinical Experience in Pediatric Children with *CBFA2T3::GLIS2* AML

2.2.5.1 Etiology of *CBFA2T3::GLIS2*AML

Pediatric *CBFA2T3::GLIS2* AML is a subtype of AML containing a cryptic inversion on chromosome 16 inv(16)(p13.3q24.3) encoding the *CBFA2T3::GLIS2* oncogenic fusion (Gruber et al, 2012; Thollier et al, 2012). This fusion was first identified in non-Down Syndrome (non-DS) acute megakaryoblastic leukemia (AMKL) subjects; a subtype of AML characterized by abnormal megakaryocyte expression of platelet-specific surface glycoproteins and found to affect approximately 30% of children with non-DS AMKL (Gruber et al, 2012; Thollier et al, 2012). Globally, the *CBFA2T3-GLIS2* rearrangement was detected in 20 of 237 cases (8.4%) with CN-AML; and of those 20 patients, 10 belonged to the M7 French-American-British subgroup (Masetti et al, 2013). AMKL in non-DS patients have often been associated with a poor prognosis, while children with Down syndrome AMKL show a favorable outcome.

Leukemias with the *CBFA2T3::GLIS2* fusion are associated with unique cell surface expression referred to as the RAM phenotype, which is identified by bright CD56 expression, dim to negative CD45, dim to negative CD38, and negative HLA-DR (MHC class II cell surface receptor encoded by the human leukocyte antigen complex on chromosome 6 region 6p21.31) and was identified from RNA collected from subjects with de novo AML (Smith et al, 2020). A study conducted by the Children's Oncology Group (COG Trial AAML0531) examined the differences among newly diagnosed subjects with de novo AML (N = 769) and identified a total of 10 subjects with the RAM immunophenotype who also carried the *CBFA2T3::GLIS2* gene fusion (Pardo et al, 2020). Additionally, in a retrospective study examining 19 subjects diagnosed with non-Down Syndrome-AMKL, there was a clear statistical correlation between RAM-phenotype and *CBFA2T3::GLIS2* fusions (Wongworawat et al, 2023).

2.2.5.2 Clinical Characteristics of *CBFA2T3::GLIS2* AML

Special features of subjects with the *CBFA2T3::GLIS2* fusion include the following: nearly all subjects are diagnosed at ≤ 5 years of age, it is characterized by a propensity for developing extramedullary disease (EMD), and the blast cells are strongly positive for CD56 and negative

for HLA-DR, CD45 and CD38, indicative of a RAM immunophenotype (Le et al, 2021). In children with the *CBFA2T3::GLIS2* fusion gene the median age is 1.5 years (Smith et al, 2020) and the 5-year event-free survival (EFS) is 8% (de Rooij et al, 2017). There are no approved therapies specifically targeting *CBFA2T3::GLIS2* AML.

The frequency of *CBFA2T3::GLIS2* fusion in pediatric subjects with AML is approximately 1.9% (39 of 2027 cases) (Smith et al, 2020). This fusion has never been found in adult subjects with AML (Gruber et al, 2012; Thollier et al, 2012; de Rooij et al, 2017).

Data from subjects with the *CBFA2T3::GLIS2* fusion (N = 16) demonstrate that they represent a particularly high-risk poor prognostic subgroup of children with AML with a significantly inferior overall survival (OS) despite maximally intensive induction treatment following diagnosis, and no effective alternative treatment options (de Rooij et al, 2017).

The 2-year survival rate after subjects are first diagnosed is only 14% for subjects with *CBFA2T3::GLIS2* AML when treated with currently available treatments. This is the worst outcome of any molecularly defined subgroup of pediatric AML. Additionally, the cumulative incidence of relapse or non-response is 86% and the median survival for these subjects is less than 10 months. Please also note that the EFS plateau is 8% which means the salvage complete remission (CR) rate to available therapies is 6/92 or 6.5% (de Rooij et al, 2017).

2.2.5.3 FOLR1 Expression in *CBFA2T3::GLIS2* and Non-clinical Efficacy Studies

Luveltamab tazevibulin is distinct from other AML therapies in that luveltamab tazevibulin specifically targets the FOLR1 receptor. Interrogation of the transcriptome from subject samples of more than 2000 AML cases, including 38 cases of *CBFA2T3::GLIS2*, demonstrated that the FOLR1 transcript was uniquely expressed in *CBFA2T3::GLIS2* AML but silent in most other types of AML, normal CD34+ cells, and bone marrow samples (Tang et al, 2022).

FOLR1 is expressed exclusively in blast cells from children with AML that carry the *CBFA2T3::GLIS2* fusion gene and is not expressed in other pediatric subtypes or adult AML. FOLR1 expression is absent in normal hematopoietic cell populations; and, in studies where the *CBFA2T3::GLIS2* fusion gene was transduced into CD34 cells (a marker for hematopoietic pluripotent stem cells [HPSCs]), FOLR1 expression increased over time. This suggests that FOLR1 is upregulated in the presence of the *CBFA2T3::GLIS2* gene (Tang et al, 2022; Le et al, 2021).

Luveltamab tazevibulin specificity and activity was evaluated in an MV4;11 AML cell line engineered to express FOLR1 (MV4;11 FOLR1+) and *CBFA2T3::GLIS2*-transduced cord blood (CB) HPSCs. Luveltamab tazevibulin exhibited high cytotoxicity against MV4;11 FOLR1+ and *CBFA2T3::GLIS2*-transduced CB HPSCs with IC_{50} of 0.1 and 4.2 nM, respectively with no cytotoxic effects on cells that did not express FOLR1 (Tang et al, 2022; Le et al, 2021). These studies demonstrate that luveltamab tazevibulin has potent cytotoxic effects at sub-nanomolar

concentrations on MV4;11 expressing FOLR1 and *CBFA2T3::GLIS2*-transduced CB HPSCs with no cytotoxic effects on cells that do not express FOLR1.

In vivo efficacy of luveltamab tazevibulin was then evaluated in MV4;11 FOLR1+ NSG xenograft models which showed potent activity leading to complete leukemia clearance after 3 weekly doses of luveltamab tazevibulin at 2.5 and 5 mg/kg. At Day 120, 75% of the tumor burden remained and at 5.0 mg/kg the tumor burden was undetectable. The anti-leukemia effects resulted in a significant increase in survival ($p = 0.002$) (Le et al, 2021). These studies demonstrate FOLR1 provides a molecular target for eradicating *CBFA2T3::GLIS2*-positive AML cells. Thus, luveltamab tazevibulin, a FOLR1-targeting ADC, may potentially provide a promising treatment option and improving outcomes in this high-risk AML subtype.

2.2.5.4 Treatment Options for *CBFA2T3::GLIS2* AML

Currently there are no approved therapies specifically targeting *CBFA2T3::GLIS2* AML. Children with the *CBFA2T3::GLIS2* fusion are treated with standard AML combination treatments of several toxic chemotherapies and eventually enrolled in clinical trials. In the rare instance where these children are not enrolled on a clinical trial, they are usually treated with regimens that have been tested in prior Children's Oncology Group (COG) studies. These combinations include but are not limited to cytarabine in combination with anthracyclines including daunorubicin, idarubicin, or mitoxantrone, etoposide, and asparaginase. The CD33-targeted ADC, gemtuzumab ozogamicin, may be added to some of these induction regimens. Depending on other molecular characteristics (such as gene mutations or deregulated gene expression), flt-3 inhibitors such as midostaurin, sorafenib, or gliteritinib may be added. However, additional molecular abnormalities have not been observed in CBFA2T3::GLIS2 AML. Consolidation and intensification therapy are adjusted based on risk group.

CBFA2T3::GLIS2 AML is an extremely high-risk subtype and current therapies are not adequate. The primary goal for subjects with *CBFA2T3::GLIS2* AML following relapse is to treat these subjects so they are able to bridge to a successful allogeneic HSC transplant; however, existing treatment options have been unsuccessful in meeting this goal.

At this time, there are no target-directed therapeutics for *CBFA2T3::GLIS2* AML. Among adult and pediatric AML subtypes, upregulation of FOLR1 is unique to this small population of pediatric AML, making luveltamab tazevibulin a potential therapeutic option for *CBFA2T3::GLIS2* AML. Based on the high frequency of induction failure/primary refractory disease and increased incidence of relapse in subjects with *CBFA2T3::GLIS2* AML, there exists an unmet medical need for this ultrarare unique AML population.

2.2.6 Summary of Luveltamab Tazevibulin Expanded Access Program Safety for Subjects with the *CBFA2T3::GLIS2* AML

2.2.6.1 Treatment-emergent Adverse Events in EA Subjects with *CBFA2T3::GLIS2* AML

The TEAEs reported for 25 subjects with AML with the *CBFA2T3::GLIS2* fusion who received luveltamab tazevibulin as a part of single subject IND EA experience collected from a retrospective review of available source documents are summarized below.

Fractionated dosing (1 to 1.4 mg/kg IV given on Days 1, 3, and 7) was used for 4 subjects early in the EA experience. Fractionated dosing was found to provide insufficient control of leukemic blasts and this dosing regimen was discontinued. For the remaining 21 subjects, luveltamab tazevibulin was administered at the 4.3 mg/kg (q2w, q3w, q4w) or 5.2 mg/kg (q2w) dose level as monotherapy, monotherapy (initial dose) followed by luveltamab tazevibulin in combination with standard AML chemotherapy treatment (subsequent doses), or given concomitantly with standard AML chemotherapy treatment (initial and subsequent doses). Combination therapies with standard AML treatment included methotrexate (MTX), fludarabine and cytarabine (AraC), venetoclax, azacytidine, decitabine, dasatinib, and plerixafor.

TEAEs were reported for 11 of 11 (100%) subjects treated with luveltamab tazevibulin monotherapy at 4.3 mg/kg. TEAEs reported at an incidence of ≥ 25% in subjects treated with luveltamab tazevibulin monotherapy at 4.3 mg/kg were anticipated in this population, and included neutrophil count decreased, anemia, platelet count decreased, WBC count decreased, pyrexia, vomiting, and AST increased. TEAEs were reported for 5 of 6 (83%) subjects treated with luveltamab tazevibulin monotherapy at 5.2 mg/kg. TEAEs reported at an incidence of ≥ 25% in subjects treated with luveltamab tazevibulin monotherapy at 5.2 mg/kg were similar to those reported for subjects receiving luveltamab tazevibulin monotherapy at 4.3 mg/kg, and included neutrophil count decreased, lymphocyte count decreased, anemia, platelet count decreased, AST increased, and blood thyroid stimulating hormone increased. The safety profile observed for luveltamab tazevibulin administered at 4.3 and 5.2 mg/kg monotherapy was considered acceptable.

TEAEs were reported for 10 of 13 (77%) subjects treated with luveltamab tazevibulin in combination with standard AML treatment. TEAEs reported at an incidence of ≥ 25% in subjects treated with luveltamab tazevibulin in combination with standard AML treatment chemotherapy were also anticipated in this population, and included neutrophil count decreased, platelet count decreased, WBC count decreased, AST increased, and ALT increased.

2.2.6.2 Grade 3+ Treatment-Emergent Adverse Events in EA Subjects with *CBFA2T3::GLIS2* AML

TEAEs ≥ Grade 3 were reported for 22 of 25 (88%) subjects treated with luveltamab tazevibulin as monotherapy or in combination with a standard AML treatment. TEAEs (≥ Grade 3) reported at an incidence of ≥ 25% were anticipated in this population and included neutrophil count

decreased, platelet count decreased, WBC count decreased, and anemia. The most common ≥ Grade 3 TEAE was neutrophil count decreased (56%).

2.2.6.3 Serious Adverse Events in EA Subjects with *CBFA2T3::GLIS2* AML

A total of 10 out of 25 (40%) subjects treated with luveltamab tazevibulin experienced SAEs. The most common SAEs occurring in 2 or more subjects were febrile neutropenia and bacteremia.

2.3 Benefit/Risk Assessment

As of 08 Nov 2022, clinical trial experience on 118 adult subjects with ovarian or endometrial cancer exposed to doses of luveltamab tazevibulin ranging from 0.5 to 6.4 mg/kg administered IV q3w is available. The adult clinical trial experience provides a context in which to consider initial clinical trial investigations in pediatric subjects (Sections 2.2.4.1 to 2.2.4.4). This is further supplemented by data reported by treating Investigators in the single subject IND EA experience which is detailed in Section 2.2.6.

To date, the benefit-risk profile of luveltamab tazevibulin has been favorable and supports further investigation of the safety and efficacy in subjects with *CBFA2T3::GLIS2* AML.

2.3.1 Risk Assessment

The Sponsor has assessed potential and identified risks for subjects with luveltamab tazevibulin based on the results from nonclinical studies, published clinical data of other ADCs for assessment of potential class effects, and the emerging safety data from 2 studies. In STRO-002-GM1 luveltamab tazevibulin was given as a single agent to subjects with advanced relapsed/refractory ovarian cancer or endometrial cancer. In STRO-002-GM2, luveltamab tazevibulin was given in combination with bevacizumab to subjects with advanced ovarian cancer.

Important identified risks characterized for luveltamab tazevibulin include neutropenia, neuropathy, arthralgia, and vomiting. Important potential risks characterized for luveltamab tazevibulin include ocular events, infusion-related reactions, and ADA formation mediated infusion-related reactions and/or increased systemic AEs due to potential neutralization of the targeting moiety of the ADC.

Potential risks associated with the procedures performed in this study include blood collection for standard blood tests, PK, and ADA analyses and for lumbar puncture. Blood samples may be performed from a vein or central line. These collections may include pain and in rare instances, infection. Lumbar puncture may cause headache, pain, and in rare cases, infection. This risk will be mitigated by careful observation of the subject during and following blood collections.

Details of recommended safety monitoring and AE management for specific AEs are provided in Table 8. Additionally, safety data from STRO-002-GM1 and STRO-002-GM2 are provided in Section 2.3.1.3 and, also in the luveltamab tazevibulin IB.

2.3.1.1 Potential Class Effects and Luveltamab Tazevibulin Safety

As presented in Table 8, AEs associated with ADCs similar to luveltamab tazevibulin (eg, FOLR1-targeting and/or tubulin-inhibitor payload) include neutropenia, ocular events, immunogenicity, infusion reactions, peripheral neuropathy, photosensitivity, thrombocytopenia, AST elevation, and ALT elevation. The FOLR1 targeting ADC, mirvetuximab, has primarily shown ocular AEs, pneumonitis, and peripheral neuropathy (Elahere™ USPI, 2022).

2.3.1.2 Reproductive Toxicity

Reproductive and developmental nonclinical toxicology studies have not been conducted with luveltamab tazevibulin, however FOLR1 expression is found in normal fallopian tubes and placenta tissues. Luveltamab tazevibulin is also expected to be teratogenic and embryotoxic based on the mechanism of action of the hemiasterlin component and may have teratogenic potential. Therefore, male subjects should avoid sexual intercourse or use a barrier method (condom) while receiving luveltamab tazevibulin and at least 6 months after the last luveltamab tazevibulin dose.

2.3.1.3 Planned Safety Monitoring with Regards to Risks

Safety monitoring in subjects should include regular review of biochemical and hematologic parameters, vital signs, physical examinations including ophthalmic examinations, and AEs. Luveltamab tazevibulin is an experimental drug that may have other side effects that are not known and cannot be predicted at this time. These side effects may be serious. Details of recommended safety monitoring and AE management for specific toxicities are provided in Table 8.

Planned subject safety management includes standard pharmacovigilance practices and routine safety monitoring. An overview of potential AEs for subjects treated with luveltamab tazevibulin and a general guidance for AE management are described below in Table 8. With exception of neutropenia and thrombocytopenia, these guidelines are predominantly based on clinical data from adults with gynecological cancers. Therefore, the management of AEs in pediatric subjects with AML should be consistent with SOC as per institutional guidelines.

Table 8: Planned Subject Safety Monitoring and Recommended Adverse Event Management for Luveltamab Tazevibulin Monotherapy

Adverse Event	Risk Mitigation	Management Plan
Neutropenia[a]	• Myelosuppression during AML treatment results in prolonged periods of severe neutropenia with increased risk of life-threatening bacterial, fungal, and viral infections. • Prophylactic antibiotic/antifungal administration is recommended for subjects who have an ANC < 500 cells/µL. • In case of trauma/lesion or a planned procedure in the setting of ≥ Grade 2 neutropenia, especially in diabetic subjects, prophylactic antibiotics should be strongly considered per institutional guidelines.	• Subjects with an ANC < 500/µL should be treated per institutional guidelines with prophylactic antimicrobial therapy. • Signs and symptoms of infection (including fever) should prompt rapid switch from prophylactic treatment to empiric or directed therapy. • Grade 4 neutropenia will be managed with a dose hold unless attributable to underlying leukemia. • Grade 3 or higher neutropenia unrelated to underlying leukemia that persists for > 14 days requires dose reduction by 1 dose level. • For subjects who are in CRh, Grade 4 or higher neutropenia will be managed with a dose hold unless attributable to underlying leukemia until the ANC recovers to ≥ 500/µL. • If recurrence of Grade 4 or higher after a dose reduction, dose will be held and then restarted at a lower dose level with an every 2 week (q2w) schedule. A 3rd episode will require an additional dose hold and restarted at the same dose with a every 3 weeks (q3w) schedule. The 4th recurrence will require the subject to discontinue study drug. • Dose reductions should be discussed with the medical monitor.

