Protocol Title:		Phase 1/2a, Single Dose Study Investigating NTLA-5001 in Subjects with Acute Myeloid Leukemia	
Protocol Number:		ITL-5001-CL-001	
Study Phase:		Phase 1/2a	
Short Title:		NTLA-5001 for Acute Myeloid Leukemia	
Sponsor	**Name:**	Intellia Therapeutics, Inc.	
	Legal Registered Address:	40 Erie Street Cambridge, MA 02139 USA	
Site of Investigation		Multi-Center, Multi-Country	
Regulatory Agency Identifier Number(s)		EudraCT: 2021-001231-13	
Protocol Date:		**Document Version**	**Date**
		Amendment v2.0	22 Dec 2021

[redacted]

INVESTIGATOR STATEMENT

ITL-5001-CL-001: Phase 1/2a, Single Dose Study Investigating NTLA-5001 in Subjects with Acute Myeloid Leukemia

I have read the protocol, including all appendices, and I agree to abide by all the provisions set forth in it. I will conduct this study as outlined herein, in compliance with current Good Clinical Practice (GCP) standards as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for GCP, all applicable local regulations and laws, and the applicable Institutional Review Board/Independent Ethics Committee (IRB/IEC) and other institutional requirements.

I also understand that this material contains confidential information belonging to Intellia Therapeutics, Inc. Except if Intellia otherwise agrees in writing, I agree to hold such information in confidence and not to disclose it to others (except where applicable by law) nor use it for unauthorized purposes. In the event of an actual or suspected breach of this obligation, Intellia is to be promptly notified.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Institution Address

_____

Date

CONTACT DETAILS OF KEY PERSONNEL

24-Hour Contact for Serious Adverse Events (SAEs) See Section 8.5.5	[redacted]
Medical Monitor (Medpace)	[redacted]
Clinical Research Contact(s)	[redacted]
Sponsor Clinical Research Contact(s)	[redacted]

1 PROTOCOL SUMMARY

1.1 Synopsis

Study Title	Phase 1/2a, Single Dose Study Investigating NTLA-5001 in Subjects with Acute Myeloid Leukemia
Protocol Number	ITL-5001-CL-001
Phase of Development	Phase 1/2a
Investigational Product	NTLA-5001
Reference Medicinal Product	Not Applicable
Study Population	The study population will consist of subjects ≥ 18 years of age who have acute myeloid leukemia (AML) that is detectable after having received standard first-line therapy. Subjects may have either measurable residual disease (MRD) detected by central laboratory analysis, or they may have hematologic relapsed/refractory disease detected by morphology. The study population will be enrolled in 2 independent Arms. Subjects in Arm 1 will have MRD identified at a frequency > 0.1% by central laboratory testing but < 5.0% AML blasts in bone marrow (BM) on locally assessed morphology, and no evidence of blasts in peripheral blood or extramedullary disease (i.e., are in complete remission [CR]/complete remission with incomplete hematologic recovery [CRi]). Subjects in Arm 2 will have ≥ 5.0% AML blasts in BM by locally assessed morphology. Subjects must have received prior therapy as follows: i) attempted remission induction therapy with 1 cycle of anthracycline-based therapy followed by a second cycle for persistent morphologic disease at the first BM assessment; or ii) attempted remission induction therapy with 1 cycle of anthracycline-based therapy followed by a second induction regimen for subjects with initial CR and early recurrence; or iii) hypomethylating agent in combination with venetoclax for at least 2 cycles of therapy and without ongoing clinical benefit; iv) Subjects with FMS-like tyrosine kinase 3 (FLT3) alterations or isocitrate dehydrogenase (IDH) mutations who are enrolled in countries where targeted therapy is standard-of-care for first line use and have targeted therapy available must have received therapy and not have ongoing clinical benefit; v) Subjects who are eligible to receive standard-of-care hematopoietic cell transplant (HCT) must have received transplant prior to study entry. Dose escalation will be performed in parallel for Arm 1 and for Arm 2, and separate safety expansion cohorts will be enrolled for Arm 1 and for Arm 2. MRD detection will be performed by a central laboratory and will use the difference from normal flow cytometry methods as described by Loken et al (2019).
Investigative Sites	Up to 10 investigative sites
Planned Number of Subjects	Up to 54 subjects in total: 18 subjects in escalation and 9 subjects in expansion for each of the 2 arms.

Objective/Endpoints	OBJECTIVES	ENDPOINTS
	Primary	
	Dose escalation: To identify dose for use in the expansion cohorts	• safety and tolerability as determined by adverse events (AEs) • dose-limiting toxicities (DLTs) (dose escalation only)
	Dose expansion: To evaluate the safety and tolerability of NTLA-5001 in subjects with AML and blasts <5% of bone marrow (Arm 1) and in subjects with AML and blasts ≥5% of bone marrow (Arm 2)	
	Secondary	
	To characterize the cell kinetics (CK) of NTLA-5001 in peripheral blood	• frequency and persistence of NTLA-5001 according to the T cell receptor (TCR) transgene copy number (via droplet digital polymerase chain reaction [ddPCR])
	To estimate the antitumor activity of NTLA-5001 in subjects with AML	• disease response (including MRD response), duration of response / remission, and disease progression (see Section 13.4)
	Exploratory	
	To estimate other cancer-related outcomes in subjects with AML	• overall survival • Eastern Cooperative Oncology Group (ECOG) performance status • quality of life (QOL) as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) instrument and length of hospital stay after NTLA-5001 infusion
	To characterize subject AAV exposure	• presence of adenovirus vector in blood and urine
	To characterize immunologic parameters and characteristics of NTLA-5001 cells after administration in subjects with AML	• plasma cytokine levels • Wilms' tumor 1 (WT1) expression on tumor • NTLA-5001 characteristics including flow cytometry, phenotype, editing, and gene expression • bone marrow immune parameters and NTLA-5001 cell kinetics

Study Design Overview	The dose escalation phase of the study will consist of up to 3 cohorts of subjects in Arm 1 and 3 cohorts of subjects in Arm 2. Each Arm 1 cohort will include up to 6 subjects, as detailed in dose escalation below. Each Arm 2 cohort will include 3 to 6 subjects. Once a dose is identified for detailed assessment of safety in Arm 1 subjects and 6 subjects have been enrolled at that dose, an expansion cohort will be opened for an additional 9 subjects in Arm 1. Once a dose is identified for detailed assessment of safety in Arm 2 subjects, a safety expansion cohort will be opened for an additional 9 subjects in Arm 2. The screening period will be up to 28 days, and a subject that meets all inclusion and none of the exclusion criteria will be enrolled into the leukapheresis phase in the Arm according to their disease burden (Arm 1 or Arm 2). During screening, MRD will be measured in bone marrow by central laboratory assessment. At study entry, Arm 1 subjects will have < 5.0% AML blasts in bone marrow on locally assessed morphology, and no evidence of blasts in peripheral blood or extramedullary disease (i.e., are in CR/CRi), and MRD identified at a frequency > 0.1% by the central laboratory, [redacted] Arm 2 subjects will have ≥ 5.0% AML blasts in BM by locally assessed morphology. Subjects may have repeat BM assessment prior to Arm assignment based whether screening biopsy was prior to study consent, on interval since screening study, change in condition, or bridging therapy. If an Arm 1 subject is found to have ≥5% bone marrow blasts at repeat BM assessment, the subject may be re-assigned to Arm 2 or, if Arm 2 is not yet enrolling subjects, the subject may receive NTLA-5001 at Dose Level -1. Each subject will undergo leukapheresis for collection of peripheral blood mononuclear cells (PBMC). [redacted] After leukapheresis, subjects who meet criteria for treatment and who have manufactured NTLA-5001 that meet release requirements will enter the treatment phase for the administration of lymphodepleting chemotherapy and study medication. Subjects may receive bridging therapy between leukapheresis and treatment. Each subject in the treatment group will receive lymphodepleting chemotherapy on Day--5, -4, and -3. A subject will be administered a single dose of NTLA-5001 on Day 0. Subjects will be observed in hospital for a minimum of 7 days following dosing, and subjects must remain within 2 hours of the location of the trial site to receive any needed follow-up assessments or care until Day 14. UK subjects will be observed in hospital for a minimum of 14 days following dosing. Additional visits will take place at Week 2, 4, 8, and 16, then at 12-week intervals through Week 112 or until the subject is no longer receiving clinical benefit. Subjects who are no longer receiving clinical benefit will continue to be followed with clinic visits to assess subject survival and AEs every 12 weeks until 112 weeks after administration of NTLA-5001. After participating in this study, all subjects will be followed as part of a long-term monitoring program per local and national regulations. All subjects will be followed for a minimum of 5 years in the UK and for a minimum of 15 years in the US. Infusion of NTLA-5001 that does not meet the intended dose or does not meet release criteria (as specified in the Cell Therapy Manual) will be considered for NTLA-5001 treatment with approval by the sponsor and investigator, except in the UK. Such subjects who receive therapy will not be counted for filling a slot in the dose escalation cohort or safety expansion cohort. In the UK, a dose of NTLA-5001 manufactured for a patient that fails release criteria or is otherwise inadequate will not be given to a patient, and no subject at a UK site may begin lymphodepleting chemotherapy before the subject's product meets manufacturing release criteria.

Dose Escalation and Dose-Limiting Toxicities

Cohort Dosing Overview

Proposed Dose Escalation Cohort Number	Planned Dose
Dose Level -1	[redacted] cells[a]
Dose Level 1	[redacted] cells
Dose Level 2	[redacted] cells
Dose Level 3	[redacted] cells

[redacted]

Dose Level 1 is the starting dose level for each Arm. Subjects who enter the treatment group in Arm 1 or in Arm 2 will be assigned to the dose level cohort currently open for enrollment for the relevant Arm. Arm 1 and Arm 2 will be enrolled in parallel.

Up to 3 subjects will be enrolled in an initial dose evaluation group and will be treated with NTLA-5001 for Arm 1 and for Arm 2. Enrollment will be staggered as follows (see figure in Section 13.8):

- Staggering of enrollment across the 2 study Arms: Arm 1 and Arm 2 will be escalated independently. If an Arm 1 subject is dosed at a new dose level before an Arm 2 subject, the Arm 1 subject will be observed through Day 28 before dosing a subject in Arm 2.
- Staggering of enrollment within a dose level cohort (either Arm 1 or Arm 2): each of the first 3 subjects will be observed for 28 days before enrolling the next subject.
- Staggering of enrollment between Dose Levels: all subjects in a dose evaluation group will be observed for 28 days before any subject is enrolled at the next Dose Level.

Once the entire dose evaluation group for a study Arm has been observed for 28 days, all data, including DLT information from all cohorts in both Arms, will be reviewed by the Sponsor and treating investigators to consider dose escalation. The following study personnel must participate in review of the study data and dose escalation decision: the Intellia Medical Lead, the Intellia Safety Lead, and any Investigator who has treated a subject in the cohort that has just completed 28-day observation.

Dose-limiting toxicities (DLTs) are defined as events with onset within 28 days of infusion as follows:

- Any Grade 4 cytokine release syndrome (CRS) per American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria, and Grade 3 CRS that does not resolve to Grade 2 within 72 hours
- Any Grade 3/4 neurotoxicity per ASTCT immune effector cell-associated neurotoxicity syndrome (ICANS) consensus grading criteria for adults
- Any Grade 4 acute GVHD of any duration; Grade 2 or 3 acute GVHD requiring systemic steroid treatment that does not resolve to ≤ Grade 1 within 7 days.
- Acute infusion reaction: Reactions related to NTLA-5001 occurring within 2 hours of infusion that are not reversible to ≤ Grade 2 within 24 hours.
- Grade 4 neutropenia or thrombocytopenia lasting more than 28 days that is not attributable to underlying disease or lymphodepletion chemotherapy
- Other severe organ toxicity that is not attributable to underlying disease or lymphodepletion chemotherapy as follows: Grade 4 toxicity that is a cardiac disorder, hepatobiliary disorder, renal disorder, respiratory disorder, or vascular

	disorder (per CTCAE); Grade 3 cardiac, respiratory, or vascular disorder that does not resolve to Grade 2 or lower within 72 hours; or Grade 3 hepatobiliary or renal disorder that does not resolve to Grade 2 or lower within 7 days. • Grade 5 events without clinical or radiological evidence of disease progression which are related to NTLA 5001. **Dose Escalation and Dose Reduction Decisions** If none of the initial dose evaluation group subjects experience a DLT, subjects in the treatment phase who have not yet received NTLA-5001 and subsequent subjects entering the treatment phase will be eligible for the next dose escalation cohort. If 1 of the initial dose evaluation group subjects experiences a DLT, enrollment will continue in the dose evaluation group for 3 additional subjects. When the last subject in the expanded dose evaluation group has been observed through Day 28: • If no subject in the expanded dose evaluation group experiences a DLT, subjects in the treatment phase who have not yet received NTLA-5001 and subsequent subjects entering the treatment phase will be eligible for the next dose escalation cohort. • If 1 or more additional subject in the expanded dose evaluation group experiences a DLT, no dose escalation will be proposed. Subjects in the treatment phase who have not yet received NTLA-5001 and subsequent subjects entering the treatment phase will be eligible for Dose Level -1 if DLTs are seen at Dose Level 1, or the next lower dose level will be declared the maximum tolerated dose (MTD), if DLTs are seen at Dose Level 2 or 3. Fewer than 2/6 subjects with DLTs will establish the MTD. If 2 or 3 of the initial dose evaluation group experiences a DLT, no dose escalation will be proposed. Subjects in the treatment phase who have not yet received NTLA-5001 and subsequent subjects entering the treatment phase will be eligible for Dose Level -1 if DLTs are seen at Dose Level 1, or the next lower dose level will be expanded to 6 subjects if DLTs are seen at Dose Level 2 or 3. Fewer than 2/6 subjects with DLTs will establish the MTD. If a dose escalation is proposed, the subsequent cohort dose may be reduced or increased by up to 50% if the Sponsor and investigator agree, based on observations in the prior cohort. At the Sponsor's discretion, up to 6 subjects may be enrolled in any dose cohort for Arm 1 or Arm 2. **Simultaneous Escalation of Arm 1 and Arm 2** The risk of severe or serious adverse events after cell therapy is correlated with a subject's tumor burden (Garcia-Manero et al, 2015; Garzon et al, 2017). Therefore, DLT information from Arm 2 subjects with ≥5% bone marrow blasts may inform dose escalation decisions for Arm 1 subjects with <5% bone marrow blasts. Simultaneous escalation of Arm 1 and Arm 2 may occur when the following criteria are met: 1. Dose escalation in Arm 2 is recommended from the current dose based on Dose Escalation and Dose Reduction criteria above; and 2. No subjects have experienced DLT at the current dose in Arm 1.
Study Duration	Individual subjects will participate in the treatment phase and follow-up phase for safety and efficacy assessments up to 112 weeks or until the subject is no longer receiving clinical benefit. Subjects who are no longer receiving clinical benefit will continue to be followed with clinic visits to safety every 12 weeks until 112 weeks after administration of NTLA-5001 (see Schedule of Activities [SoA] Section 1.3).

Inclusion Criteria	Subjects must meet the following inclusion criteria: *AML-related inclusion criteria for escalation and safety expansion cohort eligibility:* 1. AML as defined by World Health Organization (WHO) classification "AML and related neoplasms" in Arber et al, 2016. 2. Disease that is detectable (per Section 8.1.1) after standard first-line therapy, where first-line therapy is defined as: • i) attempted remission induction therapy with 1 cycle of anthracycline-based therapy followed by a second cycle for persistent morphologic disease at the first BM assessment; for subjects with CR after 1 cycle followed by early recurrence, a second induction regimen should be considered; OR ii) attempted remission induction with 1 cycle of therapy containing high dose cytarabine; OR iii) hypomethylating agent in combination with venetoclax for at least 2 cycles of therapy; • in addition, for eligible subjects in countries where such therapy is approved, an inhibitor must have been attempted for AML with FMS-like tyrosine kinase 3 (FLT3) alterations or isocitrate dehydrogenase (IDH) mutations; • in addition, a subject who is considered a candidate for standard-of-care HCT by the investigator must have received transplant prior to study entry. • Subjects who have received additional treatment after first-line therapy are eligible, assuming all other entry and exclusion criteria are met. *General Inclusion Criteria:* 3. Subjects must be ≥ 18 years of age. 4. Subjects must carry the human leukocyte antigen-A0201 (HLA-A*02:01) allele. 5. Subject must have a projected life expectancy of at least 12 weeks. 6. Subject must have an ECOG performance status of 0 to 1. 7. Subjects must have absolute total lymphocyte count >200/μL within 72 hours of leukapheresis. 8. Subjects must have adequate organ function defined as: • Cardiac ejection fraction ≥ 45% without symptoms of cardiac failure or coronary disease • Aspartate aminotransferase (AST) ≤ 2.5 × upper limit of normal (ULN) and alanine aminotransferase (ALT) ≤ 2.5 × ULN (unless considered due to leukemic organ involvement). • Bilirubin ≤ 1.5 × ULN (unless considered due to leukemic organ involvement). Note: Subjects with Gilbert's Syndrome may have a total bilirubin > 1.5 × ULN but must have direct bilirubin ≤ 1 x ULN. • Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min; determined by Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) Study equation. 9. Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures. 10. Subject must agree not to have treatment with another investigational agent for a minimum of 28 days after dosing of NTLA-5001.

Exclusion Criteria	Subjects must not meet any of the following exclusion criteria: 1. Must not have received prior therapy as follows: • Chemotherapy or other targeted antileukemic therapy within 7 days of leukapheresis. Hydroxyurea is permitted up to 72 hours prior to leukapheresis. • Hematopoietic growth factors or other immunomodulatory therapy within 7 days of leukapheresis • Systemic steroids within 3 days of leukapheresis, except physiologic steroid replacement with ≤ 0.2 mg/kg/day methylprednisolone or equivalent • Prior therapy including investigational therapy targeted to WT1 such as vaccine therapy or cell therapy • Live vaccine 28 days or fewer prior to planned administration of lymphodepleting therapy 2. Subjects with a history of allogeneic HCT are excluded if: • Subjects are less than 84 days post-transplant, or • Subjects have evidence of ongoing active graft vs host disease (GvHD) requiring systemic immunosuppressants, or • Subjects have received donor lymphocyte infusion (DLI) within 28 days of leukapheresis, or • Subjects are on active immunosuppression for GvHD prophylaxis (must be off for 30 days prior to enrollment). Physiologic steroid replacement with ≤ 0.2 mg/kg/day methylprednisolone or equivalent is permitted. [redacted] 4. Must not have signs or symptoms indicative of central nervous system (CNS) involvement by tumor. A CNS evaluation should be performed to rule out CNS involvement if indicated by signs or symptoms. 5. Must not have CNS comorbidity such as transient ischemic attacks, cerebrovascular accident, seizure disorder, or other disorder that could confound neurotoxicity assessments. 6. Must not have severe autoimmunity that has required systemic steroid therapy or other immunomodulatory therapy. 7. Must not have active disseminated intravascular coagulation (DIC), bleeding or coagulopathy during screening. 8. Must be eligible to receive lymphodepleting chemotherapy doses per protocol Section 6.1.3.3 9. Must not have leukocytosis ≥ 20,000 WBC/μL despite hydroxyurea or rapidly progressive disease (e.g., recent increase in blast count above 50%) that in the estimation of the investigator or Sponsor would compromise ability to complete study therapy. 10. Must have recovered from the acute side effects of their prior therapy, such that eligibility criteria are met. 11. Female subjects of childbearing potential are excluded: a. if unwilling to use protocol specified method of contraception (see Section 13.6) during treatment and for an additional 12 months after administration of NTLA-5001. b. who are breastfeeding or who plan to breastfeed during treatment and for an additional 12 months after administration of NTLA-5001.

