Masonic Cancer Center, University of Minnesota
Cancer Experimental Therapeutics Initiative (CETI)

Relapse Prophylaxis with IL-15 Super Agonist N-803 in Patients with Acute Myelogenous Leukemia and Myelodysplastic Syndrome Following Reduced Intensity Conditioning (RIC) Allogeneic Stem Cell Transplantation

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

Revision History

Revision #	Version Date	Revision Details	Consent Revision
	08/26/2016	Original	n/a
	09/07/2016	In response to CPRC's initial review Updated background and drug administration language as provided by Altor and other general edits and formatting	n/a
	12/13/2016	Edits prior to IRB and FDA submission Section 8.1 – add CMV/EBV monitoring and add associated 2nd objectives/endpoints (synopsis, Section 1.2, 12.2) Section 8.2.3 – delete Nantomics related research samples, delete related correlative objective/endpoint Synopsis, Section 4.2 – prohibit prior ALT-803 treatment Appendix V – add Altor's patient diary for injection reactions Section 6.1 – delete table of suggested pre-meds and update pre-med language to be on a per patient basis as needed. Section 6.5 – add a bullet point to duration of study participation to end study follow-up if patient is discharged to hospice or not returning to study site but obtain info from other sources as available Section 7.3 – add management of cytokine release syndrome and collection of CRS toxicity (Section 10, Appendix IV) Section 8 and 10 – clarify that if a patient is no longer abiding by the clinical care calendar that the schedule of research related sample collection and toxicity assessments may be adjusted or discontinued. Cover page and page 2 - Update affiliate institutions Minor edits, updates and clarifications through-out	n/a
	03/13/2017	In response to FDA potential deficiencies and IRB stips: Schema – add final treatment visit 30 day (±7 days) Section 6.1 – clarify situations where a one-time ALT-803 dose decrease is permitted; expand criteria for holding ALT-803 dose on the day of a scheduled treatment; clarify missed doses will not be made up to maintain the 8 week treatment cycles; add language for the management of patients who are unable to restart ALT-803 after a 1 week rest. Section 7.2 – add a paragraph on management of injection site reaction/skin rash to evaluate systemic rashes outside of the injection area and rashes lasting more than 7 days to rule out GVHD. Sections 10.4 and 13.5.2 – add an early study stopping rule for Grade 4/5 non-relapse toxicity; add GVHD assessment to Section 8.1 Required Clinical Care Evaluations Insert a new Appendix IV – aGVHD and cGVHD grading; renumber other appendices (and update protocol text) Insert a new Section 11.5 entitled "Teleconferences – Lead Institution and Affiliate Sites" describing planned communications	yes

Revision #	Version Date	Revision Details	Consent Revision
		between the UMN and other sites in response to an IRB stipulations Other minor edits and clarifications	
	04/03/2017	Interim version submitted to FDA only: FDA response to non-hold recommendation: • Section 8.2 - bank serum samples at the following time points for immunogenicity testing: pre cycle 1, 28-30 days after the first exposure of ALT-803, pre cycle 2, pre cycle 3, pre cycle 4, and 30-45 days after the last exposure of ALT-803, currently done at pre cycle 2 and cycle 3 • Minor edits from study initiation visit (SIV) : • Section 4.1.2 – expand definition of sustained blood counts • Section 4.2.5 – clarify any prior infection must be under control • Section 6.1 – add patient must be assessed by provider (specifically for injection site reaction and GVHD) prior to administration of that day's ALT-803 injection and to refer to the "Dose Hold" section; update pre-meds to acetaminophen 650 mg prior to each injection. • Appendix I – update to reflect changes in Section 4 Other edits: • Add Dr. Weisdorf as co-I on title page • Add Dr. Romee as PI at WU • Clarify BM aspirate samples are sent to TTL • Sections 6.1 and 9.6 – for patients weighing > 100 kg, ALT-803 dose will be calculated using a capped weight of 100 kg • Section 6.2 Supportive Care – suggest management for chills, n/v, diarrhea • Section 8.1 – clarify baseline EKG will be paid for by research as not SOC post-transplant	yes
1	05/05/2017	Incorporates all April 3, 2017 protocol version revisions plus the following: Section 6.1 – update criteria of inadequate dosing and clarify criteria for previous injection site reaction requirements for retreatment Section 1.1 – delete definition of evaluable patient from primary objective in response to changes to Section 6.1 Section 13.1 – Analysis Population updated to reflect changes in Section 6.1	no
2	10/19/2017	Clarifications related to acute GVHD: Synopsis and Section 4.1.3 – permit enrollment of patients with aGVHD that is clinically improving on topical steroids or systemic steroids, previously had to be resolved Section 6.1 – expand and clarify provider's pre-dose assessment and move dose hold section up to be part of this section for continuity, refer to a new Section 6.2 for GVHD management guidance; delete number of ALT-803 doses required for continuation on to cycle 2 and cycle 3 Section 6.5 Duration of Treatment – delete develops aGVHD requiring treatment and replace with grade IV GVHD	yes