Abbreviations and footnotes on last page of table.

Table 8: Planned Subject Safety Monitoring and Recommended Adverse Event Management for Luveltamab Tazevibulin Monotherapy (Contd)

Adverse Event	Risk Mitigation	Management Plan

Arthralgia:	• Risk assessment for rheumatologic disease should be performed prior to start of study drug.
	• Refer subjects with a known history or increased risk for rheumatologic conditions to rheumatologist prior to start of study drug.
	• Consider prophylaxis with steroids. Prednisone at 0.1 to 1 mg/kg daily for 3 days.
		• Arthralgia should be managed per institutional practice. Study drug may be held and/or dose reduced for any grade of arthralgia per treating physician.
		• During the study, if subject develops symptoms the following should be considered: medical interview, physical examination of joints, lab tests-ANA, RF, CRP, HLA-B-27, X-rays of painful joints.
		• Additional recommendations below:
		  • Grade 1: Continue treatment per protocol and recommended medical treatment (see below)*.
		  • Grade 2-3: Hold drug until resolved to ≤ Grade 1 then resume at 1 lower dose level and recommended medical treatment (see below)*.

- *Medical Treatment (SOC treatment per institutional guidelines).
- Treatment (Grade 1-2 toxicity)
  - Acetaminophen (Paracetamol) at 10 to 15 mg/kg every 6 to 8 hours per day.
  - If acetaminophen is ineffective, consider steroids at 0.1 to 1 mg/kg. Prednisone daily with taper.
  - Encourage exercise (strength training 2× per week, walking program 30 minutes per day; 5 days per week), yoga if not medically contraindicated.
  - Consider acupuncture.
- Treatment (Grade 3 toxicity)
  - Steroids at 0.1 to 1 mg/kg. Prednisone daily with taper. Acetaminophen (Paracetamol) at 10 to 15 mg/kg every 6 to 8 hours per day.
  - Consider using Gabapentin (10 to 30 mg/kg/day, max 3600 mg/day).
  - Consider additional imaging (MRI, US) and steroid injection of painful joints.
  - Consider acupuncture.
  - Refer to rheumatology and rehabilitation medicine (physiatry) for additional interventions if symptoms persist more than 4 weeks.

Abbreviations and footnotes on last page of table.

Table 8: Planned Subject Safety Monitoring and Recommended Adverse Event Management for Luveltamab Tazevibulin Monotherapy (Contd)

Adverse Event	Risk Mitigation	Management Plan
Immunogenicity: Potential class effect of luveltamab tazevibulin	• Blood samples will be collected at screening and the beginning of each cycle of treatment other than Cycle 1 Day 1 for assessment of anti-drug antibodies (ADA) to luveltamab tazevibulin. • Any samples with ADA will be assessed for the titer and epitope specificity to determine whether the ADA are directed against the antibody or the drug-linker portion of luveltamab tazevibulin, and to evaluate the neutralizing capacity of the ADA using a cell-based assay.	
Infusion reactions: Potential class effect for ADCs	• Subjects can receive medication (diphenhydramine and acetaminophen) prior to infusions	• Grade 1 to 2 infusion reactions should be managed with slower infusion rate (to ≤ 50%) or interrupt infusion per institutional guidelines. • Severe infusion reactions (Grade ≥ 3) require the immediate interruption of luveltamab tazevibulin. Do not restart infusion for the current infusion. • A slower infusion rate (to ≤ 50%) for all subsequent infusions • Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. • Subjects should be carefully observed until the complete resolution of all signs and symptoms. • For subjects who have infusion reaction symptoms on Day 2 post-study drug administration, treat per institutional guidelines and consider extending Cycle 1 Day 1 prophylaxis treatment for an additional 24 hours.

Abbreviations and footnotes on last page of table.

Table 8: Planned Subject Safety Monitoring and Recommended Adverse Event Management for Luveltamab Tazevibulin Monotherapy (Contd)

Adverse Event	Risk Mitigation	Management Plan
Ocular AEs: Potential class effect for ADCs	• Ocular assessments, performed by an ophthalmologist optometrist, or other qualified professional, are required at screening, pre-dose Cycles 2 and 3 and every 2 cycles thereafter, EOT, and at other timepoints as clinically indicated. • Physician assessment of signs and symptoms of ocular discomfort or any ocular issues should be done at each visit.	• Appropriate medical therapy including eye lubricants, corticosteroid eye drops, or referral to an ophthalmologist, optometrist, or other qualified professional may be used at the discretion of the Investigator. • Luveltamab tazevibulin should be held for ≥ Grade 2 or higher keratopathy, ≥ Grade 3 ocular toxicity, or lower grade ocular toxicity per Investigator. • Dose reduction should be considered for all Grade 3 ocular toxicity if assessed as related to study drug by the Investigator.

Peripheral neuropathy: Very frequent observed AE in subjects treated with luveltamab tazevibulin and a reported class effect for FOLR1-targeting ADCs or ADCs with a microtubule inhibitor warhead	• Identify subjects at increased risk for development of peripheral neuropathy (older adults, DM, alcoholism, Vitamin D deficiency, obese, anemia, history of nerve injury or previous history of peripheral neuropathy; family history of hereditary neuropathy) and treat reversible causes.
	• Evaluate for increased risk of falling at initial and each follow-up visit.
		• Peripheral neuropathy should be managed per institutional practice. Study drug may be held and/or dose reduced for any grade of peripheral neuropathy per treating physician. Additional recommendations below:
		  • **Grade 1**: Continue study drug with management per institutional guidelines.
		  • **Grade 2**: (1st episode > 7 days): Hold drug until resolved to ≤ Grade 1 then resume at 1 lower dose level and recommended medical treatment (see below)*.
		  • **Grade 2**: (2nd episode regardless of duration): Hold drug until resolved to ≤ Grade 1 then resume at 1 lower dose level and recommended medical treatment (see below)*.
		  • **≥ Grade 3**: (1st episode regardless of duration): Hold drug until resolved to ≤ Grade 1 then resume at 1 lower dose level and recommended medical treatment (see below)*.

Abbreviations and footnotes on last page of table.

Table 8: Planned Subject Safety Monitoring and Recommended Adverse Event Management for Luveltamab Tazevibulin Monotherapy (Contd)

Adverse Event	Risk Mitigation	Management Plan
Peripheral neuropathy (cont'd):	•	• **Grade 4**: Permanent discontinuation, if dose hold and dose reduction and supportive therapy do not result in resolution to ≤ Grade 1. • *Medical Treatment (Standard of care treatment per institutional guidelines) • Treatment (Grade 1-2 toxicity) • Consider using Gabapentin (10 to 30 mg/kg/day, max 3600 mg/day). • Encourage exercise through a walking program, leg strengthening and balance training exercises. • Counsel on strategies to minimize risk of injury to affected extremities due to impaired sensation. • Consider acupuncture, massage therapy, mind body therapies, yoga. • Treatment (Grade 3-4 toxicity) • Consider using Gabapentin (10 to 30 mg/kg/day, max 3600 mg/day). • Refer to neurologist/pain specialist and/or cancer rehabilitation for evaluation and treatment of abnormal gait, balance impairment and hand therapy for decreased fine motor skills and weakness in hands. • Consider acupuncture, massage therapy, mind body therapies, yoga.

Abbreviations and footnotes on last page of table.

Table 8: Planned Subject Safety Monitoring and Recommended Adverse Event Management for Luveltamab Tazevibulin Monotherapy (Contd)

Adverse Event	Risk Mitigation	Management Plan
Thrombocytopenia:	• Transfusion with platelets is indicated to correct bleeding manifestations and may be indicated for severe thrombocytopenia without bleeding particularly prior to an invasive procedure. The platelet count should be maintained at least ≥ 20,000/μL or per institutional guidelines. • Weekly complete blood counts and platelet counts for the first 2 cycles of treatment, and every 3 weeks thereafter.	• Platelet transfusion as needed (to prevent complications like epistaxis, etc.) • Transfusion criteria: Platelet count < 10,000 cells/μL, (or < 20,000 cells/μl and falling), induction or dropping counts or as per institutional guidelines. • Grade 4 thrombocytopenia will be managed with a dose hold unless attributable to underlying leukemia. • Luveltamab tazevibulin must be held until severity has returned to ≤ Grade 3. Grade 3 or higher thrombocytopenia unrelated to underlying leukemia that persists for > 14 days requires dose reduction by 1 dose level. • If recurrence of Grade 4 or higher after a dose reduction, dose will be held and then restarted at a lower dose level at q2w. A 3rd episode will require an additional dose hold and restarted at the same dose with a q3w schedule. The 4th recurrence will require the subject to discontinue study drug.
AST or ALT elevation: Potential class effect of FOLR1 ADC	• Study monitoring includes liver function tests as part of the chemistry labs.	• For ≥ Grade 3 AST or ALT elevation (attributed to study drug[s]), luveltamab tazevibulin must be held until resolution of the AST or ALT to Grade 1 or baseline. Dose reduction of luveltamab tazevibulin by 1 dose level when treatment resumes.
Pneumonitis; Potential class effect of ADCs	• Physician assessment of signs and symptoms at each visit.	• Management per institutional guidelines and consideration of pulmonologist consultation. • For Grade 2, study drug should be held until ≤ Grade 1 and then consider dose reduction of study drug by 1 dose level. • For ≥ Grade 3 pneumonitis consider permanently discontinuing study drug.

Abbreviations and footnotes on last page of table.

Table 8: Planned Subject Safety Monitoring and Recommended Adverse Event Management for Luveltamab Tazevibulin Monotherapy (Contd)

Adverse Event	Risk Mitigation	Management Plan
Hyponatremia	• Study monitoring includes electrolytes as part of the chemistry labs.	• Management per institutional guidelines. If syndrome of inappropriate antidiuretic hormone (SIADH) is suspected, a full work-up should be performed.

ADC = antibody-drug conjugate; AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; CR = complete remission; CRh = complete remission with partial hematologic recovery.

a. Management of neutropenia, related to study drug should be discussed with the medical monitor, and is to be managed with dose modifications as required, including dose reduction, dose delay, and/or the use of concomitant growth factor support as per institutional guidelines.

2.3.2 Benefit Assessment

Preliminary efficacy was demonstrated in subjects with *CBFA2T3::GLIS2* AML who have received luveltamab tazevibulin through EA. As of the data cutoff date of 01 Mar 2023, 25 subjects were treated with luveltamab tazevibulin. A total of 18 subjects with relapsed/refractory *CBFA2T3::GLIS2* AML had ≥ 5% bone marrow involvement with leukemic blasts at enrollment, which represents the planned subject population in this protocol. Of these 18 subjects, 4 subjects started treatment with a fractionated dose, 3 subjects started on a combination treatment, and 11 subjects received luveltamab tazevibulin monotherapy at enrollment (4.3 mg/kg q2w-q4w or 5.2 mg/kg q2w).

A total of 7 subjects of 25 were enrolled with bone marrow involvement in bone marrow involvement with leukemic blasts of < 5%. Of which, 6 subjects received luveltamab tazevibulin monotherapy (4.3 mg/kg q2w-q4w or 5.2 mg/kg q2w) and 1 subject received a combination treatment at enrollment.

A total of 7 subjects with *CBFA2T3::GLIS2* AML with ≥ 5% bone marrow involvement with leukemic blasts treated with luveltamab tazevibulin as monotherapy or in combination achieved a CR or CRh. Three (3) subjects achieved a CR while on monotherapy (luveltamab tazevibulin at 4.3 mg/kg or 5.2 mg/kg), 2 subjects achieved a CR or CRh (1 subject each) after switching from monotherapy to combination therapy and 2 subjects who started and remained on combination therapy achieved a CR and CRh. No CR or CRh response was observed in subjects who received fractionated dosing.

In the non-target population (< 5% bone marrow involvement with leukemic blasts [N = 7]), 4 subjects on monotherapy and 1 subject on combination therapy achieved an MRD-negative status.

Allogeneic stem cell transplant (SCT) may be a potentially curative therapeutic option, even for this high-risk AML. By enabling subjects to proceed to SCT, the use of luveltamab tazevibulin

may allow subjects to derive clinical benefit from its' use. At the data cut off, 4 subjects who enrolled with ≥ 5% bone marrow involvement with leukemic blasts and treated with luveltamab tazevibulin (either monotherapy or in combination), proceeded to SCT. In addition, 1 subject in the category of bone marrow involvement with leukemic blasts < 5%, also proceeded to transplant. This subject was treated with luveltamab tazevibulin at the 4.3 mg/kg q2w dosing regimen.

These data are an important step in establishing luveltamab tazevibulin as a potential therapeutic option for subjects with *CBFA2T3::GLIS2* AML. Using RT-PCR or next generation sequencing (NGS), this highly aggressive and poor prognostic *CBFA2T3::GLIS2* AML subtype can be readily identified. The expression of *CBFA2T3::GLIS2* uniquely upregulates FOLR1, making luveltamab tazevibulin an excellent therapeutic candidate (Tang et al, 2022; Le et al, 2021). Lastly, subjects with *CBFA2T3::GLIS2* AML have the worst outcome of any molecularly defined subgroup of pediatric AML and despite maximally intensive induction treatments following diagnosis, no alternative treatment options are available. Thus, luveltamab tazevibulin may provide children with *CBFA2T3::GLIS2* AML an opportunity to successfully bridge-to-transplant.

In compliance with Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (2018), appropriate expertise and advice was considered including the clinical, ethical and psycho-social problems in the field of pediatric oncology. The Sponsor engaged, consulted, and updated the study design based on feedback from COG and Innovative Therapies for Children with Cancer Consortium.

2.3.3 Overall Benefit-Risk Conclusion

Considering the measures to minimize risks to subjects in this study combined with the EA safety data and the preliminary efficacy data in this population, the potential risks are justified by the anticipated benefits that may be afforded to pediatric subjects with *CBFA2T3::GLIS2* AML treated with luveltamab tazevibulin.

Demographic data including age, sex, race, and baseline disease characteristics will be collected, where permitted. This data will be collected in order to correlate subject outcomes relative to treatment regimens proposed in this study. The purpose of this data is for statistical purposes and will be provided in the listings (per the Statistical Analysis Plan; SAP). See Sections 10.1.5 and 10.1.10 for the specific measures used to safeguard the fundamental rights and the interests of the data subjects.

3.0 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1 Objectives and Endpoints

Primary Objectives	Primary Endpoints
• Evaluate efficacy of luveltamab tazevibulin monotherapy	• Complete remission (CR) rate
Secondary Objectives	**Secondary Endpoints**
• Assess additional efficacy outcome measures	• Duration of CR • Response rate including complete remission with partial hematologic recovery (CRh) [CR + CRh] • Event-free survival (EFS) • Relapse-free survival (RFS) • Overall survival (OS)
• Evaluate safety measures	• Incidence and severity of AEs and clinical laboratory abnormalities per NCI CTCAE v5.0.
• To characterize the PK of luveltamab tazevibulin	• Concentration of luveltamab tazevibulin (ADC, TAb, and SC209) in the blood.
• Assess the immunogenic potential of luveltamab tazevibulin	• Incidence of ADAs
Exploratory Objectives	**Exploratory Endpoints**
• Evaluate other efficacy measures as applicable	• Duration of remission on combination therapy • CR + CRh on combination therapy • Proportion of subjects who proceed to transplant • Measurable residual disease (MRD)-negative response rate • Duration of MRD-negative CR
• Evaluate other safety measures as applicable	• Incidence and severity of AEs and clinical laboratory abnormalities of combination therapy per NCI CTCAE v5.0
• Evaluate potential predictive or prognostic biomarkers	• Evaluate correlation of expression of FOLR1 with efficacy

ADA = anti-drug antibodies; ADC = antibody drug conjugate; AEs = adverse events; AML = acute myeloid leukemia; CTCAE = Common Terminology Criteria for Adverse Events; FOLR1 = folate receptor alpha; NCI = National Cancer Institute; PK = pharmacokinetics; SC209 = 3-aminophenyl hemiasterlin warhead released from luveltamab tazevibulin; TAb = total antibody.

3.2 Estimand(s)

3.2.1 Primary Estimand

CR rate of receiving luveltamab tazevibulin as monotherapy in the target population:

Population: Subjects younger than 12 years of age with ≥ 5% bone marrow involvement with leukemic blasts *CBFA2T3::GLIS2* AML.

Variable: The CR while receiving luveltamab tazevibulin as monotherapy, the CR definition used for this study is consistent with outlined in Döhner et al 2016.

Treatment of interest: Luveltamab tazevibulin as monotherapy.

Intercurrent events: Treatment Policy: chemotherapy added on luveltamab tazevibulin is considered as an intercurrent event, CR first occurred after chemotherapy will not be considered.

Population-level summary: CR rate will be calculated.

3.2.2 Secondary Estimand

Duration of response in the target population:

Population: Subjects younger than 12 years of age ≥ 5% bone marrow involvement with leukemic blasts *CBFA2T3::GLIS2* AML.

Variable: Duration of CR is defined as the time from date of the first observed CR until morphologic relapse or death, whichever is first.

Treatment of interest: Luveltamab tazevibulin with or without chemotherapy.