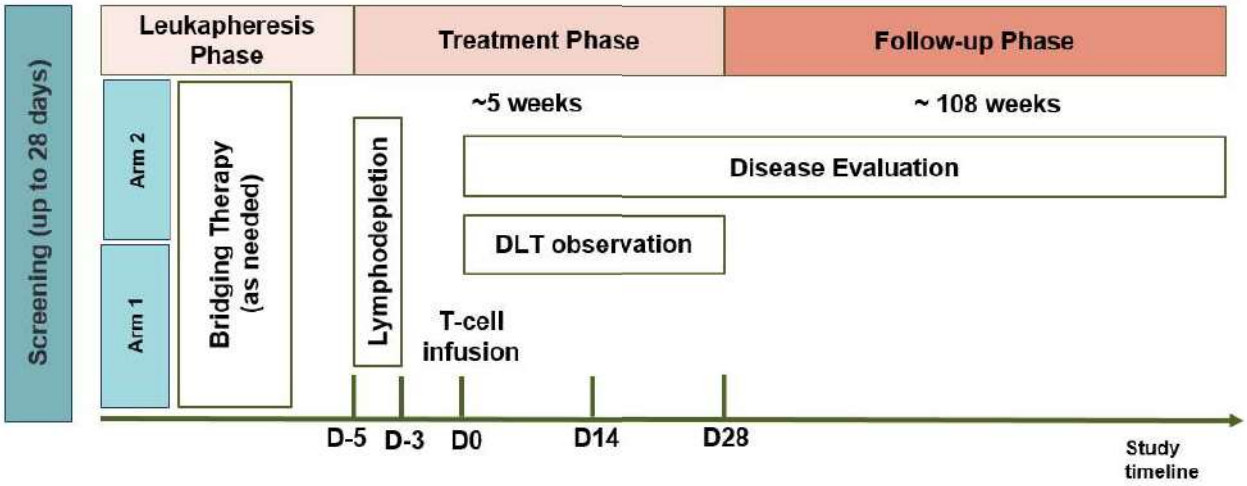
	c. with a positive pregnancy test assessed at screening and/or Day 0 by a highly sensitive urine or serum pregnancy test. 12. Male subjects with female partners of childbearing potential or female partners who are pregnant are excluded: a. if unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use a condom during treatment and for an additional 12 months after the last dose of NTLA-5001. b. if unwilling to abstain from donating sperm during treatment and for an additional 12 months after administration of NTLA-5001. 13. Must not have human immunodeficiency virus (HIV) infection, history of Hepatitis B or C infection or positive Hepatitis B surface antigen (HbsAg) or Hepatitis C virus antibody (HCVAb) test, or any uncontrolled infection at screening. 14. Must not have any condition, laboratory abnormality, or other reason that, in the investigator's opinion, could adversely affect the safety of the subject, impair the assessment of study results, or preclude compliance with the study. 15. Must be willing to comply with study procedures including follow-up as specified by the protocol or unwilling to cooperate fully with the investigator. 16. Must not have clinically significant cardiovascular impairment within 12 months of the first dose of study drug, such as history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction, cardiac revascularisation, or cardiac arrhythmia associated with haemodynamic instability. 17. [redacted]
Retesting During Screening/ Rescreening	**Retesting During Screening** Retesting is defined as repeating laboratory tests within the same screening period. If retesting goes beyond the 28-day screening period, the subject will be classified as a screen failure and will need to go through the rescreening process. **Rescreening** Subjects who fail to qualify for the study based on laboratory tests may be considered for rescreening at the discretion of the investigator if it is considered that the subject status has changed, and the subject may now qualify for the study. Screening is limited to 2 attempts (initial screening and 1 additional rescreening attempt). A new informed consent is required to be signed prior to rescreening.
Dosage and Regimens	**NTLA-5001** NTLA-5001 will be provided as a [redacted] cryobags at variable fill volumes to be stored at ≤ -150°C in a liquid nitrogen vapor phase container. The study drug will be thawed at 37°C and the dose will be prepared for infusion by qualified site personnel. Study drug preparation details will be provided in the Cell Therapy Manual. Subjects will receive premedication with anti-pyretic and H1 blocker within 1 hour prior to dosing. NTLA-5001 will be administered as an IV infusion at 10-20 mL/min. Total time from thaw to complete administration may not exceed 4 hours. **Lymphodepleting chemotherapy** Cyclophosphamide will be administered on Day -5, -4, and -3 as intravenous infusion at 500 mg/m^2 each day. Fludarabine will be administered on Day -5, -4, and -3 as intravenous infusion at 30 mg/m^2 each day.

	For chemotherapy dosing, body surface area (BSA) is calculated based on body weight for subjects weighing up to 120% of ideal body weight (IBW), and BSA is calculated based on adjusted body weight for subjects weighing >120% of IBW. IBW and adjusted weight are determined per institutional standard. Rounding is permitted per institutional standard.
Guidelines for the Management of Potential Toxicities	Recommendations for management of potential toxicities of NTLA-5001 are provided, including specific agents to be used, doses and intervals, and lines of therapy. These recommendations may be modified by the investigator to accommodate existing institutional guidelines for management of cell therapy toxicities and variations in global standard-of-care practices. • Infusion reactions should be managed initially with an anti-pyretic and H1 blocker. For persistent symptoms, subjects may receive NSAIDs. For severe reactions, subjects may receive steroids. • CRS may be managed per institutional protocols. Other guidelines include treatment of fever, hypoxia, and/or mild hypotension initially by support with oxygen, fluids, antipyretics, low-dose vasopressors, and tocilizumab. For persistent symptoms beyond 12-18 hours, subjects should receive additional tocilizumab, and additional interleukin-6 (IL-6) directed therapy such as siltuximab if no response. More severe symptoms should be treated with continued IL-6 directed therapy and corticosteroids. For subjects with severe symptoms that are persistent 24 hours after steroid administration, etanercept or anakinra should be considered. If still not improved, subjects may receive anti-T cell therapy such as alemtuzumab, cyclophosphamide, or antithymocyte globulin (ATG). • Tumor lysis syndrome (TLS) prophylaxis may be used per institutional standard. TLS diagnosed solely based on laboratory criteria will be managed initially per institutional standard with therapy directed at uric acidemia such as allopurinol or febuxostat. For persistent symptoms, subjects should receive intravenous hydration and additional uric acid therapy such as rasburicase. All subjects with clinical TLS will be admitted for in-hospital treatment and monitoring. • T cell proliferative disorder should be treated with steroids and anti-T cell therapy. • Autologous GvHD should be treated with steroids. For persistent symptoms, subjects will receive sitagliptin, ruxolitinib, or anti-T cell therapy. • Hemophagocytic lymphohistiocytosis should be treated with steroids. For persistent symptoms, subjects will receive IL-6 directed therapy and anakinra. • Potential on-target/off-tumor toxicity of NTLA-5001 will be monitored by clinical findings and laboratory analyses (see Schedule of Activities). Evidence of inflammation or dysfunction at sites expressing WT1 (i.e., kidney podocytes, mesothelial lining cells, hematopoietic cluster of differentiation 34 [CD34+] stem cells) should be managed initially by steroids. If still not improved, subjects may receive anti-T cell therapy such as alemtuzumab, cyclophosphamide, or ATG.

Concomitant Medications	**Bridging therapy:** Following leukapheresis, subjects may receive bridging therapy with low intensity regimens. Recommended regimens and the washout required prior to lymphodepleting chemotherapy are listed here: • hydroxyurea (72-hour washout) • venetoclax (2-week washout) • azacytidine (2-week washout) • decitabine (2-week washout) • cytarabine (2-week washout) • gilteritinib (4-week washout) • gemtuzumab ozogamicin (4-week washout) • enasidenib (4-week washout) • ivosidenib (4-week washout) To request use of other bridging therapy, the investigator must contact the medical monitor prior to its initiation. Continuation of hydroxyurea during the treatment phase in subjects with morphologic disease may be considered but must be approved by the medical monitor. **Prohibited medications:** • granulocyte-macrophage colony-stimulating factor (GM-CSF) • granulocyte colony-stimulating factor (GCSF) is prohibited from 72 hours of prior to lymphodepleting chemotherapy through the Week 2 visit • long-acting GCSF is prohibited from 2 weeks prior to lymphodepleting chemotherapy through the Week 2 visit • steroids are prohibited within 72 hours of lymphodepleting chemotherapy, except for physiologic steroid replacement with $\leq$ 0.2 mg/kg/day methylprednisolone or equivalent • live vaccine administration from the time of lymphodepleting chemotherapy through infusion of NTLA-5001, for at least three months after NTLA-5001 and until immune recovery following treatment
Procedures and Criteria for Pausing Enrollment	If 1 of the criteria described below is reached, further enrollment of subjects will be suspended pending assessment by the Sponsor: • any treatment-related death, or • any Grade 4 cytokine release syndrome per ASTCT consensus criteria, that does not resolve to Grade 1 within 72 hours despite therapy, or • any Grade 4 neurotoxicity per ASTCT ICANS consensus grading criteria for adults, that does not resolve to Grade 1 within 72 hours despite therapy, or • evidence of any T cell proliferative disorder, or • any grade 3 or higher GVHD or Grade 2 GVHD that does not resolve to Grade 1 in response to systemic steroid therapy within 7 days. If at the time enrollment is paused, and a subject has received lymphodepleting chemotherapy but has not yet received NTLA-5001, treatment with a lower dose of NTLA-5001 given to a prior cohort may be considered with agreement of the Sponsor and investigator. An assessment of all available information will be completed by Sponsor in conjunction with the Data Monitoring Committee (DMC). Resumption of enrollment and dosing will be decided by the Sponsor with recommendation from DMC.

Study Completion, Subject Completion, Early Discontinuation from Study (Early Termination)	**Study Completion** The study will be considered completed with the last visit by the last subject. **Subject Completion** A subject will be considered as having completed the study after completion of their Week 112 visit. Subjects who are no longer receiving clinical benefit will continue to be followed with clinic visits to safety every 12 weeks until 112 weeks after administration of NTLA-5001. Subjects who are not receiving clinical benefit may receive additional treatment or supportive care per their Investigators for the duration of the study (see SoA Section 1.3). **Early Discontinuation from Study (Early Termination)** All subjects enrolled in the study will be followed for 112 weeks unless a subject withdraws consent, is lost to follow-up, or has died. Subjects have the right to withdraw from the study at any time for any reason.
Study Termination/ Individual Study Site Termination	The Sponsor may terminate enrollment in the study, either in its entirety or at any study site, at any time. The study may then be terminated when the last subject dosed has been followed for 28 days. Regardless of the Sponsor's decision to terminate enrollment, those subjects who have received treatment with NTLA-5001 will continue to be followed in a long-term monitoring program per local and national requirements. All subjects will be followed for a minimum of 5 years in the UK and for a minimum of 15 years in the US.
Statistical Considerations	Descriptive statistics will be used to summarize the safety, tolerability, and activity of NTLA-5001 in treated subjects by cohort within each Arm.
Data Monitoring Committee (DMC)	A DMC will be established to perform periodic review of all safety data, to review any events that potentially meet the pausing criteria, and to review completed dose escalation safety data prior to enrolling the expansion population. Proceeding to expansion will be decided by the Sponsor, with the DMC providing a recommendation. In addition, consultation with the DMC may occur at any time to review data to manage subject safety. Details are included in the DMC Charter.

1.2 Schema



DLT = dose limiting toxicities

1.3 Schedule of Activities (SoA)

Table 1-1 Schedule of Activities: Screening Through Day 14 (In Patient Observation)

Study Period	SCR[a]	LP	Reassessment	Lymphodepletion			Treatment and Observation								Notes
Study Day			-12 to -6	-5	-4	-3	0	1	2	3	4	5	6	7	8-14[b]	
General and Safety Assessments																
Signing of informed consent	X															
Eligibility criteria	X	X	X*[d]													*Assessment of eligibility to enter treatment phase should be performed within 1 week prior to Day -5 (see Section 8.1.3.1).
Medical history	X															
Demographics	X															
Full physical examination	X															
Focused physical examination		X					X	X	X	X	X	X	X	X	X	Focused exam will be symptom based. The PI will inquire if the subject has experienced testicular/scrotal pain, swelling, and erythema for males and lower abdominal pain or vaginal bleeding for women, or any reproductive symptoms, whether the subject is trying to conceive, or has successfully conceived. Should a pregnancy occur a detailed in-utero assessment will be performed. Physical exam at each clinic visit will assess for any new pleural or peritoneal effusions.
ECOG assessment	X		X[d]	X*												X*: Prior to beginning lymphodepletion
Vital signs	X			X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X			X			X	X	X	X	X	X	X	X	X	
Chest x-ray	X															
Echocardiogram	X															
Prior and concomitant medications	X	X		X	X	X	X							X		Includes RBC and platelet transfusions.
Adverse event assessment	X	X		X	X	X	X	X	X	X	X	X	X	X	X	

Table 1-1 Schedule of Activities: Screening Through Day 14 (In Patient Observation) (continued)

Study Period	SCR[a]	LP	Reassessment	Lymphodepletion			Treatment and Observation								Notes
Study Day			-12 to -6	-5	-4	-3	0[e]	1	2	3	4	5	6	7	8-14[b]	
Laboratory Assessments																
Hematology	X		X[d]				X*				X			X		Refer to Section 13 for details regarding local laboratory samples. X*: Collect pre-infusion and 4 hours post-infusion.
Chemistry	X		X[d]				X*				X			X		
Coagulation	X						X*				X			X		
Urinalysis	X										X			X		
Pregnancy test	X						X									Serum pregnancy test will be done at the screening visit. Serum or urine pregnancy testing may be performed at all other visits.
SARS-CoV-2 PCR test	X															SARS-CoV-2 PCR test to be performed by the investigator's local laboratory within 7 days prior to study entry.
Serology	X															HbsAg, HCVAb, and HIVAb testing to be performed by the investigator's local laboratory.
Immunogenicity sample (serum)	X															
[redacted] vector distribution (whole blood)	X						X*	X		X		X		X		X*: Collect 1 hour and 4 hours post-infusion.
[redacted] vector shedding (urine)	X						X*	X		X		X		X		X*: Collect 1 hour and 4 hours post-infusion.
Cytokines (plasma)	X						X*	X		X		X		X		X*: Collect 1 and 4 hours post-infusion.
Cell kinetics	X						X*	X**		X		X		X	X	X*: Collect 1 and 4 hours post-infusion. X**: Collect D1 CK as close as possible to 24hrs from the time of D0 collection. For subjects at the site on Day 9, 10, and/or 11, one additional sample should be collected as close as possible to Day 11. Additional CK samples may be collected if clinically indicated for AEs.

Table 1-1 Schedule of Activities: Screening Through Day 14 (In Patient Observation) (continued)

Study Period	SCR[a]	LP	Reassessment	Lymphodepletion			Treatment and Observation								Notes
Study Day			-12 to -6	-5	-4	-3	0[e]	1	2	3	4	5	6	7	8-14[b]	
Laboratory Assessments																
PBMC	X						X*	X		X		X		X	X	X*: Collect 1 hour post-infusion. For subjects at the site on Day 9, 10, and/or 11, one additional sample should be collected as close as possible to Day 11.
Efficacy Assessments																
Bone marrow sampling and PBMC morphology	X*[c]		X**													X*: Includes cytogenic and molecular profiling. X**: Repeat assessment prior to beginning LD chemotherapy if no sample was obtained after signing consent, or >6 weeks since SCR BM or warranted by change in clinical condition or if subject has received bridging therapy other than hydroxyurea.
Study Arm assessment	X	X*														Study Arm assessment will be determined by the investigator. X*: Repeat assessment of Study Arm eligibility if repeat BM done.
EORTC QLQ-C30	X															
Study-required Procedures and Treatment																
Leukapheresis		X														
Bridging therapy (if clinically required)		X														Permitted if clinically indicated during the LP/cell manufacturing period. This bridging therapy may take place between leukapheresis and treatment. Any treatment required for bridging therapy will be collected on the concomitant medications CRF. See Section 6.1.3.2 for washout periods.
Meets entry and exclusion for treatment phase		X														Assessment of eligibility to enter treatment phase should be performed within 1 week prior to Day -5 (see Section 8.1.3.1)
Lymphodepleting chemotherapy				X	X	X										Lymphodepleting chemotherapy may be administered in the Inpatient or Outpatient setting. See Section 6.1.3.3
Premedication							X									Administer within 1 hour of NTLA-5001 dosing (see Section 6.1.3 for details).
NTLA-5001 dosing							X									
In unit observation							X	X	X	X	X	X	X	X	X*	X*: Only UK subjects are required to be hospitalized for days 8-14.

Note: All assessments on Day 0 are performed prior to infusion, unless otherwise indicated.

[redacted] AML = acute myeloid leukemia; BM = bone marrow; CK = cell kinetics; CRF = case report form; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; LD = lymphodepletion; LP = leukapheresis; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction; RBC = red blood count; SCR = screening; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

a. The screening period will be up to 28 days prior to enrollment.

b. In-patient observation on days 8-14 is required for UK subjects only.

c. Bone marrow samples collected after the completion of all prior therapy and prior to signing consent are allowed so long as the required bone marrow assessments were completed. Potential Arm 2 subjects: For subjects with ≥5% bone marrow blasts, morphology by local assessment is sufficient for eligibility. If a marrow sample collected prior to signing consent is used for enrollment, a bone marrow sampling and PBMC morphology is required between leukapheresis/bridging therapy completion and the initiation of lymphodepleting chemotherapy. Potential Arm 1 subjects: For subjects with <5% bone marrow blasts, MRD measurement by the central vendor is needed to determine eligibility. Therefore, a bone marrow sample during screening is required.

d. Subjects must be reassessed for entry into the study treatment phase within 1 week of lymphodepleting chemotherapy. Please see Section 8.1.3.1

e. All D0 blood and urine collections should be completed as close as possible to the indicated time.