Revision #	Version Date	Revision Details	Consent Revision
		Appendix VI ALT-803 Injection Reaction Diary – add instructions that a new form is to be used for each injection site and the form is to be completed until the injection reaction resolves. Other edits and clarifications Section 8.1 – replace basic metabolic panel with CMP on day 1 and day 5 Section 8.2 – create separate research related sample collection tables with Section 8.2.1 be for UMN patients and Section 8.2.2 be for affiliate sites Section 9.6 – delete sentence about dividing dose between syringes for larger volumes as not applicable in this study Section 10.1 – update definition of major and minor deviations to reflect MCC's updated DSMP Section 10.6 – update institutional reporting table to report all events meeting the definition of SAE and updated deviation Section 10.7 – update MCC's reporting requirements Other edits and clarifications throughout including: Remove affiliate names from cover sheet and contact list on page 2, update Erica Orcholski's contact info and add Jane Gau as Primary Clinical Research Coordinator Shorten follow-up for survival only from 2 additional years to 1 additional year (or 2 years from HSCT) Section 6.1 clarify ALT-803 dose calculation based on weight change Section 11.1 – expand the data management section to detail where the data will be stored Section 11.3 – update the DSMP section to include affiliate monitoring	
3	7/31/2018	Updated change in Principal Investigator (Dr. Claudio Brunstein is the new PI) and updated Affiliate Sites Manager contact info.	Yes
4	11/29/2018	Throughout document • Update the ALT-803 product name to N-803 and replace references to Altor with Nant due to the recent sale of ALT-803 to Nant • Update the treatment schedule to every 4 week dosing for a max of 10 doses based on experience with this study and other ALT-803 clinical trials that the proposed 4 weekly injections followed by 4 weeks rest was too intense and not well tolerated. • Move the start period for N-803 from Day 60-100 post-transplant to Day 42-60 post-transplant to provide immune protection earlier • Update the primary objective/endpoint to monitor for 2 years from alloHCT rather than 1 year • Add an early analysis for futility after 40 patients are enrolled (without pause in enrollment) to consider discontinuing the trial if the cumulative incidence of 2 year relapse is >34% • Update overall survival and non-relapse mortality objectives/ endpoints from 1 year to 2 years • Modify Section 8 Clinical Evaluations and Procedures to reflect updated treatment schedule.	Yes