Intercurrent events: Treatment Policy: chemotherapy added on luveltamab tazevibulin or hematopoietic stem cell transplant (HSCT) is not considered as intercurrent events, duration of response irrespective of start of add-on chemotherapy or HSCT.

Population-level summary: Median duration of response will be calculated.

3.2.3 Additional Estimands

N/A

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase 1/2, open-label study to evaluate the efficacy, safety, and PK of luveltamab tazevibulin in infants and children < 12 years of age with relapsed/refractory *CBFA2T3::GLIS2* AML.

This study will enroll subjects with relapsed/refractory *CBFA2T3::GLIS2* with ≥ 5% bone marrow involvement with leukemic blasts as determined by morphology (by local laboratory testing). Flow cytometry results (by central laboratory) will not affect subject eligibility.

The study will evaluate 2 parallel dose levels: luveltamab tazevibulin at 3.5 and 4.3 mg/kg q2w. Subjects will be randomized between the 2 dose levels at the time of enrollment to evaluate PK, safety, and efficacy across a dose range. Within a specific dose level, enrollment will employ a

rolling six design (Skolnik et al 2008). The dose limiting toxicity (DLT) evaluation period will be through Cycle 1 (28 days). Following evaluation of the safety and efficacy data on the initial enrollment of up to 3 to 6 subjects at each dose level, subsequent enrollment will be limited to the selected dose level. Stopping rules for study drug dosing and enrollment are described in Section 7.3.

All enrolled subjects will be initially assessed for eligibility during the screening period (lasting ≤ 21 days). Documentation of *CBFA2T3::GLIS2* fusion gene is required for enrollment (see Section 6.10.4). Results will be required prior to subjects receiving their first dose of luveltamab tazevibulin. Confirmation of FOLR1 expression on leukemia cells will be done retrospectively and will not be required for study enrollment.

All enrolled subjects will be initially assessed for eligibility during the screening period (lasting ≤ 21 days). Subjects will be monitored closely for AEs throughout the duration of the study and for at least 30 days after the last dose of study treatment or until initiation of another non-protocol specified systemic anti-cancer therapy, whichever occurs first. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0).

4.1.1 Starting Dose Level and Schedules

Two dose levels will be evaluated in parallel. The starting doses of luveltamab tazevibulin will be 3.5 and 4.3 mg/kg q2w in a 28-day cycle. The starting doses for this study have been selected based on the following:

1) Luveltamab tazevibulin dosed as a single agent was administered and cleared per protocol dose escalation rules in an advanced ovarian cancer population in the Phase 1 study STRO-002-GM1 (doses ranging from 0.5 to 6.0 mg/kg) given intravenously (IV) every 3 weeks (q3w). The clinical activity of luveltamab tazevibulin was observed at doses from 2.9 to 6.0 mg/kg.
2) As of 01 Mar 2023, 25 pediatric subjects with CBFA2T3::GLIS2 AML were enrolled through expanded access, of whom 21 subjects initially received luveltamab tazevibulin monotherapy doses of 4.3 mg/kg every q2w to q4w, 5.2 mg/kg q2w, or a fractionated dose (1 or 1.4 mg/kg IV on Days 1, 3, and 7 or 2.9 mg/kg IV), with 4 subjects receiving a combination treatment at enrollment.
3) Randomized dose exploration of the 4.3 mg/kg q2w dose level and a lower dose level of 3.5 mg/kg q2w has been implemented in order to generate required PK, safety, and efficacy data to confirm that 4.3 mg/kg q2w is the preferred dose and schedule for further enrollment.

4.1.2 Dosing

Cycles 1 and 2 (Dose 1-4): Subjects will receive luveltamab tazevibulin monotherapy at the assigned dose level and schedule (Figure 1). Luveltamab tazevibulin will be infused IV over 1 hour (± 5 minutes); infusion may be slowed as clinically indicated. The starting dose levels

will be Dose Levels (DL) 1a and 2a. DL1a and DL2a will be evaluated in parallel for the initial 6 to 12 subjects with 1 dose level selected for further enrollment based upon safety and preliminary anti-leukemia activity data. At Dose Level 1a, subjects will receive luveltamab tazevibulin at 3.5 mg/kg IV q2w on Days 1 and 15 of a 28-day cycle. At Dose Level 2a subjects will receive luveltamab tazevibulin 4.3 mg/kg IV q2w on Days 1 and 15 of a 28-day cycle.

Based on ongoing evaluation of accumulated safety, PK, and efficacy data, the Cycle 1 starting dose level (dose and/or schedule) may be modified, based on the recommendation of the SSC.

If a dose level is determined to be non-tolerable, subsequent subjects enrolled will not start or escalate to that dose level. Doses may be modified due to safety and tolerability, per Dose Modification for Safety Table 11.

At the completion of Cycle 1, bone marrow will be evaluated.

Should the subject experience ongoing Grade 4 neutropenia or thrombocytopenia, the decision on whether to proceed immediately to dose Cycle 2 is based on bone marrow response.

- If a subject has no evidence of leukemia in the bone marrow but experiences an AE of Grade 4 neutropenia (absolute neutrophil count [ANC] < 500/μL) or Grade 4 thrombocytopenia (platelets < 25,000/μL), the dose will be held until counts have recovered to Grade 3.
- If a subject has evidence of leukemia in the bone marrow, they will receive another cycle of luveltamab tazevibulin, even in the presence of Grade 4 cytopenia.

After Cycle 2 response assessment subjects in CRh will have Cycle 3 held for up to 28 days until neutrophil and platelet counts recover to meet the criteria in Table 17 for CR (ANC > 1 Gi/L and platelet count > 100 Gi/L). Repeat bone marrow will be performed if the last bone marrow was performed (≥ 14 days) prior to the peripheral count recovery. Should count recovery fail to occur by the end of the 28-day observation period, treatment may be resumed, as long as ANC > 0.50 Gi/L and platelets are > 50 Gi/L.

Cycle 3 (Doses 5 and 6): Subjects who are in CR/CRh will continue dosing at their Cycle 2 dose level until relapse, transplant or other intervening therapy, unmanageable AEs, or withdrawal from study treatment.

If a subject does not achieve a CR/CRh prior to the start of Cycle 3, but has tolerated the original dose level, the subject may dose-escalate 1 alpha-numeric dose level. For example, if a subject is treated at Dose Level 1a (3.5 mg/kg q2w), they may escalate to Dose Level 2a (4.3 mg/kg IV q2w). Subjects that are unable to dose-escalate due to intolerability and have not achieved a CR/CRh, may discontinue study treatment or may receive luveltamab tazevibulin at 4.3mg/kg q4w in combination with standard AML treatment regimen until relapse, transplant or other intervening therapy, unmanageable AEs, or choose to withdraw from study treatment.

Cycle 4 (Subjects who dose escalated at Cycle 3) (Dose 7+): Subjects who are in CR/CRh will continue dosing at their Cycle 3 Dose Level until relapse, transplant or other intervening therapy, unmanageable AEs, or withdrawal from study treatment. Subjects who have not achieved a CR/CRh at the conclusion of Cycle 3 may either discontinue study treatment or may receive luveltamab tazevibulin at 4.3 mg/kg q4w (or other dose level deemed safe by SSC) in combination with standard AML treatment regimen until relapse, transplant or other intervening therapy, unmanageable AEs, or choose to withdraw from treatment.

4.1.3 Dose Limiting Toxicities

4.1.3.1 Dose-Limiting Toxicity Evaluation Period

The DLT evaluation period initiates with the first dose of study drug and continues through Cycle 1 Day 28. Additionally, certain hematologic AEs with onset prior to the end of the DLT evaluation period may require continued observation for up to 14 additional days beyond Day 28 to determine if the AE meets the DLT definition. In these cases, the start of Cycle 2 may be delayed, if necessary, to Day 42 for observation and confirmation of DLTs. The Investigator should report DLTs as soon as possible to the Sponsor.

4.1.3.2 Evaluable Subjects for Dose Limiting Toxicities

Any subject receiving the prescribed doses of luveltamab tazevibulin during the DLT evaluation period (or receiving less than 100% of treatment due to a DLT), will be considered as DLT-evaluable. Subjects not receiving the prescribed doses of study drug during the DLT evaluation period, for any reason other than a DLT, may be replaced with another subject for DLT evaluation.

Any subject experiencing a DLT, should be managed according to the Dose Modification Guidelines (Section 6.7).

4.1.3.3 Dose-Limiting Toxicity Criteria

DLTs are any of the following AEs occurring within the DLT evaluation period unless the event can be clearly attributable to the underlying disease or another extraneous cause (ie, non-compliance, subject's medical history):

- Any AE resulting in a dose reduction or permanent discontinuation of luveltamab tazevibulin.
- Any AE resulting in a dose interruption of luveltamab tazevibulin leading to administration of less than the prescribed dose.
- Any Grade 5 AE.

The DLT definition for non-hematological AEs include the following, unless the event can be clearly attributable to the underlying disease or another extraneous cause (ie, non-compliance, subject's medical history):

- Any Grade 3 non-hematological AE lasting greater than 72 hours with the following exceptions:
  - Grade 3 fatigue lasting ≤ 7 days.
  - Grade 3 electrolyte abnormalities, ALT, AST, and bilirubin elevations that resolve within 72 hours to < Grade 2.
  - Grade 3 nausea, vomiting, or diarrhea that does not require hospitalization, does not prolong hospitalization, does not require total parenteral nutrition (TPN).
  - Tumor Lysis Syndrome (TLS) that resolves in 7 days with no end organ damage.
  - Grade 3 or greater infections in the setting of active leukemia.
- Any Grade ≥ 4 non-hematological AE.
- Any case of Hy's law as follows:
  - ALT and/or AST greater than 3 × upper limit of normal (ULN), and total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase [ALP]).
    - To note, for subjects with hepatic EMD who have baseline LFT > 2.5 × ULN but < 3 × ULN, DLT criteria for LFT remain. For those who start with LFT > 3 × ULN, they will not be evaluable for LFT DLT.
  - No other reason can be found to explain the combination of increased ALT/AST and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.
- Any AE that leads to dose reduction or withdrawal.

The DLT definition for hematologic AEs includes the following, unless the event can be clearly attributable to the underlying disease or another extraneous cause (ie, non-compliance, subject's medical history):

- Grade 4 hematologic toxicity as follows:
  - Any Grade ≥ 4 absolute neutrophil count lasting > 42 days or platelets lasting > 42 days from the AE onset but only in absence of persisting leukemia (> 5% bone marrow involvement with leukemic blasts).

4.1.4 Concurrent Treatment of Luveltamab Tazevibulin with Standard AML Treatment

Subjects will be allowed to receive luveltamab tazevibulin at 4.3 mg/kg (or other dose level deemed safe by SSC) once per treatment cycle (q4w) in combination with one of the SOC backbone AML treatment regimens detailed in Table 9, if such treatment is available at the treating center.

The subjects will be allowed to switch between any of the below listed combination regimens at Investigator discretion. Concurrent dosing of luveltamab tazevibulin and SOC backbone AML treatment therapy is allowed.

Table 9: Standard of Care Backbone AML Therapies Allowed Concomitantly to Luveltamab Tazevibulin

Name	Drugs
Regimen 1	Luveltamab tazevibulin + fludarabine + intermediate dose cytarabine
Regimen 2	Luveltamab tazevibulin + intermediate dose cytarabine
Regimen 3	Luveltamab tazevibulin + azacytidine
Regimen 4	Luveltamab tazevibulin + donor lymphocyte infusion (if subject has had a prior transplant)

SOC = standard of care.

Doses for the SOC Backbone therapies:

Regimen 1: Fludarabine + intermediate dose cytarabine:
Fludarabine 30 mg/m^2 IV over 30 minutes once per day (QD) on Days 1 to 5.
Intermediate dose cytarabine 2000 mg/m^2 IV over 1 to 3 hours QD on Days 1 to 5, given 4 hours after the start of fludarabine.
The subjects can receive up to 2 cycles of fludarabine and intermediate dose cytarabine.

Regimen 2: Intermediate dose cytarabine 2000 mg/m^2 IV over 1 to 3 hours QD on Days 1 to 5.
The subjects can receive up to 4 cycles of intermediate dose cytarabine.

Regimen 3: Azacytidine:
Subjects will be treated with either subcutaneous or IV azacytidine on Days 1 to 7 of a 28-day cycle. IV azacytidine will be infused over 1 hour. The number of azacytidine cycles administered is based on clinical benefit and Investigator discretion.

Guidelines for dose is dependent on subject age:

- The recommended dose for subjects ≥ 1 year of age and weighing ≥ 10 kg is 75 mg/m^2.
- For subjects < 1 year of age or weighing less than 10 kg, azacytidine dose is 2.5 mg/kg.

Regimen 4: Donor lymphocyte infusion (DLI) (if subject has had a prior transplant) at a dose and schedule determined by the Investigator. The number of DLI cycles administered is based on clinical benefit and Investigator discretion.

4.1.5 Response Evaluation

Bone marrow evaluation including flow cytometry will be performed to assess blast counts at baseline and prior to the beginning of the next cycle until Cycle 3 (on Day 28 of each cycle in

dose cohorts receiving q2w dosing, and on Day 42 of each cycle in dose cohorts receiving q3w dosing). In addition to local evaluation of bone marrow aspirate and biopsy, slides, and peripheral blood smears will be sent to a central laboratory for central morphology review to confirm the response. MRD assessment will also be performed at a central laboratory utilizing flow cytometry (details in Section 6.10.4). Subjects continuing monotherapy will have subsequent bone marrow evaluations at the conclusion of Cycles 4 and 6 and every other subsequent cycle, and at EOT. Additional assessments may be performed, if clinically indicated.

Determination of CR will be based on bone marrow central morphology review and also include the evaluation of peripheral blood blasts, neutrophils, platelet counts, and EMD as described in Section 10.2.1, Table 17.

4.1.6 Extramedullary Disease Response Evaluation:

Subjects with clinical signs of EMD require imaging evaluation prior to enrollment or during the study. All subjects with suspected or confirmed EMD disease at baseline are required to have an imaging evaluation prior to initiation of therapy. Subjects with cutaneous disease who have biopsy confirmation, do not need to have imaging. If clinically feasible, tissue biopsy should be used to determine EMD response. If tissue biopsy is not clinically appropriate, then radiographic studies including positron emission tomography scan should be used to determine EMD response. The differentiation between residual disease and residual scar tissue on radiographic studies may be difficult and the final determination of radiographic disease status should be made by the treating clinician in consultation with the local radiologist.

At screening, all subjects are required to be evaluated by lumbar puncture for the presence of CNS disease prior to initiation of therapy. Lumbar puncture will be performed based on the criteria below and each time a lumbar puncture is performed, CNS involvement will be evaluated.

- Subjects with CNS1 will receive prophylaxis therapy for CNS disease at study entry and for subsequent cycles as deemed appropriate by the Investigator.
- Subjects that begin treatment with CNS2 will receive therapy for CNS disease as described in Section 10.6, Appendix 6 (CNS Prophylaxis and Therapy).
- Subjects with clinical signs of CNS leukemia that developed during luveltamab tazevibulin treatment will require lumbar puncture and imaging evaluation to confirm CNS progression.

Images and reports used to assess extramedullary response will be collected for central response adjudication.

4.1.7 Schedule of Assessments

The study requires scheduled physical examinations, laboratory tests, blood draws for PK, blood draws for immunogenicity, electrocardiograms (ECG)s, multigated acquisition scan echocardiogram (ECHO), ophthalmic examinations, and radiographic imaging (if applicable).

Details and schedule are provided in the Schedule of Assessments (SoA) and Schedule of Pharmacokinetic Collection (Section 1.3).

Clinical laboratory assessment will be performed locally. PK, immunogenicity (ADA), and biomarker assessments will be performed at a central laboratory.

4.2 Scientific Rationale for Study Design

Please refer to Section 2.1 for rationale.

4.2.1 Study Defined Periods

4.2.1.1 Screening

Subjects will undergo screening assessments within 21 days of the first dose of luveltamab tazevibulin. Subjects will be monitored for AEs from the signing of the informed consent form (ICF), through 30 days after the last dose. Study procedure-related AEs that occur after signing of the ICF and before administration of luveltamab tazevibulin will also be collected.

4.2.1.2 Treatment

All subjects will be considered on active study treatment from the first dose of study drug until 30 days following permanent discontinuation of luveltamab tazevibulin.

4.2.1.3 Long-Term Follow-up

All subjects will be followed at approximately 3-month intervals to monitor survival status for approximately 2 years after permanent discontinuation of study drug or until death, withdrawal of participation in the study or Sponsor decision, whichever comes first.

4.3 Justification for Dose

Support for the doses planned for REFRaME-P1 have been informed by clinical data derived from the ovarian and endometrial cancer program, individual IND EA subjects, and PK/PD modeling for pediatric AML using adult data. luveltamab tazevibulin has been dosed at 0.5 to 6.0 mg/kg q3w in adults with no formal DLTs, thus even at doses higher than what is proposed for REFRaME-P1, luveltamab tazevibulin has been well tolerated. Positive clinical outcomes have also been observed with luveltamab tazevibulin at doses of 4.3 and 5.2 mg/kg q3w in adults. PK data characterizing the PK profiles of ADC, TAb, and SC209 and plasma concentration-time profiles in adults (STRO-002-GM1) demonstrate that maximum plasma concentrations of ADC and TAb were achieved within 1 hour of the end of infusion and exposures increase in a dose-proportional manner.