Table 1-2 Schedule of Activities: Assessment Phase Through End of Study

Study Period	Assessment Phase											EOS	
Study Week	2	4	8	16	28	40	52	64	76	88	100	112	
Visit Window (days)	±2	±2	±4 days					±7 days					Notes
General and Safety Assessments													
Focused physical examination	X	X	X	X	X	X	X	X	X	X	X	X	Focused exam will be symptom based. The PI will inquire if the subject has experienced testicular/scrotal pain, swelling, and erythema for males and lower abdominal pain or vaginal bleeding for women, or any reproductive symptoms, whether the subject is trying to conceive, or has successfully conceived. Should a pregnancy occur a detailed in-utero assessment will be performed. Physical exam at each clinic visit will assess for any new pleural or peritoneal effusions.
ECOG assessment	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X			X	X	X	X	X	X	X	X	X	
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X	
Chest x-ray	X	X											To review x-ray for pleural effusion. Any new effusions should be evaluated for etiology, which may include fluid sampling if no other cause can be identified.
Laboratory Assessments													
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	Serum or urine pregnancy testing may be performed.
SARS-CoV-2 PCR test	X	X	X	X		X		X					
Immunogenicity sample (serum)		X	X	X	X							X	
[redacted] vector distribution (whole blood)	X	X	X	X	X							X	

Table 1-2 Schedule of Activities: Assessment Phase Through End of Study (continued)

Study Period	Assessment Phase											EOS	
Study Week	2	4	8	16	28	40	52	64	76	88	100	112	
Visit Window (days)	±2	±2	±4 days					±7 days					Notes
Laboratory Assessments (continued)													
[redacted] vector shedding (urine)	X	X	X	X	X							X	
Cytokines (plasma)	X	X	X	X	X								
Cell kinetics	X	X	X	X	X	X	X	X	X	X	X	X	Additional CK samples may be collected if clinically indicated for AEs.
PBMC	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy Assessments													
Bone marrow sampling and PBMC morphology*		X	X	X	X	X	X	X	X	X	X	X	*: Includes cytogenic and molecular profiling and flow cytometry for AML MRD. At the investigator's discretion, an early bone marrow aspirate and biopsy may be performed at the Week 2 visit. BM sampling is to be performed until the subject achieves complete remission and has no evidence of MRD. Thereafter, subjects should undergo bone marrow sampling every 12 weeks for 1 year after remission is first documented. Subsequently, subjects in CR are not required to have additional bone marrow sampling unless clinically indicated.
Disease response assessment		X	X	X	X	X	X	X	X	X	X	X	Refer to Section 13.4 for guidance.
EORTC QLQ-C30	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted] AE = adverse event; AML = acute myeloid leukemia; BM = bone marrow; CK = cell kinetics; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOS = end of study; PBMC = peripheral blood mononuclear cell; MRD = measurable residual disease; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Table 1-3 Schedule of Activities: Safety Follow Up Visits for Subjects No Longer Receiving Clinical Benefit

Study Period	Safety Assessment Phase									Notes
Study Week	16	28	40	52	64	76	88	100	112	
Visit Window	±7 days									
Focused physical examination	X	X	X	X	X	X	X	X	X	Focused exam will be symptom based. The PI will inquire if the subject has experienced testicular/scrotal pain, swelling, and erythema for males and lower abdominal pain or vaginal bleeding for women, or any reproductive symptoms, whether the subject is trying to conceive, or has successfully conceived. Should a pregnancy occur a detailed in-utero assessment will be performed. Physical exam at each clinic visit will assess for any new pleural or peritoneal effusions.
Vital signs	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	
Adverse event assessment	X	X	X	X	X	X	X	X	X	Treatment-related adverse events and treatment-related serious adverse events only

PI = principal investigator

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LIST OF ABBREVIATIONS

Abbreviation	Description
AAV	adeno-associated virus
AE	adverse event
ALL	acute lymphocytic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	adoptive T cell therapy
ATG	antithymocyte globulin
AUC	area under the curve
BID	twice daily
BM	bone marrow
BSA	body surface area
C_{last}	last observed quantifiable concentration
C_{max}	maximum serum concentration
CAR	chimeric antigen receptor
Cas9	CRISPR-associated protein 9
CD	cluster of differentiation
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	cell kinetics
CKD-Epi	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	coronavirus disease 2019
CNS	central nervous system
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CRISPR	clustered regularly interspaced short palindromic repeats
CR_{MRD-}	complete remission without measurable residual disease
CRO	contract research organization

Abbreviation	Description
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
ddPCR	droplet digital PCR
DIC	disseminated intravascular coagulation
DLI	donor lymphocyte infusion
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response / remission
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELN	European LeukemiaNet
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EU	European Union
FDA	Food and Drug Administration (USA)
FLT3	FMS-like tyrosine kinase 3
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GCSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GvHD	graft vs host disease
HCT	hematopoietic cell transplant
HIV	human immunodeficiency virus
HLA-A0201	human leukocyte antigen-A*02:01
HLH	hemophagocytic lymphohistiocytosis
HRT	hormonal replacement therapy
IBW	ideal body weight
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICF	informed consent form

Abbreviation	Description
ICH	International Council for Harmonisation
IDH	isocitrate dehydrogenase
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IL	interleukin
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAM	lactational amenorrhea method
LD	lymphodepletion
LDH	lactate dehydrogenase
LLOD	lower limit of detection
LP	leukapheresis
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intent-to-treat
MLFS	morphologic leukemia-free state
MRD	measurable residual disease
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NHL	non-Hodgkin's lymphoma
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamics
PI	Principal Investigator
PO	orally
PR	partial remission
PRL	prolactin

Abbreviation	Description
QD	once daily
QOL	quality of life
RT-PCR	reverse transcription-PCR
SAE	serious adverse event
SAS	Safety Analysis Set
SC	subcutaneous
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
T_{last}	time of last observed quantifiable concentration
T_{max}	time to maximum concentration
TCR	T cell receptor
TEAE	Treatment-emergent adverse event
TLS	tumor lysis syndrome
TNF-α	tumor necrosis factor alpha
TRAC	T cell receptor alpha chain constant
TRBC	T cell receptor beta chain constant
UK	United Kingdom
US	United States
ULN	upper limit of normal
USA	United States of America
Vβ8	variable beta chain 8 of TCR
WBC	white blood cells
WHO	World Health Organization
WOCBP	women of childbearing potential
WT1	Wilms' tumor 1

2 INTRODUCTION

2.1 Study Rationale

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults (SEER Program, 2020). Despite advances in the management of hematologic malignancies, the development of novel targeted and immune therapies, and improvements in supportive care, the overall outcome for patients with AML remains poor.

Cancer immunotherapy has firmly established itself as a pillar of cancer therapy, providing substantial benefits to patients. Adoptive T cell therapy (ATC) using genetically engineered cells represents a promising immunotherapeutic avenue, with chimeric antigen receptor T cell (CAR-T) therapy already delivering significant clinical results, especially in patients affected by B-cell malignancies. In AML, the majority of highly expressed target antigens for cell therapy are also widely present in the hematopoietic compartment and, as a consequence, therapies aimed at targeting these antigens have shown myelosuppression in patients (Mardiana and Gill, 2020; Majzner and Mackall, 2019).

T cell receptor (TCR) cell-based gene therapy is a potent immunotherapeutic approach designed to unleash the immune system against cancer (Morris and Stauss, 2016). It relies on the targeted redirection of T cell specificity towards tumor antigens derived from the tumor-specific proteome. In contrast to CARs, TCRs can target virtually every tumor protein, independent of their cellular localization, and are reactive at lower antigen densities than CARs (Harris and Kranz, 2016). Naturally occurring tumor-specific T cells have been observed at low frequencies in healthy donors and patients and can be isolated from their lymphocyte population (Durgeau et al, 2018; Nagorsen et al, 2003; Renkvist et al, 2001).

Wilms tumor 1 (WT1) represents an ideal tumor antigen candidate as it is a nonpolymorphic intracellular protein that promotes proliferation and oncogenicity in AML and is overexpressed by a factor of 10–1,000 in AML, including leukemic stem cells, compared with normal Cytochrome (CD34+) cells (Sugiyama, 2010). WT1 encodes a nuclear zinc finger transcription factor that plays an important role in cell growth and differentiation and is involved in leukemogenesis and tumorigenesis (Yang et al, 2007). Although essential during embryogenesis, physiologic WT1 expression is limited to low levels (about 10-1000-fold lower than in AML blasts) in a few adult tissues, predominantly kidney podocytes, mesothelial lining cells and hematopoietic CD34+ stem cells (Ariyaratana and Loeb, 2007). WT1 expression is associated with poor disease outcome in AML and is rarely lost, supporting its use as a pan-leukemic marker for minimal residual disease detection (Ogawa et al, 2003; Inoue et al, 1994).

As a result, several clinical trials targeting WT1 have been conducted (Chapuis et al, 2019; Tawara et al, 2017; Di Stasi et al, 2015). TCR-based T cell therapies and vaccines have highlighted the safety profile of this therapeutic approach, but efficacy data are limited to date, which in part may be attributable to the characteristics of the epitope targeted in these studies. The most widely targeted WT1-derived epitope is the WT1(126-134) epitope, which has been found to require the immunoproteasome for natural processing and is less efficiently generated by the constitutive proteasome (Jaigirdar et al, 2016). Thus, the WT1(126-134) epitope may not be efficiently processed and presented by tumor cells.

For NTLA-5001, a high-avidity TCR has been identified from a natural repertoire of healthy donors. The targeted WT1 epitope is [redacted] which is processed by the constitutive proteasome, presented on the common allele human leukocyte antigen-A*02:01 (HLA-A0201, the most common HLA class I allele in the Caucasian population) and present on tumor cells (Doubrovina et al, 2012). NTLA-5001 T cells are engineered to replace the endogenous TCR with WT1-specific TCR for the treatment of AML. NTLA-5001 shows target specific recognition and killing of primary AML blasts and leukemia cell lines in vitro and in vivo, and low levels of off-target genome editing, suggesting that NTLA-5001 is a promising agent for human trials in subjects with AML. Background information pertaining to the clinical trial is summarized below in Section 2.2. Additional background details are available in the NTLA-5001 Investigator's Brochure.

2.2 Background

2.2.1 Disease Background

AML is a heterogeneous malignancy of myeloid cells primarily affecting older adults (SEER Program, 2020). Therapy at the time of diagnosis is predominantly based on patient factors including age and fitness. The best outcomes are achieved after intensive induction therapy, which may be followed by consolidation therapy or hematopoietic cell transplant (HCT) (Doehner et al, 2016). The introduction of combination venetoclax with hypomethylating agents in recent years as frontline therapy for older or less-fit patients also generates high response rates and may, in some subsets of patients, be associated with long-term disease control on continuous therapy (DiNardo et al, 2020). Nevertheless, most subjects will have persistent or relapsing disease, and the 5-year survival for all diagnosed patients is < 30% (SEER Program, 2020). No specific salvage regimen has emerged as the standard for treating primary refractory or relapsed AML (Megias-Vericat et al, 2018; Ravandi et al, 2015; Price et al, 2011). Therefore, enrollment in a clinical trial is recommended for patients with relapsed disease after a complete remission (CR) and for patients with persistent disease after potentially curative therapy by the European LeukemiaNet (ELN) Panel. Enrollment in a clinical trial is strongly preferred for these subjects according to National Comprehensive Cancer Network (NCCN) Guidelines (Doehner et al, 2016; Tallman et al, 2019).

2.2.2 NTLA-5001 Investigational Product Background

NTLA-5001 is an investigational genetically modified autologous T cell therapy. T cells are engineered ex vivo using CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR associated protein 9) with a WT1-specific TCR [redacted] In addition, genome editing has been used to knock out the TCRβ loci from NTLA-5001 cells, ensuring that expression of the cells' native receptors or receptors with mis-paired alpha and beta subunits is minimized. The dosage form of NTLA-5001 is a cryopreserved and thawed cell suspension for intravenous (IV) infusion.

2.2.3 NTLA-5001 Nonclinical Information

Extensive nonclinical studies both in vitro and in vivo have been conducted to characterize NTLA-5001 and substantial process development has been completed for NTLA-5001 manufacture. Results are summarized below. For additional information, please refer to the NTLA-5001 Investigator's Brochure.

Functional validation of NTLA-5001 in vitro pharmacology has been performed in cell cytotoxicity models against primary human AML blasts, WT1 expressing hematological tumor cell lines (ALL 697, K562-HLA-A0201), and [redacted] peptide-pulsed OCI-AML3 cells (low WT1 expression). NTLA-5001 cells respond to target with degranulation, cytokine and granzyme B production, activation, and proliferation as well as target cell killing. In addition, responses are improved in cells that have had both endogenous TCRα and TCRβ chains removed, suggesting that the activity of gene-modified TCR-T cells is negatively affected by the co-expression of native TCR or mis-paired TCR molecules on the cell surface.

Functional validation of NTLA-5001 in vivo pharmacology has been performed in xenograft tumor models using primary human AML blasts and the WT1-expressing hematological tumor cell line ALL 697. In immunocompromised mice, treatment of 3-day established systemic tumors with NTLA-5001 reduces or eliminates tumor progression and extends animal survival compared to treatment with T cells not recognizing WT1. The frequency and persistence of NTLA-5001 cells is also improved in these models compared to T cells that express TCR directed at targets not found on tumor cells.

NTLA-5001 specificity has been tested in vitro by assessing cross reactivity to other peptide antigens on HLA-A*02:01 and to other HLA alleles. Target cells were selected for expression of an extensive array of non-HLA-A*02:01 alleles and screened for recognition by NTLA-5001 in vitro, and potentially recognized alleles were confirmed with additional donors. [redacted], suggesting that subjects with the [redacted] should be excluded from receiving NTLA-5001. Additionally, alanine scanning has been performed to identify the minimal target epitope for the TCR, and proteins within the human genome that contain the minimal target epitope have been tested for processing and presentation of these peptides and peptide recognition by NTLA-5001. Among the processed and presented peptides, only the [redacted] peptide was recognized by NTLA-5001 with high avidity.

On-target/off-tumor reactivity of NTLA-5001 was evaluated in human tissues identified to express low levels of WT1, including renal cortical epithelial cells, visceral preadipocytes, and CD34+ bone marrow cells. Testicular endothelial cells and fallopian tube epithelial cells are also reported to express WT1; however, no donor tissues of these types with confirmed WT1 expression and HLA-A*02:01 genotype were available for testing. In co-culture with renal cortical epithelial cells and preadipocytes, NTLA-5001 cells were activated but did not result in cytotoxicity unless very high T cell to target cell ratios were used (beyond what is expected to be reached in vivo). Minimal cytokine secretion and no cytotoxicity was observed in co-culture with BM cells. Given the comparable expression of WT1 in testicular endothelial and fallopian tube epithelial cells to the other cell types tested, the risk for WT1-specific on-target/off-tumor cytotoxicity against these cells is also considered low.

NTLA-5001 has also been assessed for cytokine-independent growth to rule out any adverse effects of the genome editing steps on T cell growth regulation. NTLA-5001 was dependent on human cytokine support to survive and proliferate. No alterations in T cell growth kinetics were observed in comparison to unedited control T cells.

The manufacture of NTLA-5001 with CRISPR/Cas9 includes the induction of targeted double-strand breaks in the T cell DNA for genome editing. Comprehensive characterization of potential off-target editing and unintended DNA structural variants that may occur has been performed. Potential off-target loci were identified by computational methods and examined by sequencing. No validated off-target editing sites were identified for the selected T cell receptor alpha chain constant (TRAC) and T cell receptor beta chain constant (TRBC) directed guide RNAs.

The potential induction of mutagenesis by the manufacturing process used to generate NTLA-5001 was assessed by a panel of technologies characterizing the potential for unintended genome editing, formation of unintended DNA structural variants resulting from DNA double-strand break repair and identifying any unintended AAV transgene insertion sites in NTLA-5001. No validated off-target indels were detected in NTLA-5001 across 11 lots generated from 11 healthy donors. Low levels of DNA structural variants were detected by next-generation sequencing (NGS) and low levels above background were observed by G-banded karyotyping. However, they were non-clonal, and designated as low-level mosaicism or random gain/loss aberrations. Lastly, there was no polyploidy detected by karyotyping. No significant target-to-target translocations between TRAC and TRBC loci were measured. [redacted] Overall, these data indicate a low risk of mutagenesis to result from the manufacturing process of NTLA-5001 cells.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

As detailed in the NTLA-5001 Investigator's Brochure, potential risks of treatment have been identified through a review of the NTLA-5001 nonclinical studies, clinical data from other cell therapy products, evaluation of other potential on-target effects of WT1-directed immunotherapy, and off-target editing of T cell genes during NTLA-5001 manufacture. Potential risks and mitigations are described in Table 2-1.

Study design elements provide general risk mitigations other than those listed below. NTLA-5001 will be administered in an inpatient unit with a 7-day post dose observation period. UK subjects will be observed in hospital for a minimum of 14 days following dosing. The Sponsor will hold regular meetings with the investigators and/or the Data Monitoring Committee (DMC) to review all available subject data and the proposed dosing plan. Completion of study Part 1 enrollment and initiation of Part 2 will be decided by the Sponsor, with investigators and the DMC providing a recommendation.

Table 2-1 Potential Risks and Mitigations

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infusion-related reactions (IRRs)	Infusion-related reactions are a known side effect of cell therapy.	The risk of IRRs can be partially mitigated by the use of a pre-treatment regimen (see Section 6.1.3.1). Concomitant medications may be used to facilitate resolution of IRRs (see Section 6.7.1).
Cytokine release syndrome (CRS)	CRS is the most common severe toxicity associated with cell therapy. CRS is a systemic inflammatory response usually characterized by high fevers, sinus tachycardia, hypotension, hypoxia, depressed cardiac function, and other organ dysfunction. CRS is thought to be caused by the release of inflammatory cytokines from the CAR T cells and other immune cells.	Observation is mandated during the usual time course for CRS, including a 7-day inpatient hospitalization and an additional 7-day period during which subjects are able to receive care at the treating site. UK subjects will be observed in hospital for a minimum of 14 days following dosing. Each inpatient unit will be prepared to diagnose and treat CRS. Criteria for suspension of enrollment are included for specified CRS events. (Section 6.2.1.5) Toxicity management guidelines are included for use of oxygen, fluids, antipyretics, low-dose vasopressors, IL-6 directed therapy, steroids, and anti-T cell therapy (Section 6.7.2). See Section 13.5 for grading of CRS (Lee et al, 2019). See Section 8.5.8 for details on CRS to be classified as Adverse Events of Special Interest.
	COVID-19 infection may theoretically increase the signs and symptoms of CRS.	Subjects with evidence of infections such as COVID within 7 days of study entry are excluded from study. See Section 13.7 for additional guidance related to COVID-19.
Immune effector cell-associated neurotoxicity syndrome (ICANS)	Cell therapy is associated with neurologic toxicity called ICANS, a heterogeneous and poorly understood disorder with variable clinical presentation and severity. Toxicities are usually reversible and resolve on their own in most cases, though severe cases may require intensive care and immunosuppressive therapy.	Observation is mandated during the usual time course for ICANS, including a 7-day inpatient hospitalization and an additional 7-day period during which subjects are able to receive care at the treating site. UK subjects will be observed in hospital for a minimum of 14 days following dosing. Each inpatient unit will be prepared to diagnose and treat ICANS. Criteria for suspension of enrollment are included for specified ICANS events. (Section 6.2.1.5). Toxicity management guidelines are included for use of steroids and anti-T cell therapy (Section 6.7.3). See Section 13.5 for grading of ICANS (Lee et al, 2019). See Section 8.5.8 for details on ICANS to be classified as Adverse Events of Special Interest.