Revision #	Version Date	Revision Details	Consent Revision
		Edits based on current protocol template including • Add table of key abbreviations • Update Section 5 Patient Screening and Enrollment to current language • Update Section 10.1 to reflect current clinical deviation definitions and IRB reporting requirements	
5	06/14/2019	Update ALT-803 drug sections based on updated IB – A sufficient number of patients have been treated with ALT-803 (also known as N-803) that the toxicity profile is no longer based on IL-2. • Update Section 2.4 • Section 7 - Delete hypotension management guidelines as hypotension (change in blood pressure) is not included in the updated toxicity profile. • Section 9 - ALT-803 Formulation, Supply and Potential Toxicity – update to reflect updated IB including vial concentration for SC administration and updated toxicity profile. • Appendix V – N-803 table of risks – Delete as now in Section 9.8. Renumber Appendices and update in body of protocol. Synopsis, Section 4.1.2 and Appendix I – clarify that anti-cancer therapy that is "directed at the diseases under study" Edit to inclusion criteria Update Appendix I – Eligibility checklist to new format Other minor edits and hyperlinks added through-out the document to confirm with electronic submission to the FDA.	yes
6	07/06/2020	• Section 8 - add a Day 8 lab visit for Cycles 3 and 6 – blood work and research samples were revised downward when the study changed from a weekly injection schedule to an every 4 week injection schedule - two time points added back in to allow sufficient data collection for study endpoints • Section 7 – Delete management of CRS as CRS has been deleted from the updated IB as "N-803 did not trigger a broad-based cytokine release in vitro by either human or murine immune cells, suggesting that N-803 is unlikely to trigger a cytokine storm" • Section 9 – Delete CRS event grading and Lee ref. • Section 9.7 – add atrial fibrillation as possible risk of N-803, update risks of N-803 based on IB dated April 2020 • Remove Sarah Cooley from the title page as she has left the University of Minnesota • Update to current participating sites protocol template • Delete Appendix I – Eligibility Checklist per updated CTO policy and renumber all remaining appendices •Update Nant's name to ImmunityBio, Inc •Other edits and updates for consistency and clarity	yes
7	4/14/2022	• Updated change in Principal Investigator (Dr. Jeffrey Miller is the new PI) and updated Affiliate Sites Manager contact info.	no

TABLE OF CONTENTS

Key Abbreviations

Abbreviation	Definition
ABW	actual body weight
ADL	activities of daily living
AE	adverse event
alloHCT	allogeneic hematopoietic cell transplant
AML	acute myelogenous leukemia
CFR	Code of Federal Regulations
CNS	central nervous system
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease free survival
DLCO	diffusing capacity of the lungs for carbon monoxide
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GvHD	graft-versus-host disease
HCT	hematopoietic cell transplantation
HSCT	hematopoietic stem cell transplantation
IB	Investigator's Brochure
IBW	ideal body weight
ICH	International Conference on Harmonisation
IL-15	Interleukin-15
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
MDS	myelodysplastic syndrome
NC	nucleated cells
NCI	National Cancer Institute
NK	natural killer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression free survival
PFT	pulmonary function test
PO	per os; orally
PTLD	post-transplant lymphoproliferative disorder
rhIL-15	Recombinant human interleukin-15
RECIST	Response Evaluation Criteria in Solid Tumors
RIC	reduced intensity conditioning
SOC	Standard of care
SAE	serious adverse event
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
TNC	total nucleated cells
TRM	treatment related mortality
TTP	time to progression
ULN	upper limit of normal

Protocol Synopsis

Relapse Prophylaxis with IL-15 Super Agonist N-803 in Patients with Acute Myelogenous Leukemia and Myelodysplastic Syndrome Following Reduced Intensity Conditioning (RIC) Allogeneic Stem Cell Transplantation

Study Design:

This is a single-arm, multi-center Phase II trial using IL-15 super-agonist complex (N-803 formerly known as Alt-803) maintenance after allogeneic hematopoietic cell transplant (alloHCT) for acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). The primary objective is to determine if post-transplant N-803 effectively reduces relapse as measured by the cumulative incidence of relapse between the 1st dose of N-803 and two years after reduced intensity conditioning (RIC) alloHCT. The hypothesis is that N-803 will reduce relapse from a historical estimate of 35% to 20% in the study cohort. The rationale is that N-803 will enhance allogeneic immunity through activation and expansion of donor-derived NK cells and CD8+ T cells capable of mediating a response to remaining leukemia cells (minimal residual disease, MRD); therefore decreasing relapse rates. A secondary aim is to achieve this goal without increasing frequency or severity of graft-versus-host disease (GVHD)

In this study N-803 is given at 6 mcg/kg subcutaneously (SQ) once every 4 weeks for a maximum of 10 doses. Treatment must begin between Day 42 and Day 60 post-transplant with the goal to enroll patients as close to Day 42 as feasible as starting anti-tumor maintenance is a logical goal. GVHD prophylaxis will continue per individual institutional standard practice. Follow-up for late toxicity, disease status, and survival continues for 2 years from alloHCT.