Based on Sponsor’s experience with luveltamab tazevibulin in adult subjects with ovarian and endometrial cancer and physician input, doses of 4.3 and 5.2 mg/kg q2w were administered to EA subjects. CRs have been observed in EA subjects treated with luveltamab tazevibulin at

4.3 and 5.2 mg/kg q2w, monotherapy, and also, when luveltamab tazevibulin was administered in combination with other anti-leukemia agents. Luveltamab tazevibulin also allowed subjects to proceed to an allogeneic HSC transplant.

In order to establish the optimal dose of luveltamab tazevibulin in the setting of *CBFA2T3::GLIS2* AML, an initial cohort will enroll at 3.5 mg/kg q2w. The q3w schedule is not being prospectively investigated at this time because simulation and modeling as well as early clinical data suggest that a q2w dosing schedule is more appropriate for the treatment of AML. Additionally, as the EA experience was not a unified clinical study protocol, there were no cross-subject dose escalation or formal assessments of the maximal tolerable dose. However, review of the AEs reported from individual EA subjects suggests that the safety profile was generally similar to adults. Further, simulations modeled based on the adult PK data and in vivo mouse data, support the expectation that higher doses and more frequent dosing is required for reduction in tumor burden in this highly aggressive subtype of AML. The adult PK data also provides a margin of safety for the initial starting dose of 3.5 mg/kg q2w.

In addition to the results from the PK model, there is substantial clinical experience for this rare disease population from the EA experience. Pediatric subjects with *CBFA2T3::GLIS2* AML have already been dosed with 5.2 mg/kg q2w with acceptable tolerability. This provides additional data that support a starting dose of 3.5 kg/kg q2w with the potential to escalate to 4.3 mg/kg q2w as likely tolerable (Section 2.2.6). Commonly reported TEAEs (≥ 25%) at the 4.3 mg/kg dose included neutrophil count decreased, anemia, platelet count decreased, WBC count decreased, pyrexia, and AST increased. TEAEs, including ≥ Grade 3 TEAEs, at the 5.2 mg/kg dose were consistent with the 4.3 mg/kg q2w dose. In addition, all grade neutropenia, as well as ≥ Grade 3 neutropenia were reported at lower incidences in pediatric subjects treated at 4.3 and 5.2 mg/kg compared with adults treated in STRO-002-GM1. Thus, these data suggest that the proposed dosing for luveltamab to be explored in REFRAME-P1 will have an acceptable safety profile.

The EA experience also support administration of luveltamab tazevibulin in combination with other anti-leukemia agents, including MTX, fludarabine and AraC, venetoclax plus azacitidine, decitabine, dasatinib, plerixafor, and DLI, in that clinical benefit and an acceptable safety profile was observed. Thus, the EA experience with combination therapy justifies the use of luveltamab tazevibulin in combination with the anti-leukemic agents proposed in RERaME-P1.

4.4 Start of Study and End of Study

Milestones	Definitions	Timeline
Estimated study start	The date on which the clinical study will be open for recruitment of subjects	Q1 2024
First act of recruitment	First site open and will be the study start date, estimated to be 18 to 24 months	Q1 2024
Estimated last subject last visit	Two (2) years from last subject in	Q4 2027

4.4.1 Start of Study and First Act of Recruitment Definitions

- The study start date is the date on which the clinical study will be open for recruitment of subjects.
- The first act of recruitment is defined as the first site open and will be the study start date.

4.4.2 End-of-Treatment and End-of-Study

End-of-Treatment

The end-of-treatment (EOT) is defined as the date when all enrolled subjects have discontinued treatment and completed the EOT follow-up visit, or the trial is terminated by the Sponsor.

The planned maximum treatment duration for initial treatment therapy in this study is 2 years. The maximum treatment duration for post-CR from other therapy (eg, combination therapy) maintenance is 2 years. The maximum treatment duration for post-allogeneic therapy will be 2 years.

All subjects should return to the clinic for EOT assessments at 30 (± 7) days after the last dose of luveltamab tazevibulin has been administered and prior to administration of a new, off-protocol chemotherapy treatment. Any AEs that occur during the time from last dose to 30 days after last dose should be recorded in the source and electronic case report form (eCRF).

End-of-Study

End-of-study is defined as the date the last subject is enrolled in the study or last scheduled procedure shown in the SoA for the last subject in the study globally. The end of REFRaME-P1 is planned to be 2 years from the last subject enrolled. Subjects who withdraw from the study and trial procedures will still be followed for OS for approximately 2 years. The maximum length of the trial is planned to be approximately 5 years.

A subject is considered to have completed the study if the subject has completed all periods of the study including the last visit.

5.0 STUDY POPULATION

5.1 Inclusion Criteria

Subjects must meet the following inclusion criteria for the study entry.

1) Signed informed consent form and pediatric assent form, if applicable.
2) Diagnosis of relapsed or refractory AML with *CBFA2T3::GLIS2* fusion.

   Subjects must have refractory (induction/reinduction failure) or relapsed disease with ≥ 5% bone marrow involvement with leukemic blasts as determined by morphology (by local laboratory testing). Subjects must undergo a lumbar puncture at screening to confirm (CNS) disease. Subjects with CNS1 and CNS2 are eligible (please refer to definitions below in Inclusion Criteria #3). Flow cytometry results (by central laboratory) will not affect subject eligibility.

   US & ROW: Eligibility requires the documentation of the *CBFA2T3::GLIS2* translocation by the Next Generation Sequencing FoundationOne Heme assay.

   If past results from the FoundationOne Heme assay are available and meet suitable characteristics for Trial Boost, [Foundation Medicine's mechanism for transferring subject results from a prior test to a clinical trial], the past results may be reanalyzed to confirm molecular eligibility (see Section 6.10.4).

   EU Subjects Only: Eligibility requires the documentation of the *CBFA2T3::GLIS2* translocation performed by RQ-PCR centralized testing (see Section 6.10.4).

   Subjects meeting definition of CNS1 and CNS2 are eligible:

   a) CNS1 Disease

      CNS1 (negative) at diagnosis is defined as no blasts in cytospin cerebrospinal fluid (CSF) regardless of CSF WBC or red blood cell (RBC) counts AND does not meet CNS3c criteria.

   b) CNS2 Disease

      CNS2 disease at diagnosis is defined as any one of the following:

      i) CNS2a: Blasts present in cytospin CSF with CSF WBC < 5/µL and CSF RBC < 10/µL (atraumatic tap).

      ii) CNS2b: Blasts present in cytospin CSF with CSF WBC < 5/µL and CSF RBC ≥ 10/µL (traumatic tap).

      iii) CNS2c: Blasts present in cytospin CSF with CSF WBC ≥ 5/µL and CSF RBC ≥ 10/µL (traumatic tap) in which the WBC/RBC ratio in the CSF is less than twice that in the peripheral blood (see calculation method below).

3) Age < 12 years.
4) Lansky performance of ≥ 50.

5) Direct bilirubin < 1.5 × upper limit of normal (ULN). Subjects with Gilbert's disease will also require direct bilirubin < 1.5 × ULN.

6) ALT and AST <2.5 × ULN (unless related to leukemic involvement).
   - Subjects with hepatic EMD ALT and AST may be ≤ 5.0 × ULN.
   - To note, for subjects with hepatic EMD who have baseline LFT > 2.5 × ULN but < 3 × ULN, DLT criteria for LFT remain. For those who start with LFT > 3 × ULN, they will not be evaluable for LFT DLT.

7) Creatinine clearance or radioisotope glomerular filtration rate ≥ 70/mL/min/1.73 m^2 OR a serum creatinine based on age/gender as follows:

	Maximum Serum Creatinine (mg/dL)	
Age	**Male**	**Female**
1 to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2

The threshold creatinine values in the table were derived from the Schwartz formula for estimating glomerular filtration rate utilizing child length and stature data published by the Centers for Disease Control and Prevention.

8) Corrected QTcF < 450 msecs.

9) Left ventricular ejection fraction >50% by ECHO.

10) Female subjects that have experienced menarche and male subjects that have reached puberty must agree to undergo physician-approved reproductive education and discuss the side effects of the study therapy on reproduction with parent(s) and/or guardian(s).

11) Female subjects who have experienced menarche must have a negative pregnancy test within 7 days of the first dose of study drug. All subjects (male and female) who have undergone puberty and are potentially sexually active must agree to use a physical barrier (condoms) method during heterosexual contact. At the discretion of the treating physician females may also use additional contraceptive methods, including hormonal contraceptives. Pregnancy prevention must continue while participating in the study, during dose interruptions, and for at least 6 months following luveltamab tazevibulin.

5.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from study entry:

General Exclusion Criteria:

1) Active CNS disease at the time of enrollment (CNS3) defined as:
   a) CNS3a: Blasts present in cytospin CSF with CSF WBC ≥ 5/uL and CSF RBC < 10/uL (atraumatic tap).
   b) CNS3b: Blasts present in cytospin CSF with CSF WBC ≥5/uL in a traumatic tap (CSF RBC ≥ 10/uL) in which the WBC/RBC ratio in the CSF is twice or greater that in the peripheral blood (see calculation method below).
   c) CNS3c: Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome) OR radiographic evidence of an intracranial or intradural mass consistent with a chloroma. Retinal hemorrhage and extra-ocular orbital masses are not considered CNS leukemia.
2) Subjects with the following constitutional conditions are not eligible: Fanconi anemia, Shwachman Diamond syndrome, subjects with constitutional trisomy 21 or with constitutional mosaicism of trisomy 21, telomere disorders, germline predispositions known, or suspected by the treating physician to increase risk of toxicity with AML therapy.
3) Clinically significant active or chronic corneal disorder, particularly corneal epitheliopathy or any eye disorder that may predispose subject to this condition, or unable to comply with an age-appropriate ophthalmic examination.
4) Active or uncontrolled viral, bacterial, or fungal infection. May be receiving ongoing therapy for controlled infection.
5) Known human immunodeficiency virus, hepatitis B virus, or hepatitis C virus infection, unless on treatment and have an undetectable viral load.
6) Uncontrolled, symptomatic, intercurrent illness including but not limited to infection, congestive heart failure, cardiac arrhythmia, or social situations that would limit compliance with study requirements or in the opinion of the Investigator would pose an unacceptable risk to the subject. If the subject is in remission from a prior second malignancy, they may be considered for enrollment.
7) History of severe, immediate hypersensitivity reaction attributed to compounds of similar chemical or biologic composition to any agents used in study or in the manufacturing of the cells.
8) Subjects with a history of an allogeneic (non-autologous) hematopoietic stem cell transplant, boost infusion (any stem cell product; not including donor lymphocyte infusion [DLI]), or any organ transplant are excluded if any of the following are met:
   a) Subjects are less than 84 days post-transplant.

b) Subjects have graft-versus-host disease (GVHD) of any severity and/or receive any immunosuppressive therapy with the exception of topical steroids for cutaneous GVHD and/or systemic steroid in doses equal or less than 10 mg of prednisone daily, which are permitted if doses were not changed in the last 14 days. Prednisone dose must be adjusted for body surface area in young children. Physiologic doses of hydrocortisone for subjects with adrenal insufficiency are allowed.

c) Subjects who after relapse continue to receive cyclosporine, tacrolimus, or other agents to treat or prevent either GVHD post-bone marrow transplant or organ rejection post-transplant are not eligible. They must be off medications to treat or prevent either GVHD post-bone marrow transplant or organ rejection post-transplant for at least 28 days prior to enrollment. A stable steroid dose as mentioned above is allowed.

d) Cellular therapy: less than 30 days after the completion of DLI or any type of cellular therapy (eg, modified T cells, NK cells, dendritic cells, etc.) at enrollment. After 30 days, subjects will be eligible.

9) Prior systemic chemotherapy within 21 days prior to the first luveltamab tazevibulin infusion, with the exception of:

   a) Hydroxyurea ≥ 1 day.

   b) Azacytidine/decitabine and/or venetoclax: ≥ 7 days.

   c) ADC therapies: ≥ 3 half-lives.

10) Radiation therapy, including CNS, < 21 days prior to the start of luveltamab tazevibulin, with the exception of no time restriction if the volume of bone marrow treated is less than 10% and also the subject has measurable/evaluable disease outside the radiation field.

11) Prior treatment with folate receptor-targeting anti-cancer agent(s) or with ADCs that contain a tubulin inhibitor.

12) Prior treatment with an investigational anti-cancer treatment within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first luveltamab tazevibulin infusion.

   a) Note: ADC therapies washout period is ≥ 3 half-lives (see Exclusion #9).

5.2.1 Method of Evaluating Initial Traumatic Lumbar Puncture

If the subject has leukemic cells in the peripheral blood and the lumbar puncture is traumatic (CSF RBC ≥ 10/μL) and CSF contains WBC ≥ 5/uL and blasts on cytospin, the following algorithm should be used to distinguish CNS2c and CNS3b.

CNS2c

- The ratio of CSF WBC ÷ CSF RBC < 2 × Blood WBC ÷ Blood RBC

CNS3c

- The ratio of CSF WBC ÷ CSF RBC ≥ 2 × Blood WBC ÷Blood RBC

Example of CNS3c

CSF WBC = 60/µL; CSF RBC = 1,500/µL; blood WBC = 46,000/µL; blood RBC = 3×10^6/µL

60/1500 = 0.04 which is ≥ $2 \times 46{,}000/3.0 \times 10^6 = 0.015$

5.2.2 Input to Study Design

The Sponsor has sought lay advice from subjects' parents or legal guardians on certain aspects of the protocol (ie, clarity on procedures in the ICF) and the development program (travel time and recruitment).

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

A screen failure occurs when a subject who has consented to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of subjects who meet the criteria for screen failure to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, ICF date screen failure details, eligibility criteria, and any AE or SAE, if they are deemed related to the screening procedure by the Investigator.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened subjects should be assigned a new subject number for every screening/rescreening event. Rescreened subjects will have to repeat screening procedures if out of screening window and receive Sponsor approval to rescreen.

5.5 Criteria for Temporarily Delaying

See Section 6.7 for information for dose modifications.

6.0 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 Study Intervention(s) Administered

Table 10: Study Intervention(s) Administered

Intervention Label	Luveltamab tazevibulin (STRO-002)
Dose Formulation	Luveltamab tazevibulin is formulated at 10 mg/mL in 10 mM sodium citrate and 9% sucrose adjusted to pH 6.0, and 0.01% (w/v) polysorbate 20.
Unit Dose Strengths	Luveltamab tazevibulin will be provided as a frozen liquid formulation in glass stoppered vials at a concentration of 10 mg/mL.
Sourcing	Luveltamab tazevibulin will be provided by the sponsor.
Packaging and Labeling	Luveltamab tazevibulin is provided as a sterile liquid solution in single-use 20 mL glass vials as a frozen liquid formulation with a fill volume of not less

Intervention Label	Luveltamab tazevibulin (STRO-002)
	than 10 mL of luveltamab tazevibulin (10 mg/mL), ie, a total of 100 mg luveltamab tazevibulin. The label on the vial states: luveltamab tazevibulin (STRO-002), 100 mg/10 mL (10 mg/mL).
Preparation and Handling	Luveltamab tazevibulin will be provided as a frozen liquid formulation in glass stoppered vials at a concentration of 10 mg/mL. Luveltamab tazevibulin should be stored protected from light at -20°C ± 5°C. To thaw for use, luveltamab tazevibulin may be thawed either in the refrigerator at 2°C to 8°C or at ambient room temperature (19°C to 25°C). While luveltamab tazevibulin should be used once it has reached ambient room temperature (19°C to 25°C), it can be held at ambient room temperature (19°C to 25°C) for up to 8 hours and may be stored for up to 2 weeks refrigerated at 2°C to 8°C. Once a vial has completely thawed and is at ambient temperature, gently swirl contents to homogeneity before use. Avoid vortexing or vigorously mixing products. Diluted luveltamab tazevibulin solutions are stable for up to 24 hours at room temperature (19°C to 25°C) under ambient lighting conditions.
Storage	Luveltamab tazevibulin should be stored protected from light at -20°C ± 5°C. Do not store in a -20°C ± 5°C freezer which cycles temperature; also known as "frost-free". To thaw for use, luveltamab tazevibulin may be thawed either in the refrigerator at 2°C to 8°C or at ambient room temperature (19°C to 25°C). • While luveltamab tazevibulin should be used once it has reached ambient room temperature (19°C to 25°C), it can be held at ambient room temperature (19°C to 25°C) for up to 8 hours and may be stored for up to 2 weeks refrigerated at 2°C to 8°C. Diluted luveltamab tazevibulin solutions are stable for up to 24 hours at room temperature (19°C to 25°C) under ambient lighting conditions. Further details of study drug preparation and administration are provided in the Pharmacy Manual. It is the responsibility of the investigator to ensure that the investigational product is stored as specified by the sponsor and in accordance with applicable regulatory requirements.

6.2 SOC Backbone Chemotherapy Regimens

SOC backbone chemotherapy regimens will be obtained locally by the study sites and will be formulated, prepared, and handled according to standard practice. However, if required by local health authorities, these regimens will be provided by the Sponsor. Please refer to local prescribing information or institutional guidelines for further instructions regarding dosage, administration, and storage.