Table 2-1 Potential Risks and Mitigations (continued)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Tumor lysis syndrome (TLS)	TLS is a syndrome arising due to rapid killing of cancer cells, often in subjects with large bulky tumors or a large volume of circulating tumor cells, resulting in organ dysfunction due to the release of metabolic products from the intracellular space.	Inpatient treatment is mandated for observation during the post-infusion period. TLS prophylaxis may be used per institutional standard. Toxicity management guidelines are included for use of therapy directed at uric acidemia and intravenous hydration (Section 6.7.4). Subjects with high absolute blast counts are excluded from enrollment.
Uncontrolled T cell proliferation	NTLA-5001 cells could theoretically proliferate due to derangement of normal homeostatic mechanisms by genome engineering process.	Hematology parameters will be measured at each clinic visit. Toxicity management guidelines are included for use of steroids and anti-T cell therapy (Section 6.7.5).
Autologous GvHD	After autologous adoptive therapy, a GvHD-like syndrome which is clinically and histologically indistinguishable from allogeneic GvHD has been described in the skin, liver and gastrointestinal tract.	Physical exam at each visit with additional laboratory and diagnostic studies as indicated will assess for any skin, liver, or gastrointestinal involvement by GvHD. Toxicity management guidelines are included for use of steroids and anti-T cell therapy (Section 6.7.6).
Hemophagocytic lymphohistiocytosis (HLH)	After ATC therapy, symptoms of CRS may subsequently evolve in some subjects to HLH-like symptomatology.	Physical exam at each visit with additional laboratory and diagnostic studies as indicated will assess for signs of HLH. Toxicity management guidelines are included for use of steroids and anti-T cell therapy (Section 6.7.7).

Table 2-1 Potential Risks and Mitigations (continued)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential impact of NTLA-5001 on nontumor tissue expressing WT1 (bone marrow, testes, ovaries, fallopian tubes, pleura/peritoneum, kidney podocytes)	Recognition of target antigen expressed by normal tissue has been reported with CAR-T and TCR-T cell therapies. These risks are determined by the expression pattern of target proteins across the body's organs.	Hematology parameters will be measured at each clinic visit to provide a measure of bone marrow function. Bone marrow sampling will be performed at 2-3 month intervals during the first 112 weeks. History will include specific questions to assess reproductive history and symptoms of inflammation in the testes, female reproductive organs, abdomen, or chest. Symptoms will be evaluated promptly with imaging studies, blood tests, and sampling of endometrium or pleural/peritoneal fluid as appropriate to evaluate the cause. Physical exam at each visit will assess for any new pleural or peritoneal effusions. Urinalysis will be performed at 1 week and every 2-3 months through the study. Additional collections and analysis will occur at the Investigator's discretion. Toxicity management guidelines are included for use of steroids and anti-T cell therapy (Section 6.7.8).

ATC = adoptive T cell; CAR-T = chimeric antigen receptor T cell; COVID-19 = coronavirus disease 2019; IL = interleukin; TCR = T cell receptor; WT1 = Wilms' tumor 1

All medications and study procedures may involve risks that are unknown, unforeseen or unanticipated. As no clinical studies in humans have been conducted with NTLA-5001, all potential side effects are not yet known. New or more severe risks to health, which could be life threatening, life altering (e.g., disability) or result in death, may be identified during the conduct of this trial or afterward. New information that becomes available and is relevant to the management and care of a participating subject will be communicated promptly.

2.3.2 Benefit Assessment

As noted in Section 2.2.1, AML is a progressive and fatal condition for the majority of subjects. Though long-term remission can result from first-line therapy, treatment for persistent or recurrent disease is given to slow progression or reduce symptoms. Typical symptoms arise from impaired bone marrow function, and include poor coagulation, anemia, and susceptibility to infection. Most subjects will have persistent or relapsing disease, and the 5-year survival for all diagnosed patients is < 30% (SEER Program, 2020). In ALL and non-Hodgkin's lymphoma (NHL), targeted cell therapies have led to remarkable results, even for patients with refractory and advanced disease. The potential benefit of NTLA-5001 is as an immunotherapy agent with activity similar to existing targeted cell therapies for ALL and NHL, leading to reduction in disease burden and prolongation of life through killing of AML cells expressing WT1, which is at 10- to 100-fold the level seen on normal tissues.

In this study, NTLA-5001 activity on AML will be evaluated by serial disease assessments including bone marrow sampling, as well as clinically by time to disease progression, survival, and quality of life (QOL). It is expected that, based on the starting dose of [redacted] cells, planned dose escalation regimen, and the known potential risks of therapy, that an optimal biologically active dose will be identified in this study.

2.3.3 Overall Benefit: Risk Conclusion

The therapeutic hypothesis supporting the development of NTLA-5001 in AML has been clinically validated using cell therapy for other hematologic malignancies.

As no clinical trials of NTLA-5001 have been conducted in humans, the initial patient population being studied consists of subjects who have persistent or recurrent disease despite use of approved therapy. The selection of this subset of subjects with AML seeks to optimally balance risk and potential benefit in this first clinical evaluation of a new therapy, consistent with the established guiding principles set out in various regional and national guidelines on first-in-human clinical studies. As clinical studies in humans have not yet been conducted with NTLA-5001, all potential side effects are not yet known. As part of the risk mitigation strategy, potential risks for each subject will be monitored via a multifaceted approach, including adverse event (AE) monitoring and safety laboratory evaluations. Dose level changes for subsequent cohorts will be made after review of all data with investigators, and dose selection for the safety expansion cohort will be done in conjunction with the investigators and DMC.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
• Dose escalation: To identify dose for use in the expansion cohorts	• safety and tolerability as determined by AEs • dose-limiting toxicities (DLTs) (dose escalation only)
• Dose expansion: To evaluate the safety and tolerability of NTLA-5001 in subjects with AML and blasts <5% of bone marrow (Arm 1) and in subjects with AML and blasts ≥5% of bone marrow (Arm 2)	
Secondary	
• To characterize the cell kinetics (CK) of NTLA-5001 in peripheral blood	• frequency and persistence of NTLA-5001 according to the TCR transgene copy number (via droplet digital polymerase chain reaction [ddPCR])
• To estimate the anti-tumor activity of NTLA-5001 in subjects with AML	• Disease response (including measurable residual disease [MRD] response), duration of response / remission, and disease progression (see Section 13.4)
Exploratory	
• To estimate other cancer-related outcomes in subjects with AML	• overall survival • Eastern Cooperative Oncology Group (ECOG) performance status • QOL as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) instrument and length of hospital stay after NTLA-5001 infusion
• To characterize subject AAV exposure	• presence of adenovirus vector in blood and urine
• To characterize immunologic parameters and characteristics of NTLA-5001 cells after administration in subjects with AML	• plasma cytokine levels • WT1 expression on tumor • NTLA-5001 characteristics including flow cytometry, phenotype, editing, and gene expression • bone marrow immune parameters and NTLA-5001 cell kinetics

4 STUDY DESIGN AND DOSE RATIONALE

4.1 Overall Study Design

This is Phase 1/2a, first-in-human, single-dose study to investigate NTLA-5001 in subjects with AML. The design is according to guidance for first-in-human trials and for the investigation of advanced therapy medicinal products, including the European Medicine Agency "Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products"; and draft guidance "Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials"; and the FDA draft guidance "Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment". The design is to ensure the safety and well-being of trial subjects and to mitigate risk to the greatest extent possible.

This study consists of 2 phases: dose escalation and dose expansion. The dose escalation phase of the study will consist of up to 3 cohorts of subjects in Arm 1 and 3 cohorts of subjects in Arm 2. Each Arm 1 cohort will include up to 6 subjects, as detailed in dose escalation below. Each Arm 2 cohort will include 3 to 6 subjects. Once a dose is identified for detailed assessment of safety in Arm 1 subjects and 6 subjects have been enrolled at that dose, an expansion cohort will be opened for an additional 9 subjects in Arm 1. Once a dose is identified for detailed assessment of safety in Arm 2 subjects, a safety expansion cohort will be opened for an additional 9 subjects in Arm 2.

The screening period will be up to 28 days, and a subject that meets all inclusion and none of the exclusion criteria will be enrolled into the leukapheresis phase in Arm 1 for subjects with AML blasts <5% of bone marrow or in Arm 2 for subjects with AML blasts ≥5% of bone marrow. During screening, MRD will be measured in bone marrow by central laboratory assessment. After study entry, subjects may have repeat BM assessment prior to Arm assignment based on whether screening biopsy was prior to study consent, interval since screening study, change in condition, or bridging therapy. If an Arm 1 subject is found to have ≥5% bone marrow blasts at repeat BM assessment, the subject may be re-assigned to Arm 2 or, if Arm 2 is not yet enrolling subjects, the subject may receive NTLA-5001 at Dose Level -1.

Each subject will undergo leukapheresis for collection of peripheral blood mononuclear cells (PBMC). [redacted] After leukapheresis, subjects who meet criteria for treatment and who have manufactured NTLA-5001 that meet release requirements will enter the treatment phase for the administration of lymphodepleting chemotherapy and study medication. Subjects may receive bridging therapy between leukapheresis and treatment (see Section 6.1.3.2).

Each subject in the treatment group will receive lymphodepleting chemotherapy on Day -5, -4, and -3 (see Section 6.1.3.3). A subject will be administered a single dose of NTLA-5001 on Day 0. Subjects will be observed in hospital for a minimum of 7 days following dosing, and subjects must remain within 2 hours of the location of the trial site to receive any needed follow up assessments or care until Day 14. UK subjects will be observed in hospital for a minimum of 14 days following dosing. Additional visits will take place at Week 2, 4, 8, and 16, then at 12-week intervals through Week 112 or until the subject is no longer receiving clinical benefit.

Subjects who are no longer receiving clinical benefit will continue to be followed with clinic visits to assess subject survival and AEs every 12 weeks until 112 weeks after administration of NTLA-5001. After participating in this study, all subjects will be followed as part of a long-term monitoring program per local and national regulations. All subjects will be followed for a minimum of 5 years in the UK and for a minimum of 15 years in the US.

Infusion of NTLA-5001 that does not meet the intended dose or does not meet release criteria (as specified in the Cell Therapy Manual) will be considered for NTLA-5001 treatment with approval by the Sponsor and investigator, except in the UK. Such subjects who receive therapy will not be counted for filling a slot in the dose escalation cohort or safety expansion cohort. In the UK, a dose of NTLA-5001 manufactured for a patient that fails release criteria or is otherwise inadequate will not be given to a patient, and no subject at a UK site may begin lymphodepleting chemotherapy before the subject's product meets manufacturing release criteria.

4.1.1 Replacement of Subjects

An additional subject will be added to a dose cohort if a subject in that cohort does not receive a full dose of NTLA-5001 as per their assigned cohort or fails to complete Day 28 assessments. Any subject who experiences a DLT will be considered evaluable. Data for all subjects will be part of the safety dataset for reporting of the study.

4.1.2 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently dosed with NTLA-5001.

4.1.3 Dose Rationale

The first cohort of subjects in Arm 1 and in Arm 2 will receive [redacted]. The starting dose (Dose Level 1) was selected based on human trials of investigational TCR-T cell products that are similar in trial design due to the use of naturally occurring TCR (without affinity enhancement) and lymphodepleting chemotherapy. Dose Level 1 was chosen near the lower end of the range of recent precedents, due to nonclinical study results for NTLA-5001, suggesting the potential for increased TCR expression compared to products which do not eliminate expression of the native TCR (see Investigator's Brochure for additional detail). The dose escalation interval is similar to prior human TCR-T trials, and the highest dose (Dose Level 3) is lower than administered in several TCR-T cell product studies. Because NTLA-5001 is a cellular therapy product, it is administered via the IV route. NTLA-5001 is dosed as a single administration with the intent that cells will show long-term self-renewal after engraftment. At this time, there is no schedule proposed for re-administration of an additional dose.

4.2 End of Study

Subject Completion

A subject will be considered as having completed the study after completion of their Week 112 visit. Subjects who are no longer receiving clinical benefit will continue to be followed with clinic visits to assess safety every 12 weeks until 112 weeks after administration of NTLA-5001.

Subjects who are not receiving clinical benefit may receive additional treatment or supportive care per their Investigators for the duration of the study (see Schedule of Activities [SoA], Section 1.3).

Study Completion and Long-Term Follow-up

The study will be considered completed with the last visit by the last subject.

Early Discontinuation from Study (Early Termination)

All subjects enrolled in the study will be followed for 112 weeks unless a subject withdraws consent, is lost to follow-up, or has died. Subjects have the right to withdraw from the study at any time for any reason.

The Sponsor may terminate enrollment into the study, either in its entirety or at any study site, at any time. The study may then be terminated when the last subject dosed has been followed for 28 days. Regardless of the Sponsor's decision to terminate enrollment, those subjects who have received treatment with NTLA-5001 will continue to be followed in a long-term monitoring program needed to comply with local regulatory requirements/guidance for subjects administered a gene therapy. All subjects will be followed for a minimum of 5 years in the UK and for a minimum of 15 years in the US.

5 STUDY POPULATION

Eligibility criteria will be evaluated during the 28-day screening period. Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.1.3). Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1 Inclusion Criteria

Subjects must meet the following inclusion criteria:

AML-related inclusion criteria for escalation and safety expansion cohort eligibility:

1. AML as defined by World Health Organization (WHO) classification "AML and related neoplasms" in Arber et al, 2016.
2. Disease that is detectable (per Section 8.1.1) after standard first-line therapy, where first-line therapy is defined as:
   - i) attempted remission induction therapy with 1 cycle of anthracycline-based therapy followed by a second cycle for persistent morphologic disease at the first BM assessment; for subjects with CR after 1 cycle followed by early recurrence, a second induction regimen should be considered; OR ii) attempted remission induction with 1 cycle of therapy containing high dose cytarabine; OR iii) hypomethylating agent in combination with venetoclax for at least 2 cycles of therapy;
   - in addition, for eligible subjects in countries where such therapy is approved, an inhibitor must have been attempted for AML with FMS-like tyrosine kinase 3 (FLT3) alterations or isocitrate dehydrogenase (IDH) mutations;
   - in addition, a subject who is considered a candidate for standard-of-care HCT by the investigator must have received transplant prior to study entry.
   - Subjects who have received additional treatment after first-line therapy are eligible, assuming all other entry and exclusion criteria are met.

General Inclusion Criteria:

3. Subjects must be ≥ 18 years of age.
4. Subjects must carry the human leukocyte antigen-A0201 (HLA-A*02:01) allele.
5. Subject must have a projected life expectancy of at least 12 weeks.
6. Subject must have an ECOG performance status of 0 to 1.
7. Subjects must have absolute total lymphocyte count >200/μL within 72 hours of leukapheresis.
8. Subjects must have adequate organ function defined as:
   - Cardiac ejection fraction ≥ 45% without symptoms of cardiac failure or coronary disease
   - Aspartate aminotransferase (AST) ≤ 2.5 × upper limit of normal (ULN) and alanine aminotransferase (ALT) ≤ 2.5 × ULN (unless considered due to leukemic organ involvement).

- Bilirubin ≤ 1.5 × ULN (unless considered due to leukemic organ involvement). Note: Subjects with Gilbert's Syndrome may have a total bilirubin > 1.5 × ULN but must have direct bilirubin ≤ 1 x ULN.
- Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min; determined by Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) Study equation.

9. Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.
10. Subject must agree not to have treatment with another investigational agent for a minimum of 28 days after dosing of NTLA-5001.

5.2 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

1. Must not have received prior therapy as follows:
   - Chemotherapy or other targeted antileukemic therapy within 7 days of leukapheresis. Hydroxyurea is permitted up to 72 hours prior to leukapheresis.
   - Hematopoietic growth factors or other immunomodulatory therapy within 7 days of leukapheresis
   - Systemic steroids within 3 days of leukapheresis, except physiologic steroid replacement with ≤ 0.2 mg/kg/day methylprednisolone or equivalent
   - Prior therapy including investigational therapy targeted to WT1 such as vaccine therapy or cell therapy
   - Live vaccine 28 days or fewer prior to planned administration of lymphodepleting therapy
2. Subjects with a history of allogeneic HCT are excluded if:
   - Subjects are less than 84 days post-transplant, or
   - Subjects have evidence of ongoing active graft vs host disease (GvHD) requiring systemic immunosuppressants, or
   - Subjects have received donor lymphocyte infusion (DLI) within 28 days of leukapheresis, or
   - Subjects are on active immunosuppression for GvHD prophylaxis (must be off for 30 days prior to enrollment). Physiologic steroid replacement with ≤0.2 mg/kg/day methylprednisolone or equivalent is permitted.

[redacted]

4. Must not have signs or symptoms indicative of central nervous system (CNS) involvement by tumor. A CNS evaluation should be performed to rule out CNS involvement if indicated by signs or symptoms.
5. Must not have CNS co-morbidity such as transient ischemic attacks, cerebrovascular accident, seizure disorder, or other disorder that could confound neurotoxicity assessments.