Sixty patients are planned for enrollment with an analysis for futility after 40 patients are enrolled (while enrollment continues). The trial will be discontinued if the cumulative incidence estimate of 2 year relapse is projected at >34%. Otherwise, enrollment continues to complete the trial in the absence of excessive toxicity as monitored by early stopping rules by donor type (sibling, umbilical cord blood, unrelated and haploidentical):

1) Grade III-IV acute GVHD by Day 120 post-transplant
2) Grade 4 and 5 non-relapse toxicity by Day 120 post-transplant

Primary Objective:

The primary objective is to determine if post-transplant N-803 effectively reduces relapse from a historical estimate of 35% to 20% in the study cohort as measured by cumulative incidence of relapse between the 1st dose of N-803 and 2 years after a reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplant (alloHCT) for acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS).

Secondary Objectives:

- To evaluate the safety and tolerability of every 4 week N-803 administration
- To determine the incidence of relapse at two years after alloHCT stratified by number of doses of N-803 (1-3 or 4-10)
- To determine the frequency and severity of acute and late acute/chronic graft-versus-host disease (GVHD) by graft source
- To evaluate whether cytogenetic and flow cytometry positive minimal residual disease (MRD) post-transplant (before and after N-803) determine overall survival at 2 years post-transplant
- To determine the incidence of non-relapse mortality at 2 years post-transplant

Correlative Objectives:

- To monitor the number and function of NK cells, T cells, T regulatory cells and myeloid derived suppressor cells pre- and post-N-803 therapy and serum cytokines that could influence response
- To determine the incidence of CMV viremia or disease by Day 100 post-transplant
- To characterize N-803 immunogenicity

Eligible Diseases/ Donor Cell Sources

Patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) for whom a reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplant (alloHCT) is planned or has recently been performed. Acceptable donor sources are: sibling donor, a haploidentical donor [restricted to post-transplant cyclophosphamide GVHD prophylaxis], an unrelated donor, or umbilical cord blood (UCB) as the cell source

Key Inclusion Criteria:

- Able to begin N-803 between Day 42 and Day 60 post-transplant and meet all of the following requirements:
  - Sustained neutrophil (ANC > 1000/mcL for 3 consecutive days without growth factor) and platelet (> 30,000/ mcL without growth factors or transfusions) engraftment
  - >50% donor myeloid and lymphoid chimerism in blood or bone marrow on most recent BM evaluation
  - No morphologic evidence of relapse (<5% bone marrow blasts) on most recent BM evaluation (Day 21 or 28 post-transplant is acceptable)
  - Being followed in the outpatient setting (not an inpatient)
  - No plan of giving other anti-cancer treatment directed at the diseases under study (i.e. maintenance therapy [e.g. sorafenib for FLT3m+ AML or hypomethylating therapy], additional therapy for MDS)
- Age 18 years or older
- Karnofsky performance status ≥ 70%
- Adequate renal (creatinine ≤ 2 mg/dl) and liver (ALT and AST ≤ 3 x upper limit of normal) function
- If acute GVHD is present it must be clinically improving on topical or low dose steroids (≤ 0.3 mg/kg/day prednisone equivalent) - GVHD prophylaxis will be continued per individual institutional standard practice

Key Exclusion Criteria:

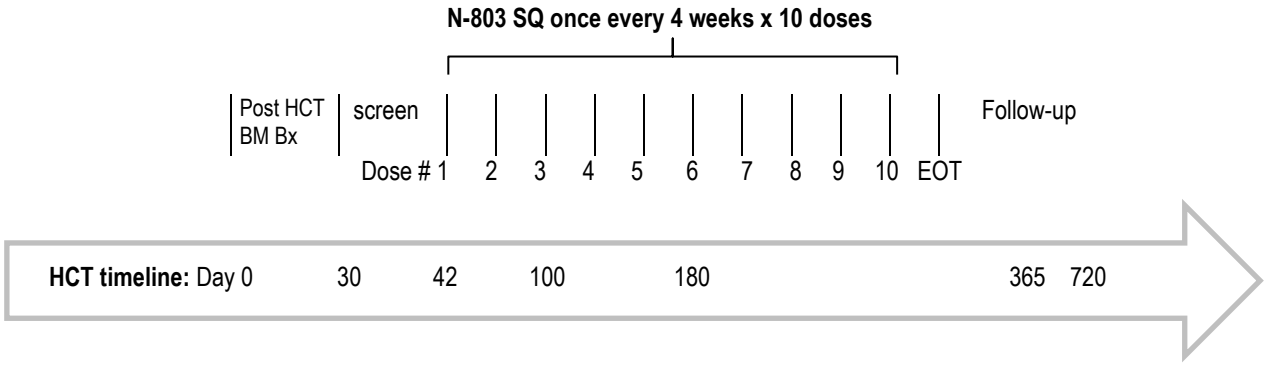
- Prior N-803 (previously known as ALT-803)
- Pregnancy
- Marked baseline prolongation of QT/QTc interval (e.g. demonstration of a QTc interval > 500 millisec)
- Active untreated bacterial, fungal, or viral infections – all prior infections must be under control following therapy and must be afebrile for at least 24 hours at time of enrollment
- Active autoimmune disease requiring systemic immunosuppressive therapy
- History of severe asthma and currently on chronic systemic medications (mild asthma requiring inhaled steroids only is eligible)

Enrollment Plan:

60 patients over 2 years with an early stopping rule for futility once 40 patients are enrolled.

With up 5 sites participating, it is expected 20-30 patients will be enrolled per year.

Schema



- Begin between Day 42 and Day 60 post-transplant, but as close to Day 42 as feasible
- All treatment is administered in the outpatient setting
- N-803 at 6 mcg/kg SQ Day 1 of a 4 week (28 day) cycle with ± 1 week window
- Continue N-803 every 4 weeks for 10 doses or until relapse, unacceptable toxicity, or patient refusal, whichever comes earlier.
- An End of Treatment (EOT) visit occurs 30 days (±1 week) after the last dose of N-803
- Disease related reassessment and follow-up based on disease specific post-transplant standard of care
- Follow-up for late toxicity, disease status, and survival will be done for 2 years from alloHCT (approximately 22 months after 1st administration of N-803)

1 Objectives

1.1 Primary Objective

The primary objective is to determine if post-transplant N-803 effectively reduces relapse from a historical estimate of 35% to 20% in the study cohort as measured by cumulative incidence of relapse between the 1st dose of N-803 and 2 years after a reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplant (alloHCT) for acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS).

1.2 Secondary Objectives

- To evaluate the safety and tolerability of every 4 week N-803 administration
- To determine the incidence of relapse at two years after alloHCT stratified by number of doses of N-803 (1-3 or 4-10)
- To determine the incidence of acute and late acute/chronic graft-versus-host disease (GVHD)
- To evaluate whether cytogenetic and flow cytometry positive minimal residual disease (MRD) post-transplant (before and after N-803)
- To determine overall survival at 2 years post-transplant
- To determine the incidence of non-relapse mortality at 2 years post-transplant

1.3 Correlative Objectives

- To monitor the number and function of NK cells, T cells, T regulatory cells and myeloid derived suppressor cells pre- and post-N-803 therapy, as well as serum cytokines reflecting the immune activation
- To determine the incidence of CMV viremia or disease by Day 100 post-transplant
- To characterize the immunogenicity profile of N-803

2 Background and Significance

2.1 Introduction and Rationale for the Approach

Acute myeloid leukemia (AML) is the most common acute leukemia in adults with 18,860 cases estimated for 2014 and an additional 800 cases in children (www.LLS.org). The incidence is increasing, as it develops in patients who survive treatment from other cancers or evolves in elderly patients with myelodysplastic syndrome (MDS). The main cause of treatment failure for AML continues to be relapse. Successful allogeneic hematopoietic cell

transplantation (HCT) requires the infusion of healthy stem cells, as well as lymphocytes capable of participating in a graft-versus-tumor/leukemia (GVL) reaction. The importance of the infused lymphocytes has been demonstrated in studies showing increased relapse after transplants with lymphocyte-depleted grafts and by the therapeutic efficacy of donor lymphocyte infusions[1-2]. Unfortunately, relapse after allogeneic HCT remains a significant problem with rates approaching 35% in patients receiving non-myeloablative conditioning (NMAC), and even higher in those with high-risk disease[3]. Optimal strategies to balance immune responses to favor GVL without harmful graft-versus-host disease (GVHD) are needed.