6.3 Preparation, Handling, Storage, and Accountability

1) At the time of delivery of the study drug to the site, the Investigator, designee, or pharmacist (where appropriate) will confirm that the supplies for the study have been received.
2) Luveltamab tazevibulin must be stored in a secure location. Accountability for luveltamab tazevibulin is the responsibility of the Investigator.
3) Luveltamab tazevibulin must:
    - Only be dispensed by a pharmacist or medically qualified staff.

- Only be dispensed to subjects enrolled in this study.
- Only be administered to the intended subject it was initially prepared for.

4) The study site must maintain accurate records demonstrating dates and amount of luveltamab tazevibulin received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed. Reconciliation must be documented and monitored for luveltamab tazevibulin supplied, dispensed, and subsequently destroyed onsite or returned to Sutro Biopharma, Inc. or its representative per study process.
5) Study site staff should refer to the Pharmacy Manual for more specific instructions on the handling, storage, and administration of luveltamab tazevibulin.

6.4 Assignment to Study Intervention

This is an open-label study with initial dose ranging and then further enrollment at a selected dose level. All subjects will be centrally assigned using Interactive Response Technology or Randomization and Trial Management System. Before the study is initiated, login information will be provided to each site.

Study intervention will be dispensed at the study visits as summarized in the SoA (Section 1.3).

6.5 Blinding, Masking

It is a single-arm study thus, blinding is not applicable.

6.6 Study Intervention Compliance

When subjects are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and the interactive voice/web response system (IVRS) system. The dose of study intervention and study participant identification will be confirmed at the time of dosing by the IVRS system.

6.7 Dose Modification

Luveltamab tazevibulin administration must be withheld for the following,

- In compliance with the guidance for AE management described in Table 8.
- Any clinically significant Grade 3 or 4 non-hematologic AE until the event resolves to Grade ≤ 2,
- AE that meets the criteria of a DLT or other AE that the Investigator determines that study treatment should be withheld.

Decisions on continued treatment at a reduced dose following the resolution of an AE should be made following a careful assessment of the risk versus benefit by the Investigator, and in

discussion with the Sponsor medical monitor or designee. The dose modification guidelines are listed in Table 11. Additional modification to dose and schedule may be recommended by the SSC.

For subjects receiving q3w week dosing (designated with a "b"), luveltamab tazevibulin will be given on Days 1 and 22 (at their assigned dose). The cycle length will be 42 days. The q3w dosing schedule will only be used for dose modification or may be implemented based on emerging study data for further prospective study based on the recommendation of the Steering and Safety Committee (SSC).

Table 11: Dose Modification Table for Safety

Dose	Modification #1	Modification #2	Modification #3
1a (3.5 mg/kg q2w)	3.5 mg/kg q3w	2.9 mg/kg q2w	Requires approval by the Sponsor medical monitor and results from ongoing efficacy, safety, and PK as assessed and recommended by the SSC
2a (4.3 mg/kg q2w)	4.3 mg/kg q3w	3.5 mg/kg q2w	
3a (5.2 mg/kg q2w)	5.2 mg/kg q3w	4.3 mg/kg q2w	
1b (3.5 mg/kg q3w)	2.9 mg/kg q2w	2.9 mg/kg q3w	
2b (4.3 mg/kg q3w)	3.5 mg/kg q2w	3.5 mg/kg q3w	
3b (5.2 mg/kg q3w)	4.3 mg/kg q2w	4.3 mg/kg q3w	

PK = pharmacokinetic; q2w = every 2 weeks; q3w = every 3 weeks; SSC = Steering and Safety committee.

For subjects who are in CRh, dosing may be held for up to 28 days for a Grade 4 neutropenia, until the absolute neutrophil count recovers to ≥ 500/ µL.

If an Investigator determines the subject is unable to adhere to treatment schedule due to noncompliance, the subject may be discontinued from the study.

Any treatment delay resulting in > 42 days between doses will result in subject's discontinuation from the study unless subject is approved to continue the study by Sponsor or designee with the exception of receipt of a stem cell transplant and then receipt of maintenance therapy following transplant.

6.7.1 Maintenance therapy (Post-transplant)

Subjects who proceed to receiving a transplant may have the option to receive luveltamab tazevibulin as a maintenance therapy at the selected dose q4w after > 60 days post-transplant, at the discretion of the Investigator, and in discussion with the Sponsor medical monitor or designee. See Table 3 for the maintenance SoA. End-of-Treatment for post-allogeneic therapy will be 2 years.

6.8 Continued Access to Study Intervention after the End of the Study

Subjects will remain in the study for as long as they are receiving clinical benefit and are not experiencing any unmanageable, intolerable AEs in the opinion of the treating physician.

6.9 Treatment of Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study intervention is not an AE, however, it may result in an AE.

In the event of an overdose, the Investigator should:

- Evaluate the subject to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Obtain a plasma sample for PK analysis as scheduled or within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.10 Prior and Concomitant Therapy

Any medication or non-live vaccines (eg, over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the subject is receiving at the time of consent or receives during the study must be recorded along with:

- Reason for use;
- Dates of administration including start and end dates; and
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.10.1 Permitted Therapy

Permitted concomitant therapies include the below.

- Supportive care (eg, antiemetics, analgesics for pain control, hematopoietic growth factors [after initiation of study drug], etc.) per Investigator's discretion and in accordance with institutional procedures.
- Dexamethasone may be used as prophylaxis for or to treat chemotherapy induced nausea per institutional guideline.
- SOC intrathecal cytarabine/triple IT (methotrexate, hydrocortisone and cytarabine) may be administered at any point during the study for either prophylaxis or treatment of CNS leukemia. For additional guidance see Section 10.6, Appendix 6.

- While infusions are reported to be well-tolerated, there is Investigator discretion to use acetaminophen and/or diphenhydramine premedication, to be given 1 hour before the infusion.
- Institutional tumor lysis syndrome and antimicrobial prophylaxis guidelines will be followed.
- Antibiotics administered as febrile neutropenia precautions.

All medications given during the study need to be recorded in the source and electronic data capture (EDC).

Live-Vaccines

The effect of luveltamab tazevibulin on the efficacy or safety of vaccines has not been studied. The administration of live attenuated vaccines is not permitted during study participation. The administration of other (non-live attenuated vaccines) is allowed and should be per institutional guidelines for subjects undergoing treatment with cytotoxic chemotherapy.

- It is recommended that live, attenuated vaccines (eg, nasal vaccines) for measles, mumps, rubella, oral polio vaccine, and varicella are not administered until 12 weeks after the last administration of luveltamab tazevibulin.
- For non-attenuated vaccines (eg, COVID-19), there are no restrictions on the administration during study treatment and they may be administered according to local institutional standards.

All medications given during the study need to be recorded in the source and EDC.

6.10.2 Prohibited Therapy

Subjects must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Concomitant use of strong or moderate cytochrome P450 (CYP)3A4 inhibitors may increase the concentration of circulating unconjugated SC209, which could potentially lead to increased AEs of luveltamab tazevibulin. Strong and moderate CYP3A4 inhibitors and inducers should be avoided but, if necessary, with no alternatives, then subjects receiving strong or moderate CYP3A inhibitors should be monitored for increased toxicity.

The following medications and supportive therapies and procedures are prohibited at all times during the study:

- Any chemotherapy agent other than luveltamab tazevibulin, unless the subject is receiving combination SOC backbone chemotherapy as part of the study.

- Any experimental agent other than luveltamab tazevibulin.
- Prior treatment with an investigational anti-cancer treatment within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first luveltamab tazevibulin infusion.

  Note: ADC therapies washout period is ≥ 3 half-lives (see Exclusion #9, Section 5.2).

6.10.3 Treatment of Infusion Reactions

Luveltamab tazevibulin will only be administered in the acute care setting with immediate access to resuscitative equipment and emergency medications. Infusion reactions should be graded per CTCAE v5.0 'infusion related reaction'. These reactions may manifest with signs and symptoms that could include, but are not limited to fever, chills, headache, rash, pruritus, arthralgia, hypo-or hypertension, bronchospasm, or other symptoms. Severe infusion reactions require the immediate interruption of study drug therapy. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms. Following an infusion reaction, subjects should be premedicated per institutional guidelines, such as with acetaminophen and diphenhydramine for future treatments. Corticosteroids premedication can be used at the Investigator's discretion or per institutional practice in subjects with prior infusion reaction.

Administration of study intervention: The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.10.4 Investigational/Diagnostic Device for Study Enrollment Screening

6.10.4.1 US & Rest of World Subjects (Excluding EU): *CBFA2T3::GLIS2* NGS Assay

The FoundationOne Heme (F1Heme) assay is designed to detect multiple classes of genomic alterations in peripheral blood, bone marrow aspirate, formalin-fixed, paraffin-embedded tissue samples, or previously extracted nucleic acids from these sample types (ie, internal or external extraction for retrospective testing) with high sensitivity and specificity.

The laboratory process used for the NGS F1Heme assay platform is a robust, multi-step protocol to generate targeted deep sequence data from adaptor-ligated sequencing libraries of Foundation Medicine Inc. (FMI)-extracted or externally extracted DNA/RNA from bone marrow aspirate, peripheral blood, or formalin-fixed, paraffin-embedded tissue samples. The workflow is executed in a laboratory operated under CLIA/CAP/NYSDOH regulations and begins with sample receipt and accessioning into a laboratory information management system, incorporates the generation of targeted sequencing data on the Illumina® platform, and culminates with a customized analysis pipeline capable of highly accurate detection of genomic alterations. Multiple steps of the process are run on automated liquid handlers to ensure consistency and efficiency. The assay includes process-matched controls in each run, and defined quality control metrics are used throughout the process to monitor sample and assay performance.

6.10.4.2 EU Subjects Only: *CBFA2T3::GLIS2* RQ-PCR Assay

The *CBFA2T3::GLIS2* RT-PCR assay is intended for use as an enrollment eligibility criterion for subjects in the EU. The *CBFA2T3::GLIS2* RT/RQ-PCR assay is defined as an in-house device (per the In Vitro Diagnostic Regulation, Article 5[5]) that is performed at a central laboratory, aiming to detect the presence of the *CBFA2T3::GLIS2* fusion transcript in RNA isolated from blood or bone marrow from subjects with AML. Isolated RNA is converted into cDNA using reverse transcriptase and amplified by PCR with primers on the opposite sites of the possible breakpoint regions. Results can be reported as "Negative" or "Positive" for the gene fusion.

The *CBFA2T3::GLIS2* PCR assay has demonstrated analytical and clinical validity for detection of *CBFA2T3::GLIS2* fusion transcript.

7.0 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Subjects will continue treatment until intolerable or unmanageable AEs or disease progression. It may be necessary for a subject to permanently discontinue study intervention, for reasons described below. If study intervention is permanently discontinued, the subject should if at all possible, remain in the study to be evaluated for EOT, overall survival and any other long-term follow-up procedures. See the SoA Section 1.3 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1 Reasons for Treatment Discontinuation

A subject must be discontinued from protocol-prescribed therapy if any of the following apply:

- Consent is withdrawn.
- Relapse of subject's underlying disease indicating need for new anti-cancer treatment outside of the study. However, subjects with isolated CNS recurrence, may receive CNS specific therapies while remaining on study treatment at Investigator discretion, in absence of alternative therapeutic options of the non-CNS disease.
- Any event, adverse or otherwise, that, in the opinion of the Investigator, would pose an unacceptable safety risk to the subject.
- Unacceptable toxicity including:
  - A DLT that does not resolve within 42 days of onset, or a second occurrence of the same DLT.
  - Dose interruptions due to an AE that delays the start of the next cycle by more than 28 days (beyond current cycle Day 56) or inability to meet retreatment criteria, will result in treatment discontinuation.

- Pregnancy.
- A concurrent illness that, in the opinion of the Investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy.
- The Investigator believes it is not in the subject's best interest to continue.
- Excessive noncompliance with treatment regimen or scheduled assessments.
- Any treatment delay resulting in > 42 days between doses (excepting the context of a stem cell transplant) unless subject is approved to continue the study by Sponsor or designee.
- The study Sponsor, health authorities, or Internal Review Board (IRB)/Independent Ethics Committee (IEC) decides that the study should be stopped.
- The Sponsor decision to close all or parts of the study or the decision may also be based on IDMC decision that benefit/risk is no longer acceptable.

7.2 Subject Discontinuation/Withdrawal from the Study.

A subject and/or their parents or legal guardians may withdraw from the study at any time, for any reason (or without providing any reason).

- Site should confirm for all withdrawal of consents whether a subject/parents/legal guardians are withdrawing consent to receive further study treatment only and whether they are continuing to consent for long-term follow-up.
- If the subject/parents/legal guardians withdraw consent for treatment, site should continue to conduct long-term follow-up per the SoA.
- If the subject/parents/legal guardians withdraw consent for disclosure of future information
    - The Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
    - The subject will be permanently discontinued from the study intervention and the study at that time.
    - If a subject is withdrawn from the study, destruction of any samples taken and not tested may be requested by the subject/parents/legal guardians, and the Investigator must document this in the site study records.
    - A subject may be withdrawn at any time at the discretion of the Investigator for safety, (behavioral, or compliance) reasons.
    - At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See Section 1.3 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3 Rolling Six Design Enrollment and Stopping Rules

The rolling six design allows for accrual of 3 to 6 subjects concurrently onto a dose level (DL1a and DL2a) based on the number of subjects currently enrolled and evaluable, the number experiencing DLTs, and the number still at risk of developing a DLT.

Determination of RP2D and MTD for the rolling 6 study design are presented in Table 12.

Table 12: Rolling Six Design Enrollment Rules

No. Enrolled	No. DLTs	No. Pending DLT evaluation	Next enrolling
3	0	0	Clear the dose level
3	0, 1	> 0	Stay at current dose level
3	≥ 2		Stop the enrollment
4	0	0	Clear the dose level
4	0, 1	> 0	Stay at current dose level
4	≥ 2		Stop the enrollment
5	0	0	Clear the dose level
5	0, 1	> 0	Stay at current dose level
5	≥ 2		Stop the enrollment
6	0, 1	0	Clear the dose level
6	0, 1	> 0	Suspend
6	≥ 2		Stop the enrollment

Modified from Skolnik et al, 2008.

Study enrollment and study drug dosing will be suspended if, at any time during the study, any of the following events are met:

- Any report of a Grade 5 AE not clearly related to the underlying disease or an extraneous cause.
- An incident of drug-induced liver injury, that meets the criteria for Hy's law (see Section 4.1.3.3 for criteria).

An event that meets the Study Level Stopping Rules will not automatically terminate the study but will result in assessment of the overall safety of the study by the Sponsor in collaboration with the SSC. The Sponsor may elect to continue the study, amend the protocol, or permanently stop the study. Protocol revisions could include changes to the following: eligibility criteria, dose reductions, the dosing regimen, the clinical monitoring plans, or other risk reduction measures to ensure safety of subjects and study integrity.

7.4 Lost to Follow-up

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

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

- The site must attempt to contact the subject/parents/legal guardians and reschedule the missed visit as soon as possible, counsel the subject/parents/legal guardians on the importance of maintaining the assigned visit schedule and ascertain whether the subject/parents/legal guardians wish to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject/parents/legal guardians (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the subject within legal and ethical boundaries for all subjects randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the subject will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8.0 STUDY PROCEDURES AND SCHEDULE

Study procedures and their timing are summarized in the SoA, Section 1.3. Protocol waivers or exemptions are not allowed.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for subject visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.

- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General/Baseline Procedures

8.1.1 Informed Consent Form (ICF)

All subjects' parents or legal guardians must sign the ICF prior to conduct of any study procedures and before the first dose of luveltamab tazevibulin can be administered. The ICF may be obtained ≤ 21 days from first dose. No study assessments may be performed until after the subject/legal guardian has read, understood, and signed the ICF. See Section 1.3 for additional details regarding all screening evaluations and timing in relationship to the ICF execution. Pediatric assent must be obtained when applicable.

8.1.2 Eligibility Review

For a subject to be enrolled in this study, documentation must be provided to the Sponsor or Sponsor's representative indicating the subject has met all the inclusion criteria and none of the exclusion criteria. Each subject will need to be approved by Sponsor or Sponsor's representative prior to enrollment.

8.1.3 Standard of Care Procedures

SOC should be provided to subjects per institutional guidelines. If there is any question whether a procedure or medication should be administered during the study, the Investigator may contact the Sponsor or Sponsor's representative at any time to discuss.

8.1.4 Medical History and Demographics

Demographic information (age, race, gender, etc.) and relevant medical history should be captured for each subject which includes oncology history, past or ongoing comorbidities, date of cancer diagnosis, prior cancer treatments and any relevant surgical procedures.

8.1.5 Concomitant Medications and Procedures

The use of any concurrent medication, from the day subjects/parents/legal guardians sign ICF until date of last luveltamab tazevibulin dose, prescription or over-the-counter, are to be recorded on the subject's source and electronic case report form (eCRF) along with the reason the medication was taken. All procedures performed during the study must also be documented on the source and eCRF. See Section 6.10 for specific permitted and prohibited concomitant medications.