6. Must not have severe autoimmunity that has required systemic steroid therapy or other immunomodulatory therapy.
7. Must not have active disseminated intravascular coagulation (DIC), bleeding or coagulopathy during screening.
8. Must be eligible to receive lymphodepleting chemotherapy doses per protocol Section 6.1.3.3
9. Must not have leukocytosis ≥ 20,000 WBC/μL despite hydroxyurea or rapidly progressive disease (e.g., recent increase in blast count above 50%) that in the estimation of the investigator or Sponsor would compromise ability to complete study therapy.
10. Must have recovered from the acute side effects of their prior therapy, such that eligibility criteria are met.
11. Female subjects of childbearing potential are excluded:
    a. if unwilling to use protocol specified method of contraception (see Section 13.6) during treatment and for an additional 12 months after administration of NTLA-5001.
    b. who are breastfeeding or who plan to breastfeed during treatment and for an additional 12 months after administration of NTLA-5001.
    c. with a positive pregnancy test assessed at screening and/or day 0 by a highly sensitive urine or serum pregnancy test.
12. Male subjects with female partners of childbearing potential or female partners who are pregnant are excluded:
    a. if unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use a condom during treatment and for an additional 12 months after the last dose of NTLA-5001.
    b. if unwilling to abstain from donating sperm during treatment and for an additional 12 months after administration of NTLA-5001.
13. Must not have human immunodeficiency virus (HIV) infection, history of Hepatitis B or C infection or positive Hepatitis B surface antigen (HbsAg) or Hepatitis C virus antibody (HCVAb) test, or any uncontrolled infection at screening.
14. Must not have any condition, laboratory abnormality, or other reason that, in the investigator's opinion, could adversely affect the safety of the subject, impair the assessment of study results, or preclude compliance with the study.
15. Must be willing to comply with study procedures including follow-up as specified by the protocol or unwilling to cooperate fully with the investigator.
16. Must not have clinically significant cardiovascular impairment within 12 months of the first dose of study drug, such as history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction, cardiac revascularisation, or cardiac arrhythmia associated with haemodynamic instability.
17. [redacted]

5.3 Criteria for Entering the Study Treatment Phase

After leukapheresis, subjects must meet criteria for treatment before lymphodepleting chemotherapy is administered. Criteria for entering the Study Treatment Phase are in Section 8.1.3.1.

6 STUDY TREATMENT(S)

6.1 Study Treatment(s) Administered

6.1.1 Investigational Product(s)

NTLA-5001 drug product is a colorless to slightly yellow, clear to slightly cloudy cell suspension. NTLA-5001 will be provided as a [redacted] cryobags at variable fill volumes to be stored at ≤ -150ºC in a liquid nitrogen vapor phase container. The study drug will be thawed at 37ºC and the dose will be prepared for infusion by qualified site personnel. Study drug preparation details will be provided in the Cell Therapy Manual. Subjects will receive premedication with anti-pyretic and H1 blocker within 1 hour prior to dosing. NTLA-5001 will be administered as an IV infusion at 10-20 mL/min. Total time from thaw to complete administration may not exceed 4 hours.

The starting dose for NTLA-5001 is [redacted] (TCR)-positive viable T cells. Each subject will receive a pre-treatment regimen outlined in Section 6.1.3.1 prior to administration of the study drug.

6.1.2 Comparator Product(s)

This is a single-arm study with no comparator.

6.1.3 Other Protocol-required Therapy

All other protocol-required therapies including, premedications, bridging therapies (if applicable), and lymphodepleting agents, that are commercially available are not provided or reimbursed by Intellia (except if required by local regulation). The investigator or institution will be responsible for obtaining supplies of these protocol-required therapies.

6.1.3.1 Premedication

Subjects will receive premedication with oral anti-pyretic (e.g., acetaminophen 650 mg or equivalent) and H1 blocker (e.g., diphenhydramine 25 mg IV) within 1 hour prior to dosing.

6.1.3.2 Bridging Therapy

Following leukapheresis, subjects may receive bridging therapy with low intensity regimens. Recommended regimens and the washout required prior to lymphodepleting chemotherapy are listed here:

- hydroxyurea (72-hour washout)
- venetoclax (2-week washout)
- azacytidine (2-week washout)
- decitabine (2-week washout)
- cytarabine (2-week washout)

- gilteritinib (4-week washout)
- gemtuzumab ozogamicin (4-week washout)
- enasidenib (4-week washout)
- ivosidenib (4-week washout)

To request use of other bridging therapy, the investigator must contact the medical monitor prior to its initiation. Continuation of hydroxyurea during the treatment phase in subjects with morphologic disease may be considered but must be approved by the medical monitor.

6.1.3.3 Lymphodepleting Chemotherapy

Lymphodepleting chemotherapy may be administered in the inpatient or outpatient setting for 3 consecutive days at 24-hour (± 3 hours) intervals.

Cyclophosphamide will be administered on Day -5, -4, and -3 as intravenous infusion at 500 mg/m^2 each day.

Fludarabine will be administered on Day -5, -4, and -3 as intravenous infusion at 30 mg/m^2 each day.

For chemotherapy dosing, body surface area (BSA) is calculated based on body weight for subjects weighing up to 120% of ideal body weight (IBW), and BSA is calculated based on adjusted body weight for subjects weighing >120% of IBW. IBW and adjusted weight are determined per institutional standard, including the timing of the body weight measurement relative to the chemotherapy dosing. Rounding is permitted per institutional standard.

6.2 Dose Modification

6.2.1 Dose-Cohort Study Escalation, Dose Reduction, and Stopping Rules

6.2.1.1 Dose Escalation Scheme

Proposed Dose Escalation Cohort Number	Planned Dose
Dose Level -1	[redacted]
Dose Level 1	[redacted]
Dose Level 2	[redacted]
Dose Level 3	[redacted]

[redacted]

Subjects who enter the treatment group in Arm 1 or in Arm 2 will be assigned to the dose level cohort currently open for enrollment for the relevant Arm. Arm 1 and Arm 2 will be enrolled in parallel.

Up to 3 subjects will be enrolled in an initial dose evaluation group and will be treated with NTLA-5001 for Arm 1 and for Arm 2. Enrollment will be staggered as follows (see figure in Section 13.8):

- Staggering of enrollment across the 2 study Arms: Arm 1 and Arm 2 will be escalated independently. If an Arm 1 subject is dosed at a new dose level before an Arm 2 subject, the Arm 1 subject will be observed through Day 28 before dosing a subject in Arm 2.
- Staggering of enrollment within a dose level cohort (either Arm 1 or Arm 2): each of the first 3 subjects will be observed for 28 days before enrolling the next subject.
- Staggering of enrollment between Dose Levels: all subjects in a dose evaluation group will be observed for 28 days before any subject is enrolled at the next Dose Level.

Once the entire dose evaluation group for a study Arm has been observed for 28 days, all data, including DLT information from all cohorts in both Arms, will be reviewed by the Sponsor and treating investigators to consider dose escalation. The following study personnel must participate in review of the study data and dose escalation decision: the Intellia Medical Lead, the Intellia Safety Lead, and any Investigator who has treated a subject in the cohort that has just completed 28-day observation.

6.2.1.2 Definition of a Dose-limiting Toxicity

DLTs are defined as events with onset within 28 days of infusion as follows:

- Any Grade 4 CRS per American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria, and Grade 3 CRS that does not resolve to Grade 2 within 72 hours
- Any Grade 3/4 neurotoxicity per ASTCT immune effector cell-associated neurotoxicity syndrome (ICANS) consensus grading criteria for adults
- Any Grade 4 acute GVHD of any duration; Grade 2 or 3 acute GVHD requiring systemic steroid treatment that does not resolve to ≤ Grade 1 within 7 days.
- Acute infusion reaction: Reactions related to NTLA-5001 occurring within 2 hours of infusion that are not reversible to ≤ Grade 2 within 24 hours.
- Grade 4 neutropenia or thrombocytopenia lasting more than 28 days that is not attributable to underlying disease or lymphodepletion chemotherapy
- Other severe organ toxicity that is not attributable to underlying disease or lymphodepletion chemotherapy as follows: Grade 4 toxicity that is a cardiac disorder, hepatobiliary disorder, renal disorder, respiratory disorder, or vascular disorder (per CTCAE); Grade 3 cardiac, respiratory, or vascular disorder that does not resolve to Grade 2 or lower within 72 hours; or Grade 3 hepatobiliary or renal disorder that does not resolve to Grade 2 or lower within 7 days.
- Grade 5 events without clinical or radiological evidence of disease progression which are related to NTLA 5001.

6.2.1.3 Dose Escalation and Dose Reduction Decisions

If none of the initial dose evaluation group subjects experience a DLT, subjects in the treatment phase who have not yet received NTLA-5001 and subsequent subjects entering the treatment phase will be eligible for the next dose escalation cohort.

If 1 of the initial dose evaluation group subjects experiences a DLT, enrollment will continue in the dose evaluation group for 3 additional subjects. When the last subject in the expanded dose evaluation group has been observed through Day 28:

- If no subject in the expanded dose evaluation group experiences a DLT, subjects in the treatment phase who have not yet received NTLA-5001 and subsequent subjects entering the treatment phase will be eligible for the next dose escalation cohort.
- If 1 or more additional subject in the expanded dose evaluation group experiences a DLT, no dose escalation will be proposed. Subjects in the treatment phase who have not yet received NTLA-5001 and subsequent subjects entering the treatment phase will be eligible for Dose Level -1 if DLTs are seen at Dose Level 1, or the next lower dose level will be declared the maximum tolerated dose (MTD), if DLTs are seen at Dose Level 2 or 3. Fewer than 2/6 subjects with DLTs will establish the MTD.

If 2 or 3 of the initial dose evaluation group experiences a DLT, no dose escalation will be proposed. Subjects in the treatment phase who have not yet received NTLA-5001 and subsequent subjects entering the treatment phase will be eligible for Dose Level -1 if DLTs are seen at Dose Level 1, or the next lower dose level will be expanded to 6 subjects if DLTs are seen at Dose Level 2 or 3. Fewer than 2/6 subjects with DLTs will establish the MTD.

If a dose escalation is proposed, the subsequent cohort dose may be reduced or increased by up to 50% if the Sponsor and investigator agree, based on observations in the prior cohort. At the Sponsor's discretion, up to 6 subjects may be enrolled in any dose cohort for Arm 1 or Arm 2.

If a subject receiving out-of-specification cells has a DLT, this finding would not be attributed to DLT tally for a specific Dose Level; but would be reviewed as part of the overall safety profile in conjunction with planned safety reviews and by the Sponsor, investigators, and DMC. The event would be considered when making dose escalation decisions, stopping rule decisions, and/or dose selection for expansion cohort.

6.2.1.4 Simultaneous Escalation of Arm 1 and Arm 2

The risk of severe or serious adverse events after cell therapy is correlated with a subject's tumor burden (Garcia-Manero et al, 2015; Garzon et al, 2017). Therefore, DLT information from Arm 2 subjects with ≥5% bone marrow blasts may inform dose escalation decisions for Arm 1 subjects with <5% bone marrow blasts. Simultaneous escalation of Arm 1 and Arm 2 may occur when the following criteria are met:

1. Dose escalation in Arm 2 is recommended from the current dose based on Dose Escalation and Dose Reduction criteria above; and
2. No subjects have experienced DLT at the current dose in Arm 1.

6.2.1.5 Criteria for Pausing or Stopping

If 1 of the criteria described below is reached, further enrollment of subjects will be suspended pending assessment by the Sponsor:

- any treatment-related death, or

- any Grade 4 CRS per ASTCT consensus criteria, that does not resolve to Grade 1 within 72 hours despite therapy, or
- any Grade 4 neurotoxicity per ASTCT ICANS consensus grading criteria for adults, that does not resolve to Grade 1 within 72 hours despite therapy, or
- evidence of any T cell proliferative disorder, or.
- any grade 3 or higher GVHD or Grade 2 GVHD that does not resolve to Grade 1 in response to systemic steroid therapy within 7 days.

If at the time enrollment is paused, and a subject has received lymphodepleting chemotherapy but has not yet received NTLA-5001, treatment with a lower dose of NTLA-5001 given to a prior cohort may be considered with agreement of the Sponsor and investigator.

An assessment of all available information will be completed by Sponsor in conjunction with the DMC. Resumption of enrollment and dosing will be decided by the Sponsor with recommendation from DMC.

6.2.2 Selection of Dose for Expansion

At the completion of dose escalation in each Arm, all subject clinical data will be reviewed by the DMC to recommend a dose or range of doses that are suitable for the safety expansion cohort. Selection of dose for expansion will be decided by the sponsor.

6.2.3 Dosage Adjustments, Delays, Rules for Withholding or Restarting, and Permanent Discontinuation

Study drug will be administered as a single dose so there will be no dose adjustments.

The infusion of study drug will be slowed or stopped in the event of an infusion-related reaction (IRR). Following resolution of a mild or moderate IRR that required interruption or slowing of study drug infusion, resumption of the infusion may occur at the investigator's discretion at a slower infusion rate. However, the time from opening of thawed study drug vials through completion of the infusion may not exceed [redacted]

Study drug administration will not be resumed for any subject following a severe IRR until the case is discussed with the Medical Monitor.

Subjects who receive a partial infusion will continue to attend all study visits and have all tests performed per the SoA (Section 1.3).

6.3 Preparation/Handling/Storage/Accountability

NTLA-5001 is a colorless to slightly yellow, clear to slightly cloudy cell suspension supplied in [redacted] bags at a targeted concentration of [redacted] Fill volumes will vary from subject to subject based on cohort dose level and subject yield. The infusion bags are to be stored at ≤ -150ºC in a liquid nitrogen vapor phase container. For administration, NTLA-5001 will be thawed and delivered by IV infusion.

The study drug dose will be prepared by a clinical site pharmacist or member of the site cell laboratory for infusion. NTLA-5001 will be administered by IV infusion at 10-20 ml/min. Total

study drug preparation and administration time from puncture of study drug infusion bag through completion of infusion may not exceed [redacted]

Details regarding the vein-to-vein shipping, manufacturing process, tracking and storage, study drug preparation and administration will be provided in the Cell Therapy Manual.

The investigator is to ensure per International Council for/Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines that study drug deliveries from the Sponsor are received by the investigator/or designee and that:

- Such deliveries are recorded,
- Study drug is handled and stored according to labeled storage conditions,
- Study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- Any unused study drug or expired drug should be destroyed in accordance with institutional guidelines.

Drug inventory and accountability records for the study drugs will be kept by the investigator/or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the eligible subjects enrolled in this study in accordance with the protocol.
- The investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of what study drug was used.
- At the conclusion or termination of this study, the investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Randomization

Randomization is not used in this study.

6.4.2 Masking

This is an open-label study. Masking is not applicable.

6.5 Study Treatment Compliance

Study drug administration (a single IV infusion) will be done at the clinic under medical supervision. The date and time of the dose administered in the clinic will be recorded in the source documents and recorded in the electronic Case Report Form (eCRF). See the Cell Therapy Manual for details on preparation and administration of the study medication.

6.6 Concomitant Therapy

At the time of NTLA-5001 administration, tocilizumab (8 mg/kg IV) must be available on site.

After the Day 28 visit and assessments, AML therapy may be initiated for subjects not receiving benefit at the discretion of the investigator.

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1 Prohibited Medications/Procedures

Prohibited medications include:

- granulocyte-macrophage colony-stimulating factor (GM-CSF)
- granulocyte colony-stimulating factor (GCSF) is prohibited from 72 hours of prior to lymphodepleting chemotherapy through the Week 2 visit
- long-acting GCSF is prohibited from 2 weeks prior to lymphodepleting chemotherapy through the Week 2 visit
- steroids are prohibited within 72 hours of lymphodepleting chemotherapy, except for physiologic steroid replacement with $\leq$ 0.2 mg/kg/day methylprednisolone or equivalent
- live vaccine administration from the time of lymphodepleting chemotherapy through infusion of NTLA-5001, for at least three months after NTLA-5001 and until immune recovery following treatment

Additionally, subjects must agree not to participate in another interventional study for a minimum of 28 days post dosing of NTLA-5001. Additional investigational interventions could confound the primary objective of the study to assess safety of NTLA-5001.

6.7 Toxicity Management

Recommendations for management of potential toxicities of NTLA-5001 are provided, including specific agents to be used, doses and intervals, and lines of therapy. These recommendations may be modified by the investigator to accommodate existing institutional guidelines for management of cell therapy toxicities and variations in global standard-of-care practices.

6.7.1 Acute Infusion Reaction

Acetaminophen/paracetamol and diphenhydramine /H1 antihistamine may be repeated every 6 hours as needed. If the subject continues to have fever, a course of nonsteroidal anti-inflammatory medication may be prescribed. It is recommended that subjects not receive corticosteroids except in the case of life-threatening emergency, because this may adversely affect NTLA-5001 cells. For additional notes regarding interruption of study drug during an acute infusion reaction, see Section 6.2.3.

6.7.2 Cytokine Release Syndrome

Cytokine release syndrome (CRS), when present, typically manifests in the first days after cellular therapy. CRS may include a prodromal syndrome characterized by flu-like syndrome with, fatigue, headache, arthralgia, myalgia, and malaise, which is then followed at CRS onset by fever, hypoxia, and/or mild hypotension. In severe cases, CRS may be characterized by hemodynamic instability and organ dysfunction. Routine monitoring during hospitalization, should include vital sign assessment every 4 hours and evaluation for CRS symptoms at least twice a day. Subjects with CRS should have laboratory assessments including daily complete chemistry panel, albumin, lactose dehydrogenase (LDH), liver enzymes, bilirubin, and coagulation panel with prothrombin time, partial thromboplastic time, fibrinogen, and D-dimer, C-reactive protein and ferritin. Adverse events of CRS are graded according to the ASTCT consensus grading scale (Section 13.5). Sites with local Standard Operating Procedures for the treatment of CRS should follow those protocols. For other sites, suggested treatment is below:

- **Prodromal symptoms** should be treated with symptomatic support and observation. Infection should be considered in the differential diagnosis and surveillance cultures or prophylactic antibiotics prescribed as warranted.
- **Initial mild signs of fever, hypoxia, and/or mild hypotension** should be treated with oxygen, antipyretics, fluids, low-dose vasopressor support (vasopressin monotherapy, dopamine monotherapy < 10 ug/kg/min), and tocilizumab (8 mg/kg IV).
- **For initial symptoms that persist beyond 12-18 hours**, subjects should be treated with additional tocilizumab a minimum of 8 hours after the first dose which may be continued for 4 doses. For subjects with symptoms that do not respond to tocilizumab, additional interleukin-6 (IL-6) directed therapy (siltuximab 11 mg/kg) should be considered.
- **More severe symptoms than fever, hypoxia, and/or mild hypotension** typically include respiratory distress despite supplemental oxygen or hemodynamic instability. Subjects should be carefully evaluated for infection and empiric therapy should be considered. Such symptoms should be treated with continued IL-6 directed therapy, and corticosteroids (methylprednisolone 2 mg/kg x 1 followed by 0.5 mg/kg q6h; or dexamethasone

0.4 mg/kg x 1 followed by 0.1 mg/kg q6h; or equivalent). Steroids should be tapered to off within 1 week. Coagulopathy should be treated with fresh frozen plasma or cryoprecipitate. Hypoxia may require high-flow oxygen by face mask or positive airway pressure ventilation. High dose vasopressors for hemodynamic support with norepinephrine, dopamine > 10 µg/kg/min, or phenylephrine may be needed.