Profound NK Cell Functional Defects After HCT. Unlike adaptive B and T cells, which express a single somatically recombined, clonally expressed antigen receptor that recognize specific or cross reactive antigen, NK cell activation is controlled by germline-encoded activating and inhibitory receptors. With the notable exception of CD16, which binds to the Fc portion of immunoglobulin and mediates ADCC, no activating receptor is functionally dominant, and each can be counteracted by inhibitory receptor signaling[4,5]. Activating and inhibitory killer cell lectin-like receptors (NKG2C and NKG2A) and KIR are encoded by gene complexes, recognize class I molecules, and are expressed in a variegated fashion[6]. These inhibitory receptors are primarily responsible for NK cell education, the process by which acquisition of function is mediated through engagement of class I MHC. After HCT, NK cells are the first cancer fighting defense as NK cells reconstitute in large numbers. However, we have identified a profound defect in the function of reconstituting NK cells for up to 6 months after HCT. Our approach is to stimulate this function as early as possible after transplant in hope of preventing relapse.

2.2 rhIL-15

Interleukin-15 (IL-15) is a cytokine and growth factor capable of expanding activated T cells and NK cells. By broad consensus, the NCI Immunotherapy Workshop (2007) ranked IL-15 as the #1 agent with "high potential for immunotherapy[7]." Based on preclinical non-human primate and early phase clinical trial data, including those at the University of Minnesota, IL-15 regimens can unquestionably be designed to prospectively and reproducibly increase T-cell and NK-cell counts.

The NCI Biological Resource Branch has manufactured E. coli-expressed recombinant human IL-15 (rhIL-15), and this is the first IL-15 product tested here at the University of Minnesota. Systemic administration of NCI rhIL-15 by daily intravenous (IV) bolus has been shown to increase the number of

circulating CD8+ T and NK cells, but the cytokine has a very short half-life. We have established the MTD for NCI-manufactured rhIL-15 using IV and subcutaneous dosing. Although safer with subcutaneous administration allowing more drug delivery, we identified limitations with the rhIL-15 in clinical testing. Specifically, high levels of free rhIL-15 decrease circulating IL-15Rα, acting as a negative feedback signal to reduce further IL-15 trans-presentation. This is the rationale in this trial for using IL-15/IL-15Rα-Fc (N-803), an IL-15 product that physiologically trans-presents IL-15.

2.3 IL-15/IL-15Rα-Fc (N-803)

This trial will evaluate an alternative IL-15 construct designed to have a prolonged serum half-life. The novel IL-15 immunoconjugate, N-803, was developed by our collaborator, Altor BioScience Corporation (Altor, Miramar, FL), to overcome some of the biologic, regulatory, and commercial limitations of monomeric NCI rhIL-15. Under natural circumstances, IL-15 and IL-15 Receptor-alpha (IL-15R) are coordinately expressed by antigen-presenting cells (i.e., monocytes and dendritic cells)[8]. During signaling by the IL-15 pathway, IL-15 bound to IL-15R is presented in trans to neighboring NK or CD8+ T cells expressing only the IL-2R receptor. At the immunologic synapse, IL15 trans-presentation appears to be a dominant mechanism for IL-15 action in vivo, providing tight physiologic control over the functions of IL-15 under homeostatic conditions and in response to immune stimuli[9]. N-803 is a soluble complex consisting of two protein subunits of a human IL-15 variant[10] associated with high affinity to a dimeric human IL-15 Receptor α (IL-15Rα) sushi domain/human IgG1 Fc fusion protein[11].