8.1.6 Survival Status

All subjects will be followed for survival per SoA (Section 1.3) until death, lost to follow-up, withdrawal of consent for survival follow-up or until end of study, whichever comes first.

8.2 Safety Evaluations

All subjects who receive at least 1 dose of study drug will be considered evaluable for safety evaluations. Any clinically relevant changes occurring during the study must be recorded on the subject's source and AE section of the eCRF. The study will be monitored by the SSC, the Sponsor, and the Sponsor's pharmacovigilance representatives.

8.2.1 Adverse Events

AEs will be collected from the date of first dose with luveltamab tazevibulin until 30 days after the last dose of study treatment or until initiation of another systemic anti-cancer therapy, whichever date occurs first. Any events occurring because of screening procedures after the subject signs the ICF should also be documented on the source and AEs eCRF. During the follow-up part of the study, any ongoing AEs of Grade 3 or higher that are considered related to study drug, as well as any ongoing SAEs regardless of relationship should be followed until resolution. During follow-up, any SAEs which are assessed as related to study treatment are required to be reported even if the onset is > 30 days after the last dose of study drug.

8.2.2 Physical Examinations

Planned timepoints for physical examinations are provided in the SoA, Section 1.3.

Full physical exam is required for screening and Cycle 1 Day 1. Symptom-directed physical exams will be done during the treatment phase (after Cycle 1 Day 1) and at the EOT visit. Physical examination includes head, eyes, ears, nose, and throat, skin, chest, cardiac, abdominal, extremities, skeletal, neurologic, and lymph node examinations. Weight will be recorded at every visit. Height will be recorded at screening visit only.

During screening and at each physical examination timepoint, the treating physician should assess whether subjects have had any signs or symptoms of ocular AEs. Assessment should include at least asking the parent/legal guardian if the subject has experienced any symptoms such as blurry vision or dry eye as indicated by any behaviors indicating discomfort and treat appropriately and/or refer subject to an ophthalmologist, optometrist, or other qualified professional as needed. All findings should be reported as AEs as appropriate. Additional tests may be performed as clinically indicated and results should be recorded in the subject's source and eCRF.

8.2.3 Vital Signs

Planned timepoints for vital signs are provided in the SoA, Section 1.3. Vital signs include upright blood pressure, heart rate, respiratory rate, and body temperature.

8.2.4 Electrocardiograms

Planned timepoints for ECGs are provided in the SoA, Section 1.3. Corrected QTcF must be < 500 msec during screening and prior to C1D1 dose for subject to meet eligibility requirements.

All ECGs will be done in triplicate using the ECG machine provided by the site unless notified by the Sponsor to use central ECGs or in cases where the local ECG machine is not available and/or working. Subjects should be in supine position and resting before study-related ECGs.

8.2.5 Clinical Laboratory Evaluations

See Section 10.3 (Appendix 3) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. Pre-treatment laboratories (Day 1 of Cycle) may be obtained within 3 days of Day 1 of a cycle.

The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study and should be repeated until the values return to normal or baseline, are no longer considered clinically significant by the Investigator or medical monitor, or until 30 days after the last dose of study drug or initiation of subsequent anti-cancer therapy (which ever data is the earliest).

- If clinically significant/any values do not return to normal/baseline within a period of time, judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
- Protocol-required laboratory tests, as defined in Section 10.3, Appendix 3, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

A summary of the assays requiring blood and the volume is presented in Table 13.

Table 13: Summary of Assays and Blood Volumes for Clinical Laboratory Analysis

Laboratory Assessments	Blood Volume per Assay (mL)
Hematology (CBC 0.5 mL + Coagulation 1.8 mL)	2.0 (2.3)
Complete metabolic panel	1.0
Uric acid	1.0
Phosphorus	1.0
Lactate dehydrogenase	1.0
Amylase, lipase, and thyroid stimulating hormone (1 mL each)	3.0
Creatine phosphokinase	1.0
Immunogenicity (ADA)	2.0
Pharmacokinetics	2.0

ADA = anti-drug antibody; CBC = complete blood count.

8.2.6 Clinical Safety Assessments

8.2.6.1 Ophthalmic Examination

Age-appropriate ophthalmic exams should be performed on each subject to rule out or describe any treatment-related ocular AEs. Ophthalmic exams should be performed per SoA, and at other timepoints as clinically indicated. Anesthesia is not required for ophthalmic examinations, however, if anesthesia is needed, it should be coordinated with the planned anesthesia for the bone marrow biopsies whenever both procedures occur in the same cycle.

8.2.6.2 Echocardiogram

Planned timepoints for ECHO tests are presented in the SoA, Section 1.3. ECHO will be done to ensure the subject has a left ventricular ejection fraction of ≥ 50% prior to enrollment. Additional tests may be performed as clinically indicated and results should be recorded in the source and eCRF.

8.2.6.3 Lansky Performance Scale

Planned timepoints for Lansky status are presented in the SoA, Section 1.3. Lansky performance status should be assessed by the same study personnel at each visit, if possible. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline Lansky performance status to avoid enrolling subjects with significant impairment. Subjects with Lansky performance Status less than 50 should not enroll in this study. See Table 14 for Lansky Performance Scale calculator.

Table 14: Lansky Performance Scale calculator

Score	Description
100	Fully active, normal.
90	Minor restrictions in physically strenuous activity.
80	Active, but tires more quickly.
70	Both greater restriction of, and less time spent in, play activity.
60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Gets dressed but lies around much of the day; no active play; able to participate in all quiet play and activities.
40	Mostly in bed, participates in quiet activities.
30	In bed, needs assistance even for quiet play.
20	Often sleeping, play entirely limited to very passive activities.
10	No play, does not get out of bed.
0	Dead

8.3 Clinical Efficacy and Response Assessments

8.3.1 Efficacy Evaluations

Planned timepoints for all efficacy and/or immunogenicity assessments are provided in the SoA, Section 1.3. See Section 9.3.3.1 for definition of the primary endpoint.

8.3.2 Response Assessments

Bone marrow evaluation will be performed to assess blast counts on Day 28 of Cycle 1 and Cycle 2 in dose cohorts receiving q2w or q4w (combination) dosing (see EMD Response Evaluation, Section 4.1). To avoid repeat procedure to re-evaluate morphology percentage, both aspirate and biopsy are required for eligibility. Bone marrow evaluation will occur on Day 42 of Cycle 1 and Cycle 2 in dose cohorts receiving q3w dosing. In addition to local evaluation of bone marrow aspirates and biopsies, slides, and peripheral blood smears will be sent to a central

laboratory for central review. Flow cytometry will be evaluated at a central laboratory. Subjects continuing monotherapy will have subsequent bone marrow evaluations at the conclusion of Cycles 4 and 6 and every other subsequent cycle. Additional assessments may be performed, if clinically indicated. Subjects who remain on study drug greater than 1 year may have bone marrow evaluations at the discretion of the treating physician, but not less than twice annually. When bone marrow biopsies and ophthalmic exams occur on the same cycle, planned anesthesia for the bone marrow biopsies should be coordinated with the planned anesthesia for ophthalmic examinations (if required).

An unscheduled bone marrow evaluation may be performed at the discretion of the Investigator.

8.3.3 Difference from Normal: Myeloid (ΔN:M) Flow Cytometry Immunophenotyping (MRD Assay)

The Difference from Normal: Myeloid (ΔN:M) Test is a semiquantitative flow cytometry assay for diagnostic phenotyping of normal, regenerating, and aberrant cell populations in pediatric and adult subjects with AML (excluding promyelocytic leukemia and Myeloid Leukemia of Down Syndrome). The reagents used to perform the ΔN:M Test includes: HLA-DR, cluster of differentiation (CD)7, CD11b, CD13, CD14, CD16, CD19, CD33, CD34, CD36, CD38, CD45, CD56, CD64, CD117, CD123, and FOLR-1. Determination of minimal residual leukemia response will be based on the ΔN:M Test results from centralized testing.

The ΔN:M Test is being run at a central laboratory as an LDT (ie, “in house test”) and the test is designed, manufactured, and used within one central lab. This test and vendor currently support clinical decision making for COG and European collaborative study group protocol subjects and pediatric subjects with AML who are treated by providers off-protocol.

The ΔN:M Test has demonstrated analytical and clinical validity for detection of an abnormal cellular population defined as the difference from normal.

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

The definitions of AEs and SAEs can be found in Section 10.4 (Appendix 4).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on all AEs or AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the treatment with luveltamab tazevibulin (see Section 7.1). This includes events reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject’s legally authorized representative).

Both AEs and SAEs of any grade occurring after informed consent and prior to the first dose of study drug should be reported as AEs/SAEs if they are deemed related to the screening procedure by the Investigator.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.4, Appendix 4.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until the follow up visit at the timepoints specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF until the follow up visit at the timepoints specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AE.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.4, Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.4 (Appendix 4).

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.4.5 Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects must be reported to the Sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.5 Pharmacokinetics and Immunogenicity

8.5.1 Evaluations

Blood samples will be obtained to determine the PK profile of luveltamab tazevibulin (assessing for TAb, total ADC and luveltamab tazevibulin major catabolite [SC209]) and assess for ADAs. The schedule for blood draws for ADA assessments is provided in Section 1.3. Details for sample processing and storage will be provided in the laboratory manual.

The schedule for PK assessments are provided in Section 1.3. Details for sample processing and storage will be provided in the laboratory manual. Blood samples for PK and ADA analysis should be collected at the requested time. Collection time is calculated from the dosing time. The actual time of collection should be noted in the CRFs. Data collected in this study may be combined with data from other studies for further analysis.

Additional exploratory assays that provide information on PK and immunogenicity may be performed on available samples if needed. To complete the testing described in this protocol,

samples may be stored up to 7 years after the end of the study, at which point they will be appropriately destroyed.

Blood samples for PK analysis should be collected at the requested time and this time calculated from the dosing time. The actual time of collection should be noted in the CRFs. Data collected in this study may be combined with data from other studies for further analysis.

8.5.2 Analytical Procedures

Samples will be analyzed for the TAb, total ADC and luveltamab tazevibulin major catabolite (SC209) by validated assays of appropriate sensitivity and specificity. The TAb measured will include all luveltamab tazevibulin derived antibody molecules, conjugated and unconjugated; while total ADC measured will include all luveltamab tazevibulin derived antibody molecules that have at least 1 drug-linker attached.

All samples collected may not be analyzed.

8.5.3 Pharmacokinetic Parameters

To characterize the PK of the ADC (luveltamab tazevibulin), the plasma concentrations of the TAb, total ADC and major catabolite (SC209) following a single dose and multiple doses will be measured by validated assays of appropriate sensitivity and specificity. The TAb measured will include all luveltamab tazevibulin derived antibody molecules, conjugated and unconjugated; while total ADC measured will include all luveltamab tazevibulin derived antibody molecules that have at least 1 drug-linker attached. This will be used to determine dose proportionality using a compartmental or noncompartmental PK method, as appropriate, for data analysis.

The primary PK variables will be described in the SAP.

8.6 Pharmacodynamics

Pharmacodynamics will be evaluated through assessment of MRD in bone marrow samples (see Section 4.1.6 and Section 8.8.1).

8.7 Genetics

The study will involve analysis of *CBFA2T3::GLIS2* gene fusion for determination of patient eligibility. In addition, the NGS-based F1 Heme assay being used for prospective (US & ROW) and retrospective (EU) central testing is designed for cancer genomic mutation profiling and can detect multiple classes of genomic alterations (such as substitutions, insertions and deletions, copy number variations, and rearrangements) as well as genomic signatures (such as microsatellite instability and tumor mutational burden). The results report from F1 Heme assay is somatic only and there is no risk of incidental findings that are germline-related. The results from F1 Heme assay may be used for biomarker analysis (Section 8.8.1).For prospective testing, the investigator may obtain an NGS report through Foundation Medicine's web portal. If allowed by

local laws, the Investigator may share and discuss the results with the subject, unless the subject chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results will not be available for samples that do not meet criteria for testing.

8.8 Biomarkers

8.8.1 Tissue from Bone Marrow and Blood Samples

AML tissue from bone marrow and blood samples will be collected to better understand the mechanism of action of drug during the study. Bone marrow samples will be analyzed for FOLR1 expression by flow cytometry and MRD. Other biomarkers may include soluble FOLR1 to better understand the impact of luveltamab tazevibulin on treatment response. Additionally, genes or genomic alterations (such as substitutions, insertions and deletions, copy number variations, and rearrangements) as well as genomic signatures (such as microsatellite instability and tumor mutational burden) obtained through F1 Heme assay may be used for biomarker analysis (Section 8.7). Samples will be collected according to the schedule described in the SoA, Section 1.3 as detailed in laboratory manual provided separately to sites.

EU subjects only: Bone marrow samples collected at baseline will be stored at a central laboratory for retrospective NGS testing at Foundation Medicine (Section 8.7).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the subject specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

All samples collected will be used for study-related testing; samples may be stored for up to 7 years after the end of study in order to complete testing, after which they will be destroyed appropriately. Study data may potentially be used/combined with other data (eg, luveltamab tazevibulin single-patient IND EA) for reasons including, but not limited to: gain deeper understanding of disease and/or drug mode of action, inform assay or diagnostic development, inform design of future studies.

Given the complexity and exploratory nature of biomarker analyses, data derived from these analyses will generally not be provided to study investigators or subjects unless required by law (with the exception of the report from Foundation Medicine for subjects that undergo prospective testing). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Note: When bone marrow biopsies and ophthalmic exams occur on the same cycle, planned anesthesia for the bone marrow biopsies should be coordinated with the planned anesthesia for ophthalmic examinations (if required). Subjects who remain on study drug greater than 1 year may have bone marrow evaluations at the discretion of the treating physician, but not less than twice annually.

8.8.2 Exploratory Analysis of Folate Receptor alpha (FOLR1/FolRα)

The FOLR1 exploratory analysis which will retrospectively examine the expression of FOLR1 in participants enrolled in the Phase 1/2 open-label clinical trial will not be used to establish eligibility for enrollment into the clinical trial. The exploratory analysis will include correlation of FOLR1 baseline expression with response to therapy in enrolled participants.

The ΔN:M Test results, generated from the sample collection at baseline, will be used to collect the FOLR1 expression by flow cytometry because the reagents used to perform the ΔN:M Test include an antibody for FOLR1. Therefore, the FOLR1 expression results can be determined through examination of the staining intensities for this antibody. The analytical validation and quality control measures used to support the performance of the ΔN:M Test support measurement of FOLR1 expression since the precisely calibrated, four-color flow cytometers used for the ΔN:M Test were validated to quantitatively determine the expression of all gene products included in the panel, which includes FOLR1.

8.9 Immunogenicity Assessments

Antibodies to luveltamab tazevibulin will be evaluated in blood samples collected from all subjects according to the SoA, Section 1.3 using a validated assay method of appropriate sensitivity and specificity to enable interpretation of the ADA data. ADA results will be summarized descriptively. Blood samples will be obtained to determine the presence of ADA. The blood samples for ADA assessment will be obtained within 2 hours before luveltamab tazevibulin infusion pre-dose, on Day1 of Cycle 1 and 2, pre-dose on Day 1 of Cycles 3 through 5, predose on Day 1 every 6 cycles (ie, every 6 months for q2w and every 4 cycles [every 4 months for q4w]) thereafter, and at the EOT visit following last dose of luveltamab tazevibulin. Additional exploratory assays that provide information on immunogenicity may be performed on available samples if needed. To complete the testing described in this protocol, samples may be stored up to 7 years after the end of the study, at which point they will be appropriately destroyed. Blood samples for ADA analysis should be collected at the requested time. The actual time of collection should be noted in the CRFs. Data collected in this study may be combined with data from other studies for further analysis. Any samples showing confirmed ADA positivity will be assessed for the ADA titer and epitope specificity of the ADA using a competition assay with SP8166 (naked antibody) and SC239 (drug-linker) to determine whether the ADA are directed against the antibody or the drug linker portion of luveltamab tazevibulin. ADA positive samples will also be tested for neutralizing capacity using a cell-based assay.

8.10 Health Economics/Medical Resource Utilization and Health Economics

This section is not applicable for this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Safety Monitoring

Bayesian sequential monitoring will be employed to perform ongoing safety monitoring targeting a toxicity rate of no more than 20% (where toxicity follows the same definition in Section 4.1.3). The criteria for suspending enrollment due to safety are in Table 15 based on a Bayesian sequential monitoring design (Thall et al, 1995). The safety stopping rule is determined by:

$$\Pr[\text{prob}(\text{toxicity}) > 0.20 \mid \text{data}] > 0.85.$$

If there is a greater than 85% chance that the toxicity rate is greater than 20%, then accrual will be suspended and the SSC (Section 10.1.6.1) will meet to review safety data including aggregated safety summaries. We assume a beta (0.4, 1.6) prior distribution for the toxicity rate, which has a mean of 0.2 corresponding to the 20% target toxicity rate. Table 16 presents the operating characteristics of the above monitoring rule.