- **For subjects with severe symptoms that are persistent 24 hours after steroid administration**, etanercept (50 mg subcutaneous [SC]) or anakinra (100 mg SC) should be considered. Subjects with persistent life-threatening symptoms may require anti-T cell therapy such as such as alemtuzumab (12 mg IV over 4 hours once daily [QD] x 5d), high dose cyclophosphamide, or antithymocyte globulin (ATG) (2 mg/kg/day IV).

The need for positive pressure ventilation or the need for multiple vasopressors in the presence of fever ≥ 38°C constitutes Grade 4 CRS. Grade 4 CRS should be reported immediately to the medical monitor. If the event does not resolve to Grade 1 CRS within 72 hours, a criterion for pausing study enrollment is reached.

6.7.3 Immune effector cell-associated neurotoxicity syndrome (ICANS)

Immune effector cell-associated neurotoxicity syndrome (ICANS) may have features that overlap with other encephalopathies but has the more specific characteristic of an awake subject who is mute and does not respond verbally or physically to an examiner. In a small number of subjects, mild CNS toxicity occurs in the absence of CRS. The great majority of subjects, CNS toxicity appears concurrent of shortly after CRS, and assessments and management of these subjects according to CRS guidelines above is indicated. If neurologic symptoms develop, assessment and grading for ICANS be completed at least every 12 hours including the 10-point ICE score assessment (Section 13.5). Subjects with Grade 2 ICANS should have neuroimaging studies to assess CNS edema. Neurotoxicity may require transfer to the ICU for close monitoring or intubation for airway protection even in the absence of severe CRS. Adverse events of CRS are graded according to the ASTCT consensus grading scale (Section 13.5).

- **Symptoms that occur in the absence of advanced ICANS (where advanced ICANS is defined as Grade 3 ICANS or Grade 2 ICANS without CRS)**, such as headache, tremor, myoclonus, asterixis, hallucinations, weakness, or imbalance may be managed symptomatically.
- **Subjects with advanced ICANS (Grade 2 ICANS and no CRS, or subjects with Grade 3 ICANS)** should be treated with corticosteroids (methylprednisolone 2 mg/kg x1 followed by 0.5 mg/kg q6h; or dexamethasone 0.4 mg/kg x1 followed by 0.1 mg/kg q6h; or equivalent). Steroids should be tapered to off within 1 week.
- **Advanced ICANS symptoms that are persistent 24 hours after steroid administration** may require anti-T cell therapy such as such as alemtuzumab (12 mg IV over 4 hours QD x5d), high dose cyclophosphamide, or ATG (2 mg/kg/day IV).

Grade 4 ICANS should be reported immediately to the medical monitor. If the event does not resolve to Grade 1 ICANS within 72 hours, a criterion for pausing study enrollment is reached.

6.7.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) after cell therapy is uncommon even in high-risk situations. However, precautions such as intravenous hydration and prophylactic allopurinol or febuxostat should be administered prior to the initiation of conditioning lymphodepleting chemotherapy in those subjects with elevated uric acid or high tumor burden.

TLS prophylaxis may be used per institutional standard. Following therapy, TLS diagnosed solely based on laboratory criteria should be managed initially per institutional standard with therapy directed at uric acidemia such as allopurinol or febuxostat. For persistent symptoms, subjects should receive intravenous hydration and additional uric acid therapy such as rasburicase. All subjects with clinical TLS should be admitted for in-hospital treatment and monitoring.

6.7.5 Uncontrolled T-cell Proliferation

NTLA-5001 cells could theoretically proliferate without control of normal homeostatic mechanisms. This risk is reduced by the use of targeted gene insertion using AAV [redacted] Other viral insertion methods, such as the use of lentivirus, cause transgene insertion at random sites, which is thought to pose a higher risk to the interruption of normal cellular functions. Lymphocytes will be monitored by hematology laboratory assessments at each visit. A lymphocyte spike is typically seen around the time of peak cell expansion after adoptive therapy, and this finding alone should not be a reason to intervene. If the WBC count rises above normal values and is sustained 14 days after infusion, the subject should be assessed for clonal T cell proliferation, including assessment of rapidly progressing AML. At each visit, history and physical should include assessment for enlarged lymph nodes or immune dysfunction. Any sustained elevation of WBC due to lymphocytosis at any time should be treated as presumed NTLA-5001 proliferation while evaluation continues, and a peripheral blood sample should be sent for evaluation of cell kinetics to assess for proliferating NTLA-5001 cells.

If uncontrolled proliferation of NTLA-5001 cells occurs, subjects may be treated with corticosteroids (methylprednisolone 2 mg/kg x1 followed by 0.5 mg/kg q6h; or dexamethasone 0.4 mg/kg x1 followed by 0.1 mg/kg q6h; or equivalent). If symptoms persist, or recur as steroids are tapered, subjects may require anti-T cell therapy such as such as alemtuzumab (12 mg IV over 4 hours QD x5d), high dose cyclophosphamide, or ATG (2 mg/kg/day IV).

6.7.6 Autologous GvHD

After autologous HCT or autologous CAR-T therapy, a GvHD-like syndrome which is clinically and histologically indistinguishable from allogeneic GvHD has been described in the skin, liver and gastrointestinal tract. Autologous GvHD is an autoimmune syndrome initiated by auto-reactive T cells that recognize self-major histocompatibility complex (MHC) class II antigens. The diagnosis of autologous GvHD can be made with clinical suspicion, inspection and biopsy of affected sites, and exclusion of other possible cases of symptoms such as infections, drug effect and engraftment syndrome.

If autologous GvHD occurs, subjects may be treated with corticosteroids (methylprednisolone 2 mg/kg x1 followed by 0.5 mg/kg q6h; or dexamethasone 0.4 mg/kg x1 followed by 0.1 mg/kg q6h; or equivalent). If symptoms persist, or recur as steroids are tapered, subjects may require sitagliptin (100–200 mg/day orally [PO]), ruxolitinib (10 mg PO twice daily [BID]), or anti-T cell therapy such as such as alemtuzumab (12 mg IV over 4 hours QD x5d).

6.7.7 Hemophagocytic Lymphohistiocytosis

After ATC, symptoms of CRS may subsequently evolve in some subjects to hemophagocytic lymphohistiocytosis (HLH)-like symptomatology. HLH related to adoptive therapy may be identified by a characteristic set of signs, including ferritin level of > 100,000 ng/mL with at least 2 of the following: Grade 3 or greater AST/ALT elevation or hyperbilirubinemia; Grade 3 or greater oliguria or increase in serum creatinine; Grade 3 or greater pulmonary edema; or hemophagocytosis in the bone marrow.

If HLH occurs, subjects may be treated with corticosteroids (methylprednisolone 2 mg/kg x1 followed by 0.5 mg/kg q6h; or dexamethasone 0.4 mg/kg x1 followed by 0.1 mg/kg q6h; or equivalent). If symptoms persist, or recur as steroids are tapered, subjects may receive tocilizumab (8 mg/kg IV) and/or anakinra (initially 2 mg/kg/day increasing by 1 mg/kg up to 8 mg/kg/day).

6.7.8 On-target/Off-tumor Toxicity

WT1 protein is expressed by a limited number of normal tissues, including CD34+ stem cells in the bone marrow, mesothelial linings of the peritoneum and pleura, testes/ovaries, fallopian tubes, and on podocytes of the kidney glomerulus. NTLA-5001 has the potential to cause inflammation or cell destruction at these sites through recognition of WT1 processed and presented on HLA class I, which is termed on-target/off-tumor toxicity. Monitoring for on-target/off-tumor toxicity includes physical examination observations, laboratory measures, and AE assessments at each visit to identify symptoms of tissue inflammation. History questions at each visit will interrogate reproductive history, testicular/scrotal pain, swelling, and erythema for males and lower abdominal pain or vaginal bleeding for women. Physical exam at each clinic visit should also assess for any new pleural or peritoneal effusions. It is recommended that positive history be followed up with work-up to assess the etiology as appropriate, including thoracic imaging, testicular US, abdominal US, pelvic exam, pregnancy test, thyroid and PRL levels, or endometrial biopsy as indicated. In addition, specific monitoring is included for signs at each of these organ sites (see Schedule of Activities). CD34+ bone marrow cells will be monitored at Week 4, 8, 16, and then at 12-week intervals for the duration of the study. Renal podocyte function will be assessed by urinalysis for proteinuria 1 week following NTLA-5001 then at each study visit.

- If signs, symptoms, and follow up evaluations suggest that bone marrow dysfunction, renal dysfunction, or mesothelial inflammation is potentially due to NTLA-5001, subjects should receive corticosteroids (methylprednisolone 2 mg/kg x1 followed by 0.5 mg/kg q6h; or dexamethasone 0.4 mg/kg x1 followed by 0.1 mg/kg q6h; or equivalent). During steroid taper, systematic assessment for recurrence of toxicity should be performed.

- If symptoms persist, or recur as steroids are tapered, subjects may require anti-T cell therapy such as such as alemtuzumab (12 mg IV over 4 hours QD x5d), high dose cyclophosphamide, or ATG (2 mg/kg/day IV).

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

In the event of an IRR, the infusion of study drug will be slowed or stopped. The following events in relation to an IRR will result in permanent discontinuation of study drug:

- The IRR is severe, and the decision is made by the investigator and/or Medical Monitor to not resume the infusion.
- The IRR is mild or moderate but does not resolve in a timeframe that allows completion of the infusion of study drug within the 4-hour window noted in Section 6.2.3.

Those subjects who receive a partial infusion will continue on study and will attend all study visits and have all tests performed per the SoA (Section 1.3). Subjects who receive a partial infusion in Part 1 will be replaced as explained in Section 4.1.1.

7.2 Discontinuation/Withdrawal from the Study

All subjects enrolled in the study will be followed for 112 weeks unless a subject:

- withdraws consent from study,
- dies, or
- is lost to follow-up.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The investigator should document all refusals and withdrawals and shall ensure that no data for the clinical trial are collected from subjects that refuse to participate in or have withdrawn from the clinical trial.

7.3 Lost to Follow-up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a

certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study. For subjects who are lost to follow-up, the investigator can search publicly available records where permitted to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

Discontinuation of specific sites or of the study as a whole are handled in Section 11.1.11.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Immediate safety concerns should be discussed with the Sponsor upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening and Enrollment

Screening

The screening period will be up to 28 days, and a subject that meets all inclusion and none of the exclusion criteria will be enrolled and proceed to the leukapheresis phase in Arm 1 for subjects with AML blasts <5% of bone marrow or in Arm 2 for subjects with AML blasts ≥5% of bone marrow.

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 (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

As outlined below, retesting during screening and rescreening is permitted.

Retesting During Screening

Retesting is defined as repeating laboratory tests within the same screening period.

If retesting goes beyond the 28-day screening period, the subject will be classified as a screen failure and will need to go through the rescreening process.

Rescreening

Subjects who fail to qualify for the study based on laboratory tests may be considered for rescreening at the discretion of the investigator if it is considered that the subject's status has changed, and the subject may now qualify for the study. Screening is limited to 2 attempts (initial screening and 1 additional rescreening attempt). A new informed consent is required to be signed prior to rescreening. See Section 11.1.3 for Informed Consent Process details.

Enrollment

The study population will be enrolled in 2 independent Arms.

Subjects in Arm 1 will have < 5.0% AML blasts in bone marrow on locally assessed morphology, and no evidence of blasts in peripheral blood or extramedullary disease (i.e., are in CR/CRi), and MRD identified at a frequency > 0.1% by the central laboratory, [redacted]

Subjects in Arm 2 will have ≥ 5.0% AML blasts in BM by locally assessed morphology.

8.1.2 Leukapheresis Phase

A subject that meets all inclusion and none of the exclusion criteria will be eligible for leukapheresis. If the investigator believes a subject may require a second leukapheresis day for any reason, the medical monitor should be contacted for discussion and planning. Subjects in the leukapheresis phase of the study may receive bridging therapy under the direction of their physicians (see Section 6.1.3.2) and should undergo associated standard-of-care assessments.

Prior to entering the treatment phase, repeat BM assessment should be performed for Arm assignment if the assessment for study entry was prior to signing consent, > 6 weeks have passed since the screening BM assessment, or if warranted by change in clinical condition, or if subject has received bridging therapy other than hydroxyurea. If an Arm 1 subject is found to have ≥5% bone marrow blasts at repeat BM assessment, the subject may be re-assigned to Arm 2 or, if Arm 2 is not yet enrolling subjects, the subject may receive NTLA-5001 at Dose Level -1.

8.1.3 Treatment Phase

[redacted] After leukapheresis, subjects who meet criteria for treatment per Section 8.1.3.1 below and who have manufactured NTLA-5001 that meet release requirements will enter the treatment phase for the administration of lymphodepleting chemotherapy (Section 6.1.3.3) and study medication (Section 6.1.1). Individual subjects will participate in the treatment phase and follow-up phase for safety and efficacy assessments up to 112 weeks or until the subject is no longer receiving clinical benefit. Subjects who are no longer receiving clinical benefit will continue to be followed with clinic visits to safety every 12 weeks until 112 weeks after administration of NTLA-5001 (see SoA Section 1.3).

8.1.3.1 Criteria for Entering the Study Treatment Phase

Subjects must be reassessed for entry into the study treatment phase within 1 week of lymphodepleting chemotherapy.

Subjects must meet all of the following inclusion criteria:

1. Subject must have a projected life expectancy of at least 6 weeks.
2. Subject must have an ECOG performance status of 0 to 2.
3. Subjects must have adequate organ function defined as:
   - AST ≤ 2.5 × ULN and ALT ≤ 2.5 × ULN (unless considered due to leukemic organ involvement).
   - Bilirubin ≤ 1.5 × ULN (unless considered due to leukemic organ involvement). Note: Subjects with Gilbert's Syndrome may have a bilirubin > 1.5 × ULN but must have direct bilirubin ≤ 1 x ULN.
   - eGFR ≥ 30 mL/min; determined by CKD-Epi Study equation.

Subjects must not meet any of the following exclusion criteria:

1. Subjects with a history of allogeneic HCT are excluded if:

- Subjects have evidence of ongoing active GvHD, or
- Subjects are on active immunosuppression for GvHD prophylaxis (must be off for 30 days prior to enrollment). Physiologic steroid replacement with ≤0.2 mg/kg/day methylprednisolone or equivalent is permitted.

2. Must not have signs or symptoms indicative of CNS involvement by tumor. A CNS evaluation should be performed to rule out CNS involvement if indicated by signs or symptoms.
3. Must not have active DIC, bleeding or coagulopathy during screening.
4. Must be eligible to receive lymphodepleting chemotherapy doses per protocol Section 6.1.3.3
5. Must not have leukocytosis ≥ 20,000 WBC/μL despite hydroxyurea or rapidly progressive disease (e.g., recent increase in blast count above 50%) that in the estimation of the investigator or Sponsor would compromise ability to complete study therapy.
6. Must not have any condition, laboratory abnormality, or other reason that, in the investigator's opinion, could adversely affect the safety of the subject, impair the assessment of study results, or preclude compliance with the study.

8.1.4 End of Study Visit

A subject will have an End of Study visit at Week 112 or at the time the subject is discontinued from efficacy assessments by the investigator because the subject is no longer receiving clinical benefit. Subjects who are no longer receiving clinical benefit will continue to be followed with clinic visits (focused physical exam, vital signs, weight, and assessment for treatment-related AEs and treatment-related serious adverse events [SAEs]) every 12 weeks until 112 weeks after administration of NTLA-5001. Subjects who are not receiving clinical benefit may receive additional treatment or supportive care per their Investigators for the duration of the study.

8.1.5 Long-term Follow up

Following participation in the study, all subjects who have received study medication in this study will undergo long-term safety monitoring in order to comply with local regulatory requirements/guidance for subjects administered a gene therapy. All subjects will be followed for a minimum of 5 years in the UK and for a minimum of 15 years in the US. Additional details on the long-term follow-up will be provided outside of this clinical study and will be in place before the first subject completes their Week 112 study visit.

8.2 General Assessments

8.2.1 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarker variability and CK of the protocol-required therapies.

8.2.2 Medical History

The investigator or designee will collect a complete medical and surgical history that started within 3 years prior to screening through time of signing of informed consent. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF.

8.3 Efficacy Assessments

8.3.1 Bone Marrow Sampling and Disease Assessment

Bone marrow aspirate and biopsy will be performed until the subject achieves complete remission and has no evidence of MRD. Thereafter, subjects should undergo bone marrow aspirates every 12 weeks for 1 year after remission is first documented. Subsequently, subjects in CR are not required to have additional bone marrow aspirations unless clinically indicated. Bone marrow will be used for hematological assessment, and local cytomorphological assessment will be performed. From each sample, mandatory evaluation of MRD by difference from normal flow cytometry will also be conducted via central laboratory analysis. The following samples will be obtained for local cytomorphological assessment and MRD measurement at the central laboratory (listed in recommended priority order):

- local cytomorphology: bone marrow smears (slides)
- MRD: aliquots for difference from normal flow cytometry
- evaluation of immune parameters and NTLA-5001 cells

For cytomorphology, if a marrow aspiration is not possible, or the aspirate does not contain any bone marrow, a core biopsy will be done. In case of core biopsies, no central MRD assessment will be possible.

8.3.2 EORTC QLQ-C30

The EORTC QLQ-C30 was developed to assess the quality of life in cancer subjects across tumor types. It is a self-reporting 30-item generic instrument which assesses 15 domains consisting of 5 functional domains (physical, role, emotional, cognitive, social), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and a global health status/quality of life scale (Aaronson et al, 1993). The recall period is the past week. The QLQ-C30 will take approximately 9 minutes to complete.

8.4 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.4.1 Vital Signs

Vital signs, including systolic and diastolic blood pressures (mm Hg), pulse rate (beats/minute) and temperature will be obtained and recorded. All vital sign measures will be obtained with the subject in the sitting or supine position.

If clinically significant worsening of a finding from screening is noted at any study visit, the abnormality will be documented as an AE on the AE page of the eCRF as defined in Adverse Events (Section 8.5.1).

8.4.2 Physical Examination

Standard, full physical examinations will be performed to assess weight, height, general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic, lymphatic system, reproductive system, and mental status. Genitourinary and rectal system exams are to be performed only if clinically indicated. Focused physical examinations should be symptom directed and consider potential sites of on target / off tumor toxicity. The PI will inquire if the subject has experienced testicular/scrotal pain, swelling, and erythema for males and lower abdominal pain or vaginal bleeding for women, or any reproductive symptoms, whether the subject is trying to conceive, or has successfully conceived. Should a pregnancy occur a detailed in-utero assessment will be performed. Physical exam at each clinic visit will assess for any new pleural or peritoneal effusions.