The IL-15 variant is a 114 aa polypeptide comprising the mature human IL-15 cytokine sequence with an Asn to Asp substitution at position 72 of helix C (N72D)[12]. The human IL-15Rα sushi domain/human IgG1 Fc fusion protein comprises the sushi domain of the human IL-15 Receptor α subunit (IL-15Rα) (aa 1-65 of the mature human IL-15Rα protein) linked with the human IgG1 CH2-CH3 region containing the Fc domain (232 amino acids). Aside from the N72D substitution, all of the protein sequences are human. N-803 has a prolonged serum half-life in preclinical animal models and has a 4-fold increase in biologic activity greater than wild-type IL-15 (IL-15 wt)[10].

2.4 N-803 by Subcutaneous Injection

IV and SC administration of N-803 were compared in early phase 1 studies in solid and hematologic tumors (QUILT-3.003, QUILT-3.004, QUILT-3.005). The decision to discontinue IV administration was based on the high Cmax

observed via this route, which was associated with markedly increased serum cytokine levels and high fever, rigors, tachycardia, and relative hypotension.[15] SC administration of N-803 results in an approximately 100-fold lower Cmax than IV and allows N-803 serum concentration to be maintained up to 96 hours post-dose with still detectable levels at 7 days (while IV N-803 declined below detection 48 - 96 hours post-administration). A PK study using SC N-803 in healthy volunteers (QUILT-1.004) showed that serum levels of N-803 remained elevated over a relatively prolonged period after a single administration of the drug; the apparent mean half-life of the complex was 20-21 hours. SC administration resulted in significant attenuation of AEs as compared to IV administration. Subjects receiving N-803 via SC administration most commonly experienced injection site reaction, mild fever, hypoalbuminemia, and chills, while those receiving IV N-803 most commonly experienced higher fever, rigors, fatigue, nausea, and hypertension. The common localized skin rash observed with SC administration of N-803 could be managed with topical steroids when necessary. In addition to its favorable tolerability and PK profile, SC administration of N-803 is associated with equivalent and possibly enhanced efficacy and biological activity. In QUILT-3.004 (hematologic malignancies), SC administration of N-803 was associated with a greater increase in circulating NK cells than IV administration.[15] In QUILT-3.002 (relapsed or refractory iNHL), the combination of rituximab with N-803 led to objective responses in 58% (7 out of 12) of SC-treated subjects and 44% (4 out of 9) of IV-treated subjects. In total, these observations show that SC administration is well tolerated, yields a lower Cmax yet more sustained serum levels of N-803 over time, and has equivalent or greater efficacy and biological activity as compared to IV administration.

Refer to the updated Investigator Brochure (dated April 2020) for additional details.

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2.5 Study Rationale

As we perform more transplants in older adults using reduced intensity conditioning, relapse rates are unacceptably high irrespective of graft source[13,14]. Currently there is no effective maintenance therapy available for this patient population. We also described an NK cell defect early after HCT. IL-15 is an optimal cytokine to improve NK and T cell function; potentially improving graft versus tumor effect and reducing the relapse risk after RIC transplants. We have tested a number of IL-15 products and IL-15/IL-15Rα-Fc (N-803) seems to be the best candidate for use in this setting.

While some studies continue to dose escalate (currently 15 and 20 mcg/kg are under study); we are testing immune activation in a minimal residual setting and will use a lower safe dose (N-803 6 mcg/kg SQ). We have chosen to be conservative in the dosing here 1) because of the complexity of patients early post-transplant and 2) because of the use in the prophylactic setting. In addition, we have shown that 6 mcg/kg is safe, especially with subcutaneous dosing, where as unlike IV N-803, subcutaneous dosing is associated with less severe constitutional symptoms compared to IV dosing. In addition, we have immunologic data suggesting that 6 mcg/kg is biologically active.