Table 15: Suspension Boundaries for Toxicity During Expansion

Total Number of Treated Subjects	Suspending Accrual if ≥ Number of Subjects with Toxicity
1	Not Applicable
2-3	2
4-7	3
8-11	4
12-15	5
16-19	6
20-23	7
24-26	8

Table 16: Operating Characteristics for Subject Accrual Suspension Rules

True Toxicity Rate	Accrual Suspension Probability Based on 26 Subjects	Sample Size (percentiles)		
		25th	50th	75th
0.19	0.295	17	-	-
0.20	0.333	14	-	-
0.26	0.574	7	19	-
0.30	0.720	5	11	-
0.40	0.938	3	6	11

An internal SSC (Section 10.1.6.1) consisting of representatives from Clinical Development, Drug Safety, Biostatistics, other functional representatives, as needed, and at least one principal Investigator will meet at least quarterly to review safety data for potential safety risks or more frequently if needed. If it is determined that there is a high probability of observing more than 20% toxicities, enrollment will be suspended and the SSC will be convened to make a recommendation on the continuation, modification, or discontinuation of the study.

9.2 Analysis Sets

Analysis Set	Description
Safety Population	All subjects who receive at least 1 dose of study drug will be included in the Safety Population. The safety population will be used for safety analyses and demographics, baseline characteristics, and study drug administration.
mITT Population	Modified Intent-to-Treat (mITT) Population includes all subjects who receive at least 1 dose of study drug and have baseline bone marrow blast, MRD, and extramedullary disease evaluation.
CR Evaluable Population	Subjects who are in mITT and have bone marrow blasts ≥ 5% at baseline and also have at least 1 evaluable post-baseline hematology, extramedullary disease, and bone marrow aspiration and biopsy assessment.
DLT Evaluable Population	All subjects who complete at least the DLT observation period or discontinue from the study treatment due to a DLT will be included.
PK Population	All subjects who receive at least 1 dose of study drug and have sufficient plasma concentration samples to estimate PK parameters will be included in the PK Population. Eligibility for inclusion into the PK population will be completed by the PK expert for the study following review of plasma concentration data.

DLT = dose limiting criteria; MRD = measurable residual disease; PK = pharmacokinetic.

9.3 Statistical Analyses

9.3.1 General Considerations

Data will be summarized by descriptive statistics, including number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of subjects.

A detailed description of analysis methods will be provided in the SAP.

9.3.2 Subject Characteristics

Demographic data including age, sex, race and baseline disease characteristics including cancer history and prior cancer therapy will be summarized and presented in data listings.

9.3.3 Efficacy Endpoint Analysis

9.3.3.1 Primary Endpoint

The primary endpoint is the CR rate with luveltamab tazevibulin as monotherapy. CR is defined as:

- Marrow blasts < 5% by morphological examination
- ANC > 1 Gi/L
- Platelet count > 100 Gi/L
- Absence of leukemic blasts in the peripheral blood by morphological examination, and
- No evidence of EMD.

The CR rate is defined as the percent of subjects with CR observed within luveltamab tazevibulin as monotherapy. A subject without any post-baseline evaluable bone marrow assessment will be as a non-responder to treatment. The corresponding 95% exact CI for CR rate will be calculated by the Clopper-Pearson method. The primary endpoint will be based upon the mITT population for the selected dose. A sensitivity analysis will be performed utilizing CR Evaluable Population for the selected dose.

9.3.3.2 Secondary Efficacy Endpoints

The secondary endpoints will be based upon the population specified in each of the sections below.

9.3.3.2.1 Duration of CR

Duration of response for CR is defined as the time from date of the first observed CR until morphologic relapse or death whichever is first. Subjects who are alive and leukemia-free at the time of the statistical analysis will be censored at the time of their last disease assessment. The

median duration of response time along with the corresponding 95% confidence interval (CI) will be calculated using Kaplan-Meier methods.

9.3.3.2.2 Relapse-Free Survival

Relapse-free survival for CR/CRh responders is defined as the time between the date of first CR or CRh and relapse or death due to any cause, whichever comes first. Subjects who are alive and relapse free at the time of the statistical analysis, RFS will be censored at the last assessment date. The RFS will be summarized using Kaplan-Meier method.

9.3.3.2.3 Overall Survival

Overall Survival is defined as the time between the first dose and death due to any cause. Subjects who do not have a date of death will be censored on the last date for which a subject was known to be alive. The Kaplan-Meier method will be used to summarize OS.

The following additional analyses will be investigated.

9.3.3.2.4 Event-Free Survival

EFS is defined as the time between the date of first dose and the induction treatment failure, relapse for those who have induction treatment success or death due to any cause, whichever comes first. Subjects who are alive and event-free at the time of the statistical analysis, EFS will be censored at the last assessment date. The EFS will be summarized using Kaplan-Meier method.

9.3.3.2.5 Response including CRh

The response including CRh rate is defined as the percent of subjects with CR or CRh observed during luveltamab tazevibulin monotherapy dosing. CRh is defined as:

- Marrow blasts < 5% by morphological examination with ANC > 0.5 Gi/L and platelet count > 50 Gi/L, but the count recovery criteria for CR are not met,
- Absence of leukemic blasts in the peripheral blood by morphological examination, and
- No evidence of EMD.

A subject without any post-baseline evaluable bone marrow assessment will be as a non-responder to treatment. The corresponding 95% exact CI for CR/CRh rate will be calculated by the Clopper-Pearson method.

9.3.4 Exploratory Endpoints

9.3.4.1 FOLR1

The correlation between the CR and FOLR1 expression levels may be explored if applicable.

9.3.4.2 Transplantation Rate

The transplantation rate is defined as the percent undergoing a transplant of any kind during the study. The corresponding Clopper Pearson 95% confidence interval will be calculated.

9.3.4.3 Duration of MRD-negative CR

Duration of MRD-negative CR is defined as the time from date of the first observed MRD-negative response until MRD test is no longer negative, morphologic relapse, extramedullary relapse or death whichever is first. Subjects who are alive and are MRD-negative at the time of the statistical analysis will be censored at the time of their last disease assessment. The median along with the corresponding 95% CI will be calculated using Kaplan-Meier methods.

9.3.4.4 MRD-negative Rate

The secondary endpoint MRD-negative rate of receiving luveltamab tazevibulin as monotherapy will be considered. MRD-negative is defined as MRD < 0.01%. A subject without any post-baseline evaluable MRD assessment will be as a non-responder to treatment. The corresponding 95% exact CI for MRD-negative rate will be calculated by the Clopper-Pearson method. The analysis will be performed utilizing the MRD Evaluable Population. The analysis will also be performed on mITT.

9.3.4.5 MRD-negative on Combination therapy

The MRD-negative rate on combination therapy is defined as the percent of subjects who achieve MRD-negative status after starting combination therapy with luveltamab tazevibulin. The corresponding 95% exact CI will be calculated by the Clopper-Pearson method. The duration of response will be calculated using Kaplan-Meier method and summarized by cohort.

The following additional 2 analyses will be investigated, if possible.

9.3.4.6 Durable Response Rate

Durable response rate is defined as the proportion of subjects achieving CR or CRh lasting at least 3 months or until transplantation if earlier among all subjects evaluable for the durable response rate assessment. The corresponding Clopper Pearson 95% CI will be calculated for the durable response rate.

9.3.4.7 CR/CRh on Combination therapy

The CR/CRh rate on combination therapy is defined as the percent of subjects who archive CR after starting combination therapy with luveltamab tazevibulin. The corresponding 95% exact CI for CR rate will be calculated by the Clopper-Pearson method. The duration of response for CR/CRh rate on combination therapy will be calculated using Kaplan-Meier method.

9.3.5 Safety Analyses

All safety data will be summarized using descriptive statistics based on safety population. Study drug administration will be presented in a listing.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify all AEs with respect to system organ class and preferred term. TEAEs are defined as AEs with onset at the time of or following the start of treatment with study drug, or AEs that were present prior to the treatment but worsened after treatment initiation, or AEs that were present and resolved prior to treatment and reappeared after treatment initiation. The severity of an AE will be classified using NCI CTCAE v5.0. The number and percentage of subjects with TEAEs will be summarized by system organ class, preferred term, and initial treatment dose. Summaries in terms of severity and relationship to study drug will be provided. TEAE by age category (< 1year vs ≥ 1year) will also be summarized, if appropriate. All SAEs will be summarized similarly. Subject listings of AEs causing study drug discontinuation will be produced. A data listing for all deaths will be provided as well.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and be summarized by the number and percentage of subjects taking each medication, classified using WHO ATC/DDD (Anatomical Therapeutic Chemical (ATC) as the classification system and the Defined Daily Dose [DDD]) classes and preferred terms.

The observed values and changes from baseline for clinical laboratory tests will be summarized by study visit descriptively for each clinical laboratory analyte. Shift tables will be provided to show the proportions of subjects with changes in laboratory outcomes among specific abnormalities if data is available.

For vital signs and ECG measurements, descriptive summaries of observed values and changes from baseline will be presented by study visit. Subjects who are post-allogeneic HSCT will be monitored closely for the development of acute graft versus host disease.

9.3.6 Pharmacokinetic Analyses

PK assessments will include but are not limited to, area under the curve (AUC), AUC up to the last measurable concentration (AUC_{last}), maximum serum concentration (C_{max}), half-life ($t_{½}$), clearance (CL), and volume in steady state (V_{ss}); parameters will be calculated using noncompartmental techniques plasma drug concentration, if sufficient. The parameters will be summarized descriptively.

9.3.7 Biomarker Analyses

Samples may be collected to better understand the impact of FOLR1 expression on response to treatment drug. FOLR1 expression will be presented in a listing.

9.3.8 Immunogenicity Analyses

The detection and characterization of antibodies to the drug will be performed using a validated assay to enable interpretation of the ADA data. ADA results will be presented in a data listing.

9.4 Sample Size Determination

Initially enroll up to 6 DLT evaluable subjects per dose level. Once a particular dose is selected, enrollment will be expanded to total 18 subjects for that dose level. Sample size of 18 subjects will provide a type I error rate of 0.025 (1-sided) and power of 80% to distinguish the target response (CR) rate of 30% and historic response rate of 5%. The target response rate is supported by preliminary efficacy results from EAP data. There is no second CR (CR2) rate reported in subjects with *CBFA2T3::GLIS2* AML. The historic response rate is based on outcomes data from COG Myeloid Disease Committee experts in this population.

9.5 Missing Data

Statistical considerations and methodology for handling missing data will be detailed in the SAP.

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following, as applicable:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.2 Financial Disclosure

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

10.1.3 Informed Consent Process

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential subject or their legally authorized representative defined as parents, guardians or care givers and answer all questions regarding the study.
- Potential subjects must be informed that their participation is voluntary. They or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be reconsented, as applicable, to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or their legally authorized representative.

10.1.4 Recruitment Strategy

The trial will rely upon clinical sites, Investigators, the COG, support groups, and study personnel to identify and recruit eligible subjects. A site's ability to recruit eligible subjects will be evaluated prior to being selected for the study. Eligible subjects will be enrolled continuously until the required enrollment numbers have been met (competitive enrollment). In an effort to improve overall trial experience, the Sponsor has consulted with subjects and study site

personnel to highlight key protocol assessments that can be streamlined to reduce subject burden where possible. Additionally, the Sponsor will follow the relevant guidance related to the enrollment of diverse subject populations in this trial, as well as continuing to evaluate strategies to support clinical trial diversity within clinical sites and in the study overall.

10.1.5 Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.
- The subject must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6 Committees Structure

10.1.6.1 Steering and Safety committee (SSC) and Independent Data Monitoring Committee (IDMC)

Steering and Safety Committee (SSC)

The SSC will routinely monitor the evolving safety, efficacy, and PK data, as needed and available; and will provide recommendations to support decisions regarding the study conduct, including decisions for escalating dose escalation cohorts, identifying and confirming safety issues, modification of ongoing dosing or starting doses (eg, emerging PK data supports q4w dosing), and guidance on potential study modifications based on accumulating safety data, study conduct, and/or emerging external information.

This committee will comprise of select members of the Sponsor clinical team, selected Investigators, and members of the contract research organization who have responsibilities for managing and/or participation in the ongoing review of study subjects. The SSC may invite additional members to attend or participate in meetings as required (eg, pharmacokineticist).

Independent Data Monitoring Committee (IDMC)

An independent IDMC will be appointed to support the Sponsor in safeguarding the interests of study subjects, and to assess the safety and efficacy of treatment with luveltamab tazevibulin. The IDMC will be comprised of qualified clinicians and a biostatistician, all independent from the Sponsor and investigational sites, selected to avoid conflict(s) of interest. The IDMC will review and assess ongoing safety data and emerging risk/benefit balance at regular intervals and on an ad-hoc basis when required. The IDMC will also provide an independent response assessment at minimum for all subjects intended to support the filing. The IDMC's specific activities will be detailed in the IDMC charter, which will define the processes, including meeting proceedings and structure, data assessments, documentation and recordkeeping, process for IDMC recommendations, and regulatory reporting, as applicable. Additional details will be provided in the Independent Data monitoring committee charter.

10.1.6.2 Institutional Review Board Approval (IRB)/Independent Ethics Committee (IEC)

This protocol and any material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator to an IRB/IEC. This also applies to protocol amendments.

The Sponsor, (Sutro Biopharma, Inc.) will supply relevant data for the Investigator to submit the study protocol and additional study documents to the IRB/IEC. The principal Investigator will submit the study protocol for review and approval by an IRB/IEC, according to national law and/or local regulations, and will provide the IRB/IEC with all appropriate materials.

Verification of the IRBs/IECs unconditional approval of the study protocol and the written informed consent form will be transmitted to the Sponsor or designee.

No subject will be admitted to the study until appropriate IRB/IEC approval of the study protocol has been received, the Investigator has obtained the signed and dated informed consent form, and the Sponsor is notified.

The Principal Investigator will submit appropriate reports on the progress of the study to the IRB/IEC at least annually in accordance with applicable national law and/or local regulations and in agreement with the policy established by the IRB/IEC and Sponsor.

The IRB/IEC must be informed of all subsequent study protocol amendments and of SAEs or SUSARs occurring during the study that are likely to affect the safety of the subjects or the conduct of the study.

10.1.7 Safety Oversight and Clinical Monitoring

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of regulatory authorities, the Sponsor and its

representatives, and the IRB/IEC for each study site. The Sponsor may delegate some administrative aspects of this study to a duly authorized representative including, but not limited to, study initiation, monitoring, and management of SAE reports.

The data will be collected using an EDC system by remote data entry on eCRFs. The Sponsor or their representative's monitor is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to the subjects' medical records and other study-related records needed to verify the entries on the eCRFs.

Ongoing study oversight will be provided by Sponsor or designated contract research safety team, site monitors, medical monitors, and clinical research assistants. In addition to ongoing SSC and IDMC team meetings, the Sponsor may schedule ad-hoc meetings including the REFRaME-P1safety team and study Investigators.

10.1.8 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of subjects.

The first act of recruitment is the first open site and will be the study start date.

Study/Site Termination

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

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

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

<u>For study termination:</u>

- Discontinuation of further study intervention development.

<u>For site termination</u>:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.

- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the Investigator.
- Total number of subjects included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.9 Electronic Case Report Forms (eCRFs)

The data will be collected using an EDC system by remote data entry on eCRFs. Sites will receive training on the EDC system. All users will be supplied with unique login credentials.

- The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.
- For each subject consented, an eCRF must be completed promptly after data collection. This also applies to records for those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF consistent with the source documentation.
- All laboratory data and Investigator observations on the results and any other clinically significant test results must be documented on eCRFs.
- Full information regarding electronic data capture and completing eCRFs is included in the Investigator files.

10.1.10 Data Collection, Retention, and Monitoring

The Investigator should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (Section 8 of ICH E6 GCP consolidated guidance) and General Data Protection Regulation (GDPR) (Article 89) and as required by the applicable regulatory requirement. The Investigator should take measures to prevent accidental or premature destruction of these documents. Essential documents should be retained 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. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. The financial aspects of the trial should be documented in an agreement between the Sponsor and the Investigator. Upon request of the monitor, the Sponsor, auditor, IRB/IEC, or regulatory authority, the Investigator should make available for direct access all requested trial-related records.

10.1.11 Protocol Deviations

Deviations to the protocol inclusion and exclusion criteria will not be allowed. Protocol deviations should be reported to the Sponsor and/or Sponsor's representative and the IRB/IEC according to policy as they occur or are discovered.

10.1.12 Reporting of Serious Breaches

Any breach of the clinical study protocol version applicable at the time of the breach, which is likely to affect to a significant degree the safety of the study subjects, and/or the rights of a trial participant, and/or the reliability of the data generated in the clinical trial, is serious and should be reported. Any breach, meeting these criteria, should be reported as per region-specific guidelines of the Sponsor becoming aware of a serious breach.

The Sponsor is responsible for the notification in Europe via the EU portal and EU database in accord with Article 71 of the Regulation (EU) No 536/2014 within 7 calendar days of the Sponsor becoming aware of a serious breach. The Sponsor may delegate this task to a service provider by means of a written agreement.