If clinically significant worsening of findings from baseline is noted at any study visit, the change will be documented as an AE on the AE page of the case report form (CRF). Clinical significance is defined as any variation in physical findings, which has medical relevance that could result in an alteration in medical care (see Section 8.5.1). The investigator will continue to monitor the subject until the investigator determines that the findings are no longer clinically significant.

Note: Any finding assessed by the investigator to be associated with the underlying AML, unless judged by the investigator to be more severe than expected for the subject's condition, will not be reported as an AE.

8.4.3 Chest X-ray

All subjects will have an upright posterior-anterior and lateral chest x-ray taken during screening, Study Week 2, and Study Week 4.

8.4.4 Echocardiogram

All subjects will have a baseline transthoracic echocardiogram (TTE) during screening, including assessments of systolic and diastolic left ventricular function and right ventricular function as well as ejection fraction.

8.4.5 Clinical Safety Laboratory Assessments

See Section 13 for the list of clinical laboratory tests to be performed. Details of how blood and urine samples will be collected, processed, and stored will be in the study laboratory manual. All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual.

- The investigator must review the laboratory report, document this review, and record in the AE section of the CRF any clinically relevant changes occurring during the study. The laboratory reports must be filed with the source documents. Clinically significant abnormal

laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- All abnormal laboratory tests with values considered clinically significant during participation in the study should be repeated until the values are no longer considered clinically significant by the investigator.
- Non-protocol specified laboratory assessments performed at the institution's local laboratory that are needed to manage a subject should be reported as a SAE or AE if they are deemed clinically significant by the investigator (see Section 8.4).

8.4.6 Adverse Events

AE collection will begin from time of informed consent and continue through the Week 112 visit. AEs will be documented at each clinic visit but can be collected at any time. Any AE that meets the definition of a Serious Adverse Event (SAE) will also be reported on a separate form to the Sponsor.

See Section 8.5 for information regarding AE collection and data handling.

Note: Any finding assessed by the investigator to be associated with the underlying AML, unless judged by the investigator to be more severe than expected for the subject's condition, will not be reported as an AE.

8.5 Adverse Events and Other Safety Aspects

8.5.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs should be described using a diagnosis whenever possible, instead of individually reporting underlying symptoms. When a clear diagnosis cannot be identified each symptom should be reported as a separate AE.

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the eCRF accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, physical exam) should be defined as an AE only if the abnormality meets 1 of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication

- The abnormality or investigational value is clinically significant in the opinion of the investigator.

8.5.2 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be recorded according to the National Cancer Institute (NCI)-CTCAE guidelines (Version 5.0). CRS and ICANS AEs will be recorded according to ASTCT consensus grading (Section 13.5). The items that are not stipulated in the NCI-CTCAE guidelines or ASTCT consensus grading will be assessed according to the criteria in Table 8-1 and entered into the eCRF.

Table 8-1 Criteria for Grading Events Not Stipulated by NCI-CTCAE Guidelines or ASTCT Consensus Grading

Grade	Assessment Standard
1-Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2-Moderate	Minimal, local or noninvasive intervention indicated limiting age-appropriate instrumental activities of daily living
3-Severe	Medically significant but not immediately life threatening, hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4-Life Threatening	Life threatening consequences, urgent intervention indicated
5-Death	Death related to adverse event

8.5.3 Criteria for Causal Relationship to the Study Drug

The investigator must provide the causality assessment for an AE. AEs that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	Criteria for Causal Relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

8.5.4 Definition of a Serious Adverse Event (SAE)

An AE is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an AE is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Safety events of interest on the medicinal products administered to the subject as part of the study (e.g., study drug, pre-treatment regimen) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s).
- Suspected abuse/misuse of the medicinal product(s).
- Inadvertent or accidental exposure to the medicinal product(s).
- Medication error involving the medicinal product(s) (with or without subject exposure to the Sponsor medicinal product, e.g., name confusion).

All of the events of interest noted above should be recorded on the eCRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked 'serious' and the SAE Report Form.

8.5.5 Reporting of Serious Adverse Events (SAEs)

All SAEs will be collected from the signing of the ICF through a subject's Week 112 visit.

In the case of a SAE, the investigator must contact the Sponsor or designee by telephone immediately (within 24 hours of awareness).

The investigator should complete and submit an SAE Report Form containing all information that is required by the Regulatory Authorities to Sponsor designee (within 24 hours of awareness). The SAE Report is to be sent to:

[redacted]

SAEs will be reviewed by the sponsor medical monitor, in consultation with the global safety physician, and further queries issued, if necessary. If there is no evidence for the designation of an event as serious (in line with the protocol definition, Section 8.5.4) or there is no apparent evidence for the positive investigator causality assessment, the sponsor medical monitor may query or discuss with the investigator. However, if agreement is not reached, the investigator assessment will be respected and not changed by Intellia. The same is true if there is evidence to suggest a positive causality assessment for an SAE that has been assessed as unrelated by the investigator.

If there are any other questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor or his/her designee (See Contact Details of Key Sponsor's Personnel).

Follow-up information for the event should be sent within 24 hours of the awareness.

Full details of the SAE are to be recorded on the medical records and on the eCRF in addition to the SAE form.

The Sponsor has a legal responsibility to record and notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to ensure that the regulatory authority, IEC, and investigators are informed within the applicable timeframe. Documentation of the submission to and receipt by the IEC of expedited safety reports is to be retained by the site.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.5.6 Follow-up of Adverse Events and Serious Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized in the opinion of the investigator. After 112 weeks, any continuing AEs will be followed under a separate long-term follow-up protocol.

If during AE follow-up, the AE progresses to an SAE, or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor.

8.5.7 Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study the investigator should report the information to the Sponsor/delegated CRO within 24 hours. A signed ICF may be requested from a pregnant female partner of a male subject before any information about the pregnancy can be collected or reported to the Sponsor. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the Sponsor /delegated CRO within 24 hours using the pregnancy notification form.

As noted in Section 8.5.4, a pregnancy outcome that results in congenital anomaly or birth defect is considered a SAE. When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with

the report procedure for SAEs. Additional information regarding pregnancy outcomes that meet SAE criteria are noted below.

- "Spontaneous abortion" includes miscarriage, abortion, and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, the death should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator.
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth and followed up through 2 years.
- Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination.

If during the conduct of a clinical trial, a male subject makes his partner pregnant, the subject is asked to report the pregnancy to the investigator. The investigator will report the pregnancy to the Sponsor/delegated Contract Research Organization (CRO) using the pregnancy notification form and follow-up as described above.

8.5.8 Adverse Events of Special Interest

The following events and/or laboratory finding will be designated as AEs of special interest based on the predicted pharmacology, the nonclinical safety profile, possible off-target effects and/or adverse reactions seen in other cell therapies. Additional information is provided in the NTLA-5001 Investigator's Brochure.

- IRRs
- CRS
- ICANS
- TLS
- T cell proliferative disorders
- Autologous GvHD
- Hemophagocytic lymphohistiocytosis
- Adverse events attributed to impacts on the testes, ovaries, fallopian tubes, bone marrow, pleura, peritoneum, or kidney podocytes.

8.6 Treatment of Overdose

In the event of an NTLA-5001 overdose, the subject should receive supportive care, as applicable and monitoring. The Medical Monitor should be notified and the quantity of the excess dose, as well as the duration of the overdose, should be documented in the eCRF.

8.7 Cell Kinetics

Details of sample collection and processing for CK analyses will be included in the laboratory manual.

Blood samples will be collected to assess the frequency time profiles of NTLA-5001 in the cryopreserved PBMC population. Details of the bioanalysis will be described in the bioanalysis plan. See SoA (Section 1.3) for details on visits. NTLA-5001 cells will be quantified using ddPCR for the TCR transgene and flow cytometry (cells that label as positive for Vβ8 TCR subunit and peptide-MHC dextramer) will be used for exploratory purposes. Samples will be evaluated using a validated method following regulatory guidelines.

Additional CK samples may be collected if clinically indicated for AEs.

8.8 Pharmacodynamics

Details of sample collection and processing for pharmacodynamics (PD) analyses will be included in the study laboratory manual.

Blood samples and bone marrow samples will be collected to assess the frequency of AML blasts. Details of the PD evaluation and analysis will be described in the bioanalysis plan. See SoA (Section 1.3) for details on visits. AML blasts will be determined by site pathologists according to standard local practices. Measurable residual disease will be determined by a central laboratory vendor using flow cytometry according to the difference from normal technique (Loken et al, 2019). Samples will be evaluated using a validated method following regulatory guidelines.

8.9 Biomarkers

Biomarker analysis for circulating cytokines will be performed using Simoa and multiplex Luminex methods.

8.10 Immunogenicity

Serum samples will be collected for analysis of immunogenicity. Immunogenicity testing will be performed on an as needed basis, according to local regulations.

8.11 Health Economics

No health economics data is being collected in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypothesis

No hypothesis testing is to be performed in this first-in-human study.

9.2 Sample Size Determination

The number of subjects to be included is typical for this kind of study, and the results will constitute sufficient safety, tolerability, PD, and CK data without exposing too many subjects.

Dose escalation will consist of up to 3 dose escalation cohorts in each of 2 Arms. Each Arm 1 cohort will include up to 6 subjects, as detailed in Section 4.1. Each Arm 2 cohort will include 3 to 6 subjects. Therefore, up to 36 evaluable subjects are anticipated to be enrolled in this portion of the study.

Once a dose is identified for detailed safety assessment in an Arm, a safety expansion cohort will be opened for up to 9 additional subjects to be dosed at that dose level. Thus, up to a total of 18 subjects will be dosed in safety expansion cohorts across the 2 Arms.

9.3 Analysis Sets (Populations for Analysis)

For purposes of analysis, the following analysis sets are defined in Table 9-1.

Table 9-1 Analysis Sets

Population	Description
DLT Evaluable Set	All subjects who receive a dose of NTLA-5001 and either experience DLT(s) regardless of whether a full dose was administered or receive the full assigned dose without DLTs and complete Day 29 assessments. Subjects without DLTs who do not receive the full dose of NTLA-5001 as per their assigned dose cohort are not evaluable for DLTs.
Safety Analysis Set	All subjects who receive NTLA-5001
Cell Kinetics (CK) Analysis Set	All subjects who receive NTLA-5001 with at least one evaluable CK sample
Full Analysis Set (FAS)	All subjects who undergo leukapheresis
Efficacy Evaluable Set	All subjects who receive a dose of NTLA-5001 in agreement with their assigned dose level after successful manufacture of the NTLA-5001 cell therapy product

9.4 Statistical Analyses

This section is a summary of the planned statistical analyses. The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. CK, CK/PD, and immunogenicity analysis plans will be described in separate document(s).

Descriptive statistics, including 'n', mean standard deviation and/or standard error, median, range, and geometric mean for numerical variables (as applicable), and frequency and percentages for categorical variables, will be presented.

The Safety Analysis Set (SAS) will be used for all clinical data summaries of safety and tolerability. The Efficacy Evaluable Set will be used for all disease assessment related efficacy analysis.

9.4.1 Endpoints and Analyses

Descriptive statistics will be used to summarize the safety, tolerability and activity of NTLA-5001 in treated subjects by cohort within each Arm in dose escalation and for each Arm in safety expansion.

The analysis of safety and tolerability will be a comprehensive evaluation of AEs and/or toxicity, based on occurrence of AEs and DLTs, results of clinical laboratory tests, cytokines, vital signs results, changes in physical examination and need for concomitant medications. Acute tolerability through Week 4 and overall safety profile through Week 112 will be assessed.

Cell kinetics will be assessed via TCR transgene copy number and the proportion of T cells expressing the TCR transgene in PBMC and bone marrow through Week 112 after treatment.

Evaluations will include the following:

- Subject BM will be classified into an AML response group at each assessment according to modified ELN recommendations (Section 13.4). Based on these results, all dosed subjects with AML will be assessed for AML according to Doehner et al (2016) at each postbaseline BM by the investigators. Responder criteria to estimate efficacy in Arm 1 and Arm 2 appear below.
- BM results will be used to determine the following efficacy endpoints:
  - For Arm 1:
    - Rate of objective response, where response is CR without measurable residual disease ($CR_{MRD}-$).
    - Duration of response / remission (DOR) for subjects with objective response, from first response until MRD is measured above the lower level of detection for the central laboratory assay, or death from any cause, whichever occurs first.
    - Time to clinical progression, defined as time to BM blast count $\geq$ 5.0% or time to start of next AML therapy that is needed per investigator's judgment
  - For Arm 2:
    - Rate of objective response, where response is $CR_{MRD}-$, CR, complete remission with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), and partial remission (PR).
    - Rate of composite CR, where composite CR is the sum of $CR_{MRD}-$, CR, and CRi.
    - DOR for subjects with composite CR, from first response to progression or death due to any cause, whichever occurs first.
  - Analysis of immune parameters and NTLA-5001 cells

- Overall survival: through Week 112.
- The frequency and persistence of TRAC and TRBC edits: Samples will be enriched by selection of cells with surface expression of variable beta chain 8 (Vβ8), and the sequence of TRAC and TRBC1/2 genes will be determined by NGS while NTLA-5001 cells are detectable.
- Gene expression patterns in NTLA-5001 cells: Samples will be enriched by selection of cells with surface expression of Vβ8, and profiling of gene expression will be performed using single cell RNA sequencing while NTLA-5001 cells are detectable.
- The translocation rates in NTLA-5001 cells: Samples will be enriched by selection of cells with surface expression of Vβ8, and translocations will be detected in NTLA-5001 cells by NGS while NTLA-5001 cells are detectable.
- Plasma cytokine levels measured in peripheral blood prior to treatment and after NTLA-5001 infusion.
- Measurement of WT1 expression on AML will be assessed prior to treatment and over time by reverse transcription-PCR (RT–PCR) at a central laboratory.
- ECOG Performance Status: as determined by the investigator at each visit.
- QOL as measured by the EORTC QLQ-C30 instrument at Week 4, 8, 16, and every 12 weeks thereafter
- Length of hospital stay from the time of NTLA-5001 infusion

Cell Kinetics Endpoint

The CK Analysis Set will be used to assess and characterize CK of NTLA-5001 and will be presented and summarized via summary statistics tables, listings, and plots by dose levels and clinical endpoints, if applicable. The CK of NTLA-5001 will be summarized by estimating the CK parameters illustrated in Table 9-2, if applicable, and will be presented and summarized by dose cohort and clinical outcomes. The relationship between CK parameters and certain safety, activity, and PD variables may be explored via appropriate modeling.

Table 9-2 Cell Kinetic Parameters

Parameter	Definition
AUC	The area under the concentration-time curve of NTLA-5001 in peripheral blood
C_{max}	The maximum (peak) observed in peripheral blood or other body fluid drug concentration after single dose administration
T_{max}	The time to reach maximum (peak) peripheral blood or other body fluid drug concentration after single dose administration
C_{last}	The last observed quantifiable concentration in peripheral blood
T_{last}	The time of last observed quantifiable concentration in peripheral blood
$t_{1/2}$	The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve in peripheral blood

9.4.2 Safety Analyses

AEs/SAEs will be coded and tabulated using the current version (as of study start) of Medical Dictionary for Regulatory Activities (MedDRA). Each AE will be classified by System Organ Class (SOC) and preferred term.

Treatment-emergent AEs (TEAEs) are defined as those AEs that started on or after the dose of study medication or worsened after the dose of study medication. Only TEAEs will be summarized. The incidence of TEAEs will be presented by the number and percent of subjects who experienced the TEAE.

Each subject will be counted only once in the incidence for each term (overall incidence, SOC, or preferred term). The incidence of treatment-related TEAEs will be summarized by SOC and preferred term. The incidence of serious TEAEs, and the incidence of treatment-related SAEs will be tabulated similarly.

In addition, the incidence of TEAEs will be summarized by SOC, preferred term, and maximum severity based on CTCAE grade, by relationship to NTLA-5001.

Clinical laboratory data, ECG parameters and other safety data will be summarized with descriptive statistics. Details will be described in the SAP.

10 DATA MONITORING COMMITTEE (DMC)

An independent DMC will be established to review any events that meet pausing criteria and to review completed dose escalation safety data prior to enrolling the expansion population. The DMC will include, at a minimum, 2 physicians with experience treating hematologic malignancies with T cell therapy (who are not clinical trial investigators) and 1 statistician.

Proceeding to expansion will be decided by the Sponsor, with the DMC providing a recommendation. In addition, consultation with the DMC may occur at any time to review data to manage subject safety. All decisions by the DMC will be communicated electronically to the trial Investigators within 48 hours of the Sponsor's notification. Details are included in the DMC Charter.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Regulatory, Ethical, and Study Oversight Considerations

11.1.1 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 GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., subject recruitment advertisements) must be submitted to an IRB/IEC for review and approval before the study is initiated at a clinical study site.

Any substantial amendments to the protocol will require regulatory and IRB/IEC approval before implementation of changes made to the study design at the clinical study site, except for changes necessary to eliminate an immediate hazard to study subjects.

If there is significant public emergency (e.g., pandemic, environmental, etc.), the continuity of clinical study conduct, and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, noninvasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. No waivers will be granted for study entry criteria. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to the public emergency and will remain in effect only for the duration of the public emergency.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC.
- Taking appropriate urgent safety measures to protect subjects against any immediate hazard and notify Sponsor promptly.
- Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures and in parallel the Sponsor.
- 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 IEC, European directive 2001/20 and its replacement regulation 536/2014 for clinical studies when the latter comes into operation, and all other applicable local regulations.

New information that becomes available and is relevant to the management and care of a participating subject will be communicated promptly to all participating investigators.

11.1.2 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.

11.1.3 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed, voluntarily signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent process was completed and signed informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor, regulatory authorities and other applicable individuals upon request.

A new informed consent is required to be signed prior to any rescreening activities.

11.1.3.1 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

The investigator or his/her representative will inform the subject orally as soon as possible whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.

The investigator must update their ICF and submit it for approval to the IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout his/her participation in the study. The investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

11.1.4 Data Protection

The Sponsor considers individual subject information obtained as a result of this study to be confidential and processing of such data should be performed in strict adherence to regional data protection laws. No identified or identifiable personal data should be disclosed by anyone involved in the performance of the clinical study without justifiable reasons and in compliance with the applicable laws and rules. The following measures will be implemented to lawfully process personal data including health-related data arising from the study:

- A subject will be assigned a unique identifier by the Sponsor. Any subject's records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.
- The subject is informed of the specific purpose of processing personal health-related data arising from the study in order for the subject to give the consent freely, unambiguously and specifically in accordance with the requirements set out in the applicable data protection law.
- The subject is informed that his/her medical records containing health-related information may be accessed by the Sponsor, Sponsor's authorized representative(s), the IEC members, and representatives of the regulatory authorities for a specific and legitimate purpose relating to medical research.
- Internal policy has been established to guide all Sponsor personnel and contractors engaged by the Sponsor involved in the performance in the study to ensure compliance with the applicable data protection laws. In addition, a Privacy Statement has been developed consistent with the requirements set out in Article 13 of the General Data Protection Regulation (European Union [EU] Regulation 2016/679), providing detailed information concerning this collection and processing of personal data which will be applied to all trial sites.