10.1.13 Publication Policy

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

10.2 Appendix 2: Efficacy Assessment

10.2.1 Response evaluation criteria in AML

Table 17: Response Criteria

Response	Criteria
Complete Remission (CR)	Marrow blasts < 5% by morphological examination, Absolute neutrophil count (ANC) > 1 Gi/L, Platelet count > 100 Gi/L, Absence of leukemic blasts in the peripheral blood by morphological examination, and No evidence of extramedullary disease.
CR with Partial Hematological Recovery (CRh)	Marrow blasts < 5% by morphological examination, ANC > 0.5 Gi/L and platelet count > 50 Gi/L, but the count recovery criteria for CR are not met, Absence of leukemic blasts in the peripheral blood by morphological examination, and No evidence of extramedullary disease.
Complete Remission, MRD-negative (CR MRD-negative)	A bone marrow with <5% blasts by morphology; and MRD < 0.01%; and Absolute neutrophil count (ANC > 1 Gi/L) Platelet count > 100 Gi/L, Absence of leukemic blasts in the peripheral blood by morphological examination, No evidence of extramedullary disease

EMD = extramedullary disease; PCR = polymerase chain reaction; WBC = white blood cell.

10.3 Appendix 3: Clinical Laboratory Tests

- The tests detailed in Table 18 will be performed by the local laboratory.
- Pre-treatment laboratories (Day 1 of cycle) may be obtained within 3 days prior to Day 1 of a cycle. If labs were taken the day immediately prior dosing with luveltamab tazevibulin, they do not need to be repeated on dosing day.
- If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations and results should be recorded in the source and eCRF.

Table 18: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters

Hematology	• Platelet count
	• Red blood cell (RBC) count
	• RBC indices
	  • Mean corpuscular volume (MCV)
	  • Mean corpuscular hemoglobin (MCH)
	  • %Reticulocytes
	• White blood cell (WBC) count with differential absolute neutrophil count (ANC):
	  • Neutrophils
	  • Lymphocytes
	  • Monocytes
	  • Eosinophils
	  • Basophils
	  • Blasts
	• Hemoglobin
	• Prothrombin time (INR)
	• Partial thromboplastin time
	• Fibrinogen
	• Hematocrit

Footnotes presented on next page.

Table 18: Protocol-required Safety Laboratory Tests (Contd)

Laboratory Tests	Parameters	
Clinical chemistry[a]	• Blood urea nitrogen (BUN) or urea • Potassium • Creatinine • Sodium • Calcium • Glucose [non-fasting] • Phosphorus • Uric acid	• Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) • Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) • Alkaline phosphatase2 • Total and direct bilirubin • Total protein • Albumin • Lactate dehydrogenase
Routine urinalysis[b]	• Specific gravity • pH, glucose, protein, blood, ketones, by dipstick • Microscopic examination (if blood or protein is abnormal)	
Other screening tests	• Amylase • Lipase • Thyroid Stimulating Hormone (includes T3 and T4)[C] • Creatinine phosphokinase	

T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

a. Creatinine clearance will need to be performed by the Cockcroft Gault equation, a renal scan or 24-hour urine collection.

b. Urinalysis should be performed on freshly voided clean sample (protein, glucose, blood, pH, and ketones). If findings are abnormal based on Investigator judgment, then a microscopic evaluation will be performed to assess the abnormal findings.

c. TSH is obtained in screening (≤ 21 days prior to first dose), and at end of treatment. TSH is obtained at Cycle 4 (pre-dose) and every 3 subsequent cycles. If TSH is abnormal at end of treatment, T3 and T4 should be repeated. Additional tests may be performed, per Investigator's discretion.

Investigators must document their review of each laboratory safety report.

10.4 Appendix 4: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1 Definition of AE

AE Definition

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the subject's condition).
- Exacerbation of a chronic or intermittent pre-existing condition after study intervention administration including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>not</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
    - Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.4.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

Events or Outcomes Not Qualifying as Serious Adverse Events

The following are not considered SAEs:

- Preplanned or elective hospitalization including social and/or convenience situations (eg, respite care) emergency room visits or outpatient observation.
- Events of progression of the subject's underlying cancer as well as events clearly related to progression of the subject's cancer (signs and symptoms of progression) should not be reported as a SAE unless the outcome is fatal within the safety reporting period.
- Diagnosis of progression of disease or hospitalization due to signs and symptoms of disease progression alone should not be reported as SAEs.

10.4.3 Definition of SUSAR

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as a suspected Adverse Reaction that occurs in the trial and that is both unexpected and serious.

Suspected adverse reactions (SAR) are those AEs of which a reasonable causal relationship to any dose administered of the investigational medicinal product and the event is suspected. Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP or SmPC for an authorized medicinal product).

For this study the IB is used to assign expectedness. If a previously reported non-serious adverse reaction occurs as a serious reaction, the reaction will be considered to be unexpected and reported as a SUSAR. Each fatal SAR will also be reported as a SUSAR if not included and justified in the RSI of the IB. Serious adverse reactions occurred once will not be considered expected (unless a strong written rationale is provided and approved by the Regulatory Authority). Single occurrences will therefore be considered unexpected and reported as SUSAR.

10.4.4 Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Assessment of Intensity

The severity assessment for an AE or SAE should be completed using the NCI-CTCAE v5.0 (published 27 Nov 2017). Any AE or SAE not listed in the NCI-CTCAE v5.0 will be graded per Investigator clinical judgment by using the standard grades as follows:

- **Grade 1 (Mild):** Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- **Grade 2 (Moderate):** Sufficient discomfort is present to cause interference with normal activity.
- **Grade 3 (Severe):** Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.
- **Grade 4:** Life-threatening AE
- **Grade 5:** Death related to the AE.

The Investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

Relationship to Luveltamab Tazevibulin

When assessing causality, Investigator's should utilize medical judgment to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, dechallenge, or rechallenge.

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

Expectedness

An AE is considered unexpected if it is not mentioned in the IB, or if the specificity of the event is not consistent with the IB.

10.4.5 Reporting of AEs

Any AE from the time the first dose of luveltamab tazevibulin is administered through 30 days after the last dose or date of initiation of subsequent anti-cancer therapy will be recorded on the source and AE eCRF. Any AEs that occur after signing the ICF but prior to the first dose of luveltamab tazevibulin should be recorded as medical history. Any SAEs that occur after signing the ICF but prior to first dose of luveltamab tazevibulin that are related to study procedures should be reported and recorded on the AE eCRF. During the Follow-Up Phase, AEs of Grade 3 or higher that are considered related to study drug, as well as all related SAEs, should be followed until resolution or initiation of subsequent anti-cancer therapy.

AEs should be reported in standard medical terminology consistent with source documentation. Whenever possible, the Investigator should combine signs and symptoms that constitute a single disease entity or syndrome into a final diagnosis. For example, fever, cough, and shortness of breath may be reported as pneumonia, if that is a reasonable diagnosis.

10.4.6 Reporting of SAEs

All SAEs must be reported to the appropriate Sponsor contact person by study-site personnel within 24 hours of their knowledge of the event as follows:

- SAEs that occur from the first dose of study drug until 30 days after the last dose of study drug.
- SAEs that occur after signing the ICF and prior to the first dose of study drug if the event is related to study procedures.
- SAEs that occur > 30 days after the last dose of study drug if assessed as related to study drug by the Investigator.

Information regarding SAEs will be transmitted to the Sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the Sponsor within 24 hours. The Sponsor will determine the need for an expedited report to regulatory authorities and will perform any necessary reporting. The Sponsor will notify study

Investigators of all SUSAR reports. Investigator is responsible for reporting all SUSARs to the IRB/IEC.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves,
- The event stabilizes,
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct, or
- It becomes unlikely that any additional information can be obtained (subject or healthcare practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

All SAEs that meet the above criteria MUST be immediately reported to the study Pharmacovigilance Vendor and Sutro Safety within the timeframes detailed in Table 19.

Table 19: Serious Adverse Event Reporting Requirements

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours	All SAEs should be reported to the Study Pharmacovigilance Vendor and Sutro Safety within 24 hours of site knowledge of the event. SAE report forms should be completed and sent to: PVDS-NA@premier-research.com PVDS-ROW@premier-research.com

10.4.7 Reporting of SUSARs

The Sponsor will keep detailed records of all AEs which are reported to them by the Investigator or Investigators and will report electronically and without delay to Health Authorities (eg, FDA, EudraVigilance) all relevant information about any SUSAR.

Timelines for SUSAR reporting are as follows:

- Initial fatal or life-threatening SUSARs will be reported to the competent authorities, ethic committees, and investigative sites as soon as possible but no later than 7 calendar days from initial receipt of the SAE by Sponsor.

- All other SUSARs will be reported to the competent authorities, ethic committees, and investigative sites as soon as possible but no later than 15 calendar days from initial receipt of SAE by Sponsor.

10.5 Appendix 5: General Contraceptive and Barrier Guidance

Female and male subjects who have reached puberty must agree to undergo physician-approved reproductive education. Side effects of the study therapy on reproduction and the need to avoid pregnancy or partner pregnancy must be discussed with them and their parent(s) or guardian(s). The importance of abstinence from heterosexual intercourses will be emphasized.

As we cannot predict the effect of luveltamab tazevibulin on the efficacy of hormonal methods of birth control in females, all subjects who have undergone puberty and are potentially sexually active must agree to use a physical barrier (condoms) method during heterosexual contact. At the discretion of the treating physician females may also use additional contraceptive methods, including hormonal ones. Pregnancy prevention must continue while participating in the study, during dose interruptions, and for at least 6 months following luveltamab tazevibulin discontinuation.

All subjects and their parent(s) or guardian(s)will be instructed to notify the Investigator if a pregnancy is discovered either during luveltamab tazevibulin treatment or within 6 months of last luveltamab tazevibulin dose.

10.6 Appendix 6: CNS Prophylaxis and Therapy

CNS status definitions:

CNS 1, 2 and 3 are defined in Inclusion Criteria (Section 5.0 – Inclusion Criteria).

Refractory to CNS treatment: Subjects who have persistent CNS2 at the end of Cycle 2.

CNS Prophylaxis for Subjects with CNS1 or CNS2

CNS1 subjects at diagnosis will receive IT AraC or ITT (intrathecal triple therapy) during screening period or within 8 days of Day 1 therapy.

CNS2 subjects will receive ITT once a week during Cycle 1 until CSF is clear. A minimum of 4 ITT is recommended and no more than 6 ITT. ITT therapy can extend into Cycle 2, if needed.

Criteria to start Cycle 2 and beyond: CNS prophylaxis is at the discretion of the Investigator intrathecal cytarabine and ITT.

If after 2 cycles CNS2 disease is still present, the subject is no longer eligible to receive single-agent monotherapy and intermediate dose cytarabine may be added.

Table 20: Dosage for Single Agent Cytarabine Intrathecal Prophylaxis

Age	Cytarabine
<1 year	**20 mg**
≥ 1 - < 2 years	**30 mg**
≥ 2 - < 3 years	**50 mg**
≥ 3 years	**70 mg**

Table 21: Dosages for Prophylaxis Intrathecal Triple Therapy

Age	Methotrexate	Hydrocortisone	Cytarabine
<1 year	6 mg	12 mg	18 mg
≥ 1 - < 2 years	8 mg	16 mg	24 mg
≥ 2 - < 3 years	10 mg	20 mg	30 mg
≥ 3 years	12 mg	24 mg	36 mg

10.7 Appendix 7: Protocol Amendment Summary of Changes

Overall Rationale:

The overall rationale for the updated REFRaME-P1 V3.1, Amendment 2.1 dated 30 Sep 2024 is to address Health Authority queries. This amendment represents cumulative changes to the original protocol.

Summary of Changes in the Current Amendment:

Section # and Name	Description of Change	Brief Rationale for Change
Global Changes	• Versioning and hyperlinking updated. • Minor editorial edits associated with consistent use of terms throughout protocol, updated abbreviations, and added Section headers.	• Administrative change. • For readability and clarity.
	• In reference to slides for bone marrow evaluations, “and peripheral blood smears” was added.	• For clarity.
Protocol Approval Page	• Signatories updated.	• Administrative change.
Section 1.1, Synopsis and Section 4.1.2, Dosing	• Updated Dosing language for Cycle 1 and 2 (Doses 1-4) to state that should count recovery fail to occur by the end of the 28-day observation period, treatment may be resumed as long as ANC > 0.50 Gi/L (Value was previously ANC > 500 Gi/L).	• Corrected an error.
Section 1.1, Synopsis and Section 5.1, Inclusion Criteria	• Inclusion criteria (IC) #5: “Subjects with Gilbert’s disease will also require direct bilirubin < 1.5 × ULN”. • IC #8: QTcF was updated from < 500 msecs to QTcF < 450 msecs. • IC #10: Removed “of childbearing potential” and replaced with “have experienced menarche”.	• Per Health Authority query. • Per Health Authority query. • Per Health Authority query.

Section # and Name	Description of Change	Brief Rationale for Change
Section 1.1, Synopsis and Section 5.1, Inclusion Criteria (cont'd)	• IC #11: Updated IC to: Female subjects who have experienced menarche must have a negative pregnancy test within 7 days of the first dose of study drug. All subjects (male and female) who have undergone puberty and are potentially sexually active must agree to use a physical barrier (condoms) method during heterosexual contact. At the discretion of the treating physician females may also use additional contraceptive methods, including hormonal contraceptives. Pregnancy prevention must continue while participating in the study, during dose interruptions, and for at least 6 months following luveltamab tazevibulin.	• To align with Section 10.5 and per Health Authority query.
	• Removed IC #12.	• Condensed IC #11 and #12.
Section 1.3, Schedule of Assessments (SoA)	• Added 3 new columns in Tables 1 and 2 for "Cycle 4 and onwards" to add assessments for thyroid stimulating hormone.	• Per Health Authority query.
	• Updated Amylase, lipase, and TSH assessment in Tables 1 and 2 to include Amylase and lipase, and Thyroid tests.	• Per Health Authority query and to provide clarity.
	• Footnote for amylase and lipase, and Thyroid tests in Tables 1 and 2 were updated based on changes to assessments for these labs.	• Per Health Authority query and to provide clarity.
	• Added a Day 15 assessment for Vital signs in Tables 1 and 2.	• Per Health Authority query.
	• Added a footnote for vital signs in Tables 1, 2, and 3 to state that vital signs should be collected prior to infusion of luveltamab tazevibulin.	• Per Health Authority query.

Section # and Name	Description of Change	Brief Rationale for Change
Section 1.3, SoA (cont'd)	• Footnote for bone marrow evaluation for sample collection of bone marrow samples, biopsies, aspirates, and peripheral blood smears was updated in all tables.	• For clarity.
	• Footnote for bone marrow evaluation for Tables 1 and 2: indicated that the day of collection for Cycle 4 was **Day 28** (Table 1) or **Day 42** (Table 2) and for Cycle 6 day of collection was also **Day 28** [Table 1] or **Day 42** [Table 2].	• For clarity.
	• Referred to Section 8.8 for biomarker testing, with the exception of, AML, FOLR1, and *CBFA2T3::GLIS2* which are specified in the footnote.	• For clarity and guidance.
	• Footnote for complete blood count in Table 1 and 2. Added that collections may be performed at the Investigator's discretion.	• For clarity.
	• Footnote for Ophthalmic exams: Added language from Section 8.8.1 to provide instructions for times when bone marrow evaluations and and ophthalmic exams occur on the same cycle.	• For consistency and clarity.
	• Footnote for CPK in Table 1 and Table 2 was updated to clarify that CPK would be obtained in screening, pre-dose on dosing days of each cycle beginning at C1D15 (Table 1) or C2D22 (Table 2).	• For clarity.
Section 1.3, SoA Section 2.3.1.3, Planned Safety Monitoring with Regards to Risks Section 8.2.2, Physical Examinations	• Wording related to ophthalmic examinations was updated to include not only ophthalmologists but also optometrists or other qualified professionals.	• For clarity.
Section 2.3.1.2, Reproductive Toxicity	• Created a new section from language presented in Section 8.4.5.	• Per Health Authority query.

Section # and Name	Description of Change	Brief Rationale for Change
Section 5.4, Screen Failures	• Updated the last sentence to: Minimal information includes demography, ICF date screen failure details, eligibility criteria, and any AE or SAE, if they are deemed related to the screening procedure by the Investigator.	• Per Health Authority query.
Section 8.4.5, Pregnancy	• Condensed this section. Also moved 1st paragraph to a Section 2.3.1.2.	• Per Health Authority query.
Section 8.7, Genetics	• Provided information on what genetic testing will be performed in this study.	• Per Health Authority query.
Section 8.8.1, Tissue from Bone Marrow and Blood Samples	• Provided additional information on what bone marrow and blood samples will be used for. Also provided information on sample storage and handling.	• Per Health Authority query.
Section 10.3, Appendix 3: Clinical Laboratory Tests	• Second bullet: Updated the first sentence to include that pre-treatment laboratories could be obtained within 3 days prior to Day 1 of the cycle. • Added amylase to “Other screening tests”. • Added footnote to provide guidance on assessment schedule for TSH, T3, and T4.	• Per Health Authority query. • Corrected an error. • Per Health Authority query.
Section 10.4.4, Appendix 4: Recording and Follow-Up of Adverse Events and/or Serious Adverse Events	• In “Relationship to Luveltamab Tazevibulin”, added that when assessing causality, Investigator’s should utilize medical judgement to determine the cause of the AE.	• Per Health Authority query.
Section 10.5, Appendix 5: General Contraceptive and Barrier Guidance	• Condensed general contraceptive language for females and males.	• Per Health Authority query.

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