11.1.5 Notification of Serious Breach

The Sponsor is responsible for ensuring compliance of the study with the applicable laws and the approved study protocol. The Sponsor will notify the relevant regulatory authority or authorities of a serious breach of the applicable laws or the approved study protocol within required timeframe of becoming aware of the breach. Whether or not a notification should be submitted will be based on an assessment of whether the breach will likely affect to a significant degree the safety and rights of a trial subject or the reliability and robustness of the data generated in the clinical trial. To this end, the trial sites, investigators and the relevant ancillary staff as well as contractors are required to fully cooperate with the Sponsor to render such an assessment.

11.1.6 Data Management

Data Management will be coordinated by the Sponsor. All study-specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF completion guidelines. Coding of medical terms and medications will be performed using MedDRA and World Health Organization Drug Dictionary, respectively.

All subject data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

11.1.7 Clinical Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

Retention of study documents will be governed by the Clinical Trial Agreement.

11.1.8 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though he/she did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn.
- Received incorrect dose or infusion error (e.g., exceeds time requirement for administration of infusion).
- Received excluded concomitant treatment.

When a deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the investigator must contact the Sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File.

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

11.1.9 Source Documents

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF including description of procedures for the identification of data to be recorded directly on the CRF considered as source data.
- The investigator is responsible for ensuring that the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are hand-written on paper or entered electronically
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source data documents.

11.1.10 Quality Assurance

The Sponsor is implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs) to ensure that trials are conducted, and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, CRFs, and source documents. Direct access to these documents will be required by the auditors.

11.1.11 Study and Site Start and Closure

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

The end of trial in all participating countries is defined as the Last Subject's Last Visit.

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

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

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

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

- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator will promptly inform the subject and must ensure appropriate subject therapy and/or follow-up.

If the ITL-5001-CL-001 study is prematurely terminated or suspended, Sponsor will provide an alternate method to perform long-term follow-up of any subject that was enrolled and received study medication per regulatory gene therapy requirements.

11.1.12 Publication Policy

Publication of the study results is discussed in the Clinical Trial Agreement. The Sponsor will submit a clinical trial summary report to the relevant regulatory authorities following the end of the study within 1 year of the completion of the study or earlier if required by law.

12 REFERENCES

1. Aaronson NK, Ahmedzai A, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. J Natl Cancer Inst. 1993;85(5):365-376.
2. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.
3. Ariyaratana S and Loeb DM. The role of the Wilms tumour gene (WT1) in normal and malignant haematopoiesis. Expert Rev Mol Med. 2007;9:1-17.
4. Chapuis AG, Egan DN, Bar M, et al. T cell receptor gene therapy targeting WT1 prevents acute myeloid leukemia relapse post-transplant. Nat Med. 2019;25(7):1064-1072.
5. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-586.
6. DiNardo C, Jonas B, Pullarkat V, et al. A randomized, double-blind, placebo-controlled study of venetoclax with azacitidine vs azacitidine in treatment-naive patients with acute myeloid leukemia ineligible for intensive therapy: VIALE-A. EHA25 (2020) Virtual Congress. LB2601.
7. Di Stasi A, Jimenez AM, Minagawa K, Al-Obaidi M, Rezvani K. Review of the Results of WT1 Peptide Vaccination Strategies for Myelodysplastic Syndromes and Acute Myeloid Leukemia from Nine Different Studies. Front Immunol. 2015;6:36.
8. Doehner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2016;129(4):424-447.
9. Doubrovina E, Carpenter T, Pankov D, et al. Mapping of novel peptides of WT-1 and presenting HLA alleles that induce epitope-specific HLA-restricted T cells with cytotoxic activity against WT-1+leukemias. Blood. 2012;120(8):1633-1646.
10. Durgeau A, Virk Y, Corgnac S, Mami-Chouaid F. Recent Advances in Targeting CD8 T-Cell Immunity for More Effective Cancer Immunotherapy. Front Immunol. 2018;9:14.
11. Garcia-Manero G, Tibes R, et al.. Phase 1 dose escalation trial of ilorasertib, a dual aurora/VEGF Receptor Kinase Inhibitor, in patients with hematologic malignancies. Invest New Drugs. 2015 Aug;33(4):870-80.
12. Garzon R, Savona M, et al. A phase 1 clinical trial of single-agent selinexor in acute myeloid leukemia. Blood. 2017 Jun 15;129(24):3165-3174.
13. Harris DT, Kranz DM. Adoptive T Cell Therapies: A Comparison of T Cell Receptors and Chimeric Antigen Receptors. Trends Pharmacol Sci. 2016;37:220–230.
14. Inoue K, Sugiyama H, Ogawa H, et al. WT1 as a new prognostic factor and a new marker for the detection of minimal residual disease in acute leukemia. Blood. 1994;84:3071-3079.
15. Jaigirdar A, Rosenberg SA, Parkhurst M. A high-avidity WT1-reactive T-cell receptor mediates recognition of peptide and processed antigen but not naturally occurring WT1-positive tumor cells. J Immunother. 2016;39(3):105-116.

16. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.
17. Loken MR, Brodersen LE, Wells DA. Monitoring AML Response Using "Difference from Normal" Flow Cytometry. In: Druley T. (eds) Minimal Residual Disease Testing. Springer, Cham. 2019.
18. Majzner RG, Mackall CL. Clinical lessons learned from the first leg of the CAR T cell journey. Nat Med. 2019;25(9):1341-1355.
19. Mardiana S, Gill S. CAR T Cells for Acute Myeloid Leukemia: State of the Art and Future Directions. Front Oncol. 2020;10:697.
20. Megias-Vericat JE, Martinez-Cuadron D, Sanz MA, et al. Salvage regimens using conventional chemotherapy agents for relapsed/refractory adult AML patients: a systematic literature review. Ann Hematol. 2018;97(7):1115-1153.
21. Morris EC, Stauss HJ. Optimizing T-cell receptor gene therapy for hematologic malignancies. Blood. 2016;127:3305-3311.
22. Nagorsen D, Scheibenbogen C, Marincola FM, et al. Natural T Cell Immunity against Cancer. Clinical Cancer Research. 2003;9:4296-4303.
23. Ogawa H, Tamaki H, Ikegame K, et al. The usefulness of monitoring WT1 gene transcripts for the prediction and management of relapse following allogeneic stem cell transplantation in acute type leukemia. Blood. 2003;101:1698–1704.
24. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.
25. Price SL, Lancet JE, George TJ, et al. Salvage chemotherapy regimens for acute myeloid leukemia: Is one better? Efficacy comparison between CLAG and MEC regimens. Leuk Res. 2011;35(3):301-304.
26. Ravandi F, Ritchie EK, Sayar H, et al. Vosaroxin plus cytarabine versus placebo plus cytarabine in patients with first relapsed or refractory acute myeloid leukaemia (VALOR): a randomised, controlled, double-blind, multinational, phase 3 study. Lancet Oncol. 2015;16(9):1025-1036.
27. Renkvist N, Castelli C, Robbins PF, Parmiani G. A listing of human tumor antigens recognized by T cells. Cancer Immunol Immunother. 2001;50(1):3-15.
28. Sugiyama H. WT1 (Wilms' tumor gene 1): biology and cancer immunotherapy. Jpn J Clin Oncol. 2010;40:377–387.
29. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Leukemia – Acute Myeloid Leukemia (AML). National Cancer Institute (2020); https://seer.cancer.gov/statfacts/html/amyl.html.
30. Tallman MS, Wang ES, Altman JK, et al. Acute Myeloid Leukemia, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(6):721-749.

31. Tawara I, Kageyama S, Miyahara Y, et al. Safety and persistence of WT1-specific T-cell receptor gene–transduced lymphocytes in patients with AML and MDS. Blood. 2017;130:1985–1994.

32. Yang L, Han Y, Suarez Saiz F, Minden MD. A tumor suppressor and oncogene: The WT1 story. Leukemia. 2007;21(5):868-876.

13 APPENDICES

13.1 Appendix 1 Clinical Laboratory Tests

- The tests detailed in Table 13-1 will be performed by a central laboratory. See Laboratory Manual for further details.
- The use of local laboratories will be permitted, at the investigator's discretion if they are required for immediate clinical decisions
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. 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 entered into the CRF.
- The tests detailed in Table 13.2 will be performed by a bioanalytical laboratory. All samples will be sent to the central laboratory for central sample collection management.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 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.

Table 13-1 Protocol-Required Laboratory Assessments Performed by a Central Laboratory

Hematology	**Clinical Chemistry**	**Urinalysis**
Platelet count	Albumin	Specific gravity
Red blood cell (RBC) count	Blood urea nitrogen (BUN)	pH
Hemoglobin	Creatinine	Glucose
Hematocrit	Glucose nonfasting	Protein
RBC Indices:	Potassium	Blood
MCV	Sodium	Ketones
MCH	Chloride	Bilirubin
MCHC	Carbon dioxide	Urobilinogen
RDW	Calcium	Nitrite
% Reticulocytes	Aspartate aminotransferase (AST)	Leukocyte esterase
White blood cell (WBC) count with differential:	Alanine aminotransferase (ALT)	Microscopic examination (if blood or protein is abnormal)
Neutrophils	Alkaline phosphatase	
Lymphocytes	Total and direct bilirubin	
Monocytes	Total Protein	
Eosinophils	Creatine kinase	
Basophils	Lactose dehydrogenase (LDH)	
Coagulation	**Other Safety**	**Pregnancy**
aPTT	C-reactive protein	Serum test at screening
PT	Ferritin	Urine test at subsequent visits
INR		
Fibrinogen		
D-dimer		

aPTT = activated partial thromboplastin time, INR = international normalized ratio, LDL= low density lipoprotein, MCH = mean cell hemoglobin, MCHC = mean cell hemoglobin concentration, MCV = mean corpuscular volume, PCR = polymerase chain reaction, PT = prothrombin time, RDW = red blood cell distribution width

Table 13.2 Protocol-Required Laboratory Assessments Performed by a Bioanalytical Laboratory

Cytokines		Other	
GM-CSF	IL-8/CXCL8	Pharmacodynamics: AML in PBMC and BM	Cell kinetics
IFN-γ	IL-10	Biomarkers: AML expression of WT1	Immunogenicity
IL-1α	IL-12(p70)		Exploratory immunology parameters
IL-1β	IL-13		
IL-4	IL-17A		
IL-5	IL-23		
IL-6	TNF-α		

AML = acute myeloid leukemia; BM = bone marrow; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; IL = interleukin; PBMC = peripheral blood mononuclear cells; TNF = tumor necrosis factor, WT1 = Wilms tumor 1

Investigators must document their review and assessment of abnormal values and clinical significance of each laboratory safety report.

13.2 Appendix 2 Sponsor Signatory

ILT-5001-CL-001: Phase 1/2a, Single Dose Study Investigating NTLA-5001 in Subjects with Acute Myeloid Leukemia

I, the undersigned, have approved this version of the clinical trial protocol.

13.3 Appendix 3 ECOG Performance Status

Eastern Cooperative Oncology Group Performance Status Scale

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

Source: Oken et al, 1982

ECOG = Eastern Cooperative Oncology Group

13.4 Appendix 4 Hematological Responses Criteria Definitions

Hematological Response	
CR $_{MRD-}$	Less than or equal to 5% blasts in the bone marrow No evidence of extramedullary disease Full recovery of peripheral blood counts: Platelets > 100,000/µl, and ANC > 1,000/µl MRD not detected [redacted]
CR	Less than or equal to 5% blasts in the bone marrow No evidence of extramedullary disease Full recovery of peripheral blood counts: Platelets > 100,000/µl, and ANC > 1,000/µl MRD detected [redacted]
CRh	Less than or equal to 5% blasts in the bone marrow No evidence of extramedullary disease Partial recovery of peripheral blood counts: Platelets > 50,000/µl, and ANC > 500/µl
CRi*	Less than or equal to 5% blasts in the bone marrow No evidence of extramedullary disease Incomplete recovery of peripheral blood counts Platelets < 100,000/µl or ANC < 1,000/µl
MLFS	Less than or equal to 5% blasts in the bone marrow No evidence of extramedullary disease Insufficient recovery of peripheral blood counts: platelets ≤ 50,000/µl and/or ANC ≤ 500/µl
Partial Remission (PR)	Bone marrow blasts 6-25% with at least a 50% reduction from baseline
Progressive Disease	An increase from baseline of at least 25% of bone marrow blasts or an absolute increase of at least 5,000 cells/µL in the number of circulating leukemia cells
Non-Response	None of the above
Hematological Relapse	Proportion of blasts in bone marrow > 5% or Blasts in peripheral blood after documented CR/CRh/CRi
Extramedullary Disease	
Extramedullary disease	If clinical signs of extramedullary lesions are present, responses are assessed by modified Cheson criteria (Cheson et al, 2007).
Molecular Response	
MRD response	MRD < 0.1% [redacted]
MRD complete response	MRD not detected [redacted]
MRD relapse	Re-appearance of MRD leukemic cells after MRD complete response

ANC = absolute neutrophil count; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete recovery of peripheral blood counts; MLFS = morphologic leukemia-free state; MRD = measurable residual disease; PR = partial remission

* When criteria are met for both CRh and CRi, CRh should be reported. When criteria are met for both CRi and blast-free marrow, CRi should be reported.

13.5 Appendix 5 CRS and ICANS Grading

CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or† Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Encephalopathy Assessment Tools for Grading of ICANS

ICE
Orientation: orientation to year, month, city, hospital: 4 points Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point Attention: ability to count backwards from 100 by 10: 1 point

Scoring: 10, no impairment;
7-9, grade 1 ICANS;
3-6, grade 2 ICANS;
0-2, grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

13.6 Appendix 6 Contraceptive Guidance and Collection of Pregnancy Information

13.6.1 Definitions

Women of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
     - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
   - Permanent sterilization methods (for the purpose of this study) include:
     - Documented hysterectomy
     - Documented bilateral salpingectomy
     - Documented bilateral oophorectomy
     - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

     Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
   - If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] ○ oral ○ intravaginal ○ transdermal ○ injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] ○ oral ○ injectable
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d) True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Note: Periodic abstinence (such as calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

13.6.2 Collection of Pregnancy Information

Male Subjects with Partners Who Become Pregnant

The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the

Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be up to 2 years following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects Who Become Pregnant

The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy.

The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will be 2 years postdelivery. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at ≥ 22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor as described in Section 8.5.7.

13.7 Appendix 7 Coronavirus Disease 2019 (COVID-19) Guidance

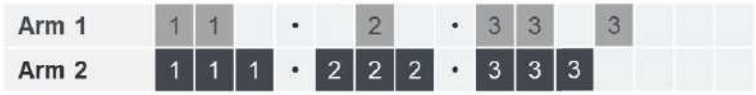
- Subjects who test positive for coronavirus disease 2019 (COVID-19) using a test consistent with the institutional standard of care or who are exhibiting symptoms consistent with COVID-19 should not be enrolled in the study until complete resolution of symptoms and 2 subsequent negative results for COVID-19 with an approved PCR-based test.
- If the ICF cannot be signed or collected in person due to COVID-19 restriction, alternative approaches of obtaining and documenting informed consent may be utilized in according with local regulatory guidance.
- If an enrolled subject is exhibiting symptoms consistent with COVID-19, contact the Medical Monitor within 1 business day to ensure appropriate documentation and management of study activities.
- If a subject is unable to travel to the site for protocol-specified study visits and procedures, he/she can remain in the trial, provided that safety monitoring can occur. Alternatives, such as telemedicine to conduct visits, should be considered.
- On-site monitoring visits may be replaced by remote monitoring visits during COVID-19. Additionally, remote source document verification may be utilized for critical data points.
- Additional COVID-19 guidance from Food and Drug Administration (FDA), European Medicines Agency (EMA), and Medicines and Healthcare Products Regulatory Agency (MHRA) should be followed in consultation with medical monitor.
- A risk assessment indicates interaction between the administration of NTLA-5001 and COVID-19, seasonal influenza, and pneumococcal vaccines are unexpected. The immunizing effects of COVID-19, seasonal influenza, and pneumococcal vaccinations may be reduced in subjects if the vaccination is administered during periods of immunosuppression. Immunosuppression could occur in subjects due to the effects of AML on bone marrow function and/or during the time from lymphodepleting chemotherapy until bone marrow recovery from its effects. Lymphodepletion may also reduce the established immune protection from any infectious agents including COVID-19. Thus, the timing of COVID-19 vaccination for subjects entering study should be planned by the treating physician with these considerations in mind.

13.8 Appendix 8 Subject Accrual Order During Dose Escalation

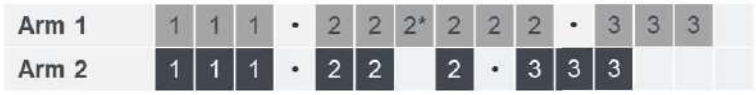
Selected examples shown through dose selection in each Arm. Accrual of six subjects in cohorts prior to expansion is not shown. Each square represents 1 subject with dose level indicated by number. Symbol "*" indicates DLT. Symbol "•" indicates dose escalation decision.

1. No DLT observed

2. No DLT observed, Arm 1 accrual slower



3. Single DLT in Arm1, DL2

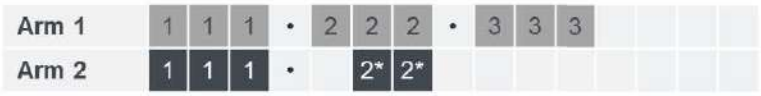


4. Single DLT in Arm1 DL2, Arm 1 accrual slower

5. Single DLT in Arm 2, DL2

6. MTD reached in Arm 1, DLT seen in 2/5 subjects at DL2†

7. MTD reached in Arm 2, DLT seen in 2/2 subjects at DL2



8. MTD reached in Arm 2, DLT seen in 2/3 subjects at DL2, Arm 1 accrual slower

† In Example #6 above, the MTD for subjects in Arm 1 is reached at a dose lower than the dose under evaluation in Arm 2. Accruing subjects in the order of Example #6 is not expected, because the risk of severe or serious adverse events after cell therapy is correlated with a subject's tumor burden (Garcia-Manero et al, 2015; Garzon et al, 2017). If, as in Example #6, the MTD for Arm 1 is reached at or below the dose under investigation in Arm 2, enrollment in Arm 2 will be paused and data reviewed by the Principal Investigators, Sponsor, and the DMC.

DL = dose level; DLT = dose-limiting toxicities; MTD = maximum tolerated dose