The cumulative experience with ALT-803 (initially from Altor BioSciences) has grown and we published the first-in-human experience in 31 transplant patients as the rationale for this trial[15]. This paper also details the immune activation and long half-life of subcutaneous (SQ) dosing, the approach we use here. We have treated 8 subjects with weekly SQ dosing in this current trial and learned that weekly dosing is simply not feasible because injection site reactions (very common in all cohorts tested) take more than one week to resolve. In addition, pre-clinical data suggest that higher levels of IL-15 may lead to NK cell exhaustion[16]. During the progress of this trial, BioSciences became a wholly-owned subsidiary of ImmunityBio, Inc. While there is no change in the drug, they now refer to it as N-803, reflecting the business acquisition. ImmunityBio, Inc. has also performed additional studies in normal volunteers (unpublished) showing that dosing intervals should probably be 3-4 weeks to prevent exhaustion and maximize immune activation. Every 4-week dosing was chosen to amend this trial based on this new information recognizing the higher risk cohort and to maximize patient convenience with this maintenance therapy strategy. In addition, the treatment plan was revised to initiate N-803 dosing closer post-HCT (from a window of Day 60 - Day 100) to as close to Day 42 as feasible, and no later than Day 60 post-transplant. Starting anti-tumor maintenance earlier is a logical goal, while continuing GVHD prophylaxis per individual institutional practice. This decision is supported by an ongoing clinical study (NCT02782546) which administers 4 doses of N-803 subcutaneously between on Day +7 and Day +17 after a RIC allo-HCT (Day 0)/haploidentical NK cells on Day +7 without an increased incidence of GVHD (Todd Fehniger, MD - personal communication).

3 Study Design

This is a single-arm, multi-center Phase II trial using IL-15 super-agonist complex (N-803) maintenance after allogeneic hematopoietic cell transplant (alloHCT) for acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). The primary objective is to determine if post-transplant N-803 effectively reduces relapse as measured by the cumulative incidence of relapse between the 1st dose of N-803 (Day 42 to Day 60 post-transplant) and two years after RIC alloHCT. The rationale is that N-803 will enhance allogeneic immunity through activation and expansion of donor-derived NK cells and CD8+ T cells capable of mediating a response to remaining leukemia cells (minimal residual disease, MRD); therefore decreasing relapse rates. A secondary aim is to achieve this goal without increasing frequency or severity of graft-versus-host disease (GVHD).

In this study N-803 is given at 6 mcg/kg subcutaneously (SQ) once every 4 weeks to a maximum of 10 doses. Treatment must begin between Day 42 and Day 60 post-transplant with the goal to enroll patients as close to Day 42 as feasible as starting anti-tumor maintenance is a logical goal. GVHD prophylaxis will continue per individual institutional standard practice. Follow-up for late toxicity, disease status, and survival continues for 2 years from alloHCT.

Sixty patients are planned for enrollment with an analysis for futility after 40 patients are enrolled (while enrollment continues). The trial will be discontinued if the cumulative incidence estimate of 2 year relapse is projected at >34%. Otherwise, enrollment continues to complete the trial in the absence of excessive toxicity as monitored by early stopping rules.

We hypothesize that risk of acute graft versus host disease (GVHD) and Grade 4-5 non-relapse toxicity following N-803 treatment could vary by donor type. Therefore, we will count events towards the stopping rules separately for each donor type (sibling, umbilical cord blood, unrelated, and haploidentical) as follows:

1) Grade III-IV acute GVHD by Day 120 post-transplant
2) Grade 4 and 5 non-relapse toxicity by Day 120 post-transplant

Note: Overall enrollment is irrespective of donor type. If a stopping rule is met for one donor type, enrollment will be suspended for that group only. Enrollment for all other donor groups may continue until the maximum study size is reached.

4 Patient Selection

Study entry is open to adults 18 years and older regardless of gender, race or ethnic background. While there will be every effort to seek out and include females and minority patients, the patient population is expected to be no different than other transplant studies for AML and MDS at the participating institutions.

Depending on institutional practices, the patient may be presented with the study prior to transplant; however, final eligibility cannot be established until post-transplant. The treatment consent must be signed within 28 days of planned treatment start. If the consent is signed during pre-screening, the patient must sign a new consent or initial and date the prior consent if it is still the current IRB-approved consent.

4.1 Inclusion Criteria

4.1.1 Diagnosis of acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) for whom an allogeneic hematopoietic stem cell transplant using a reduced intensity conditioning is planned or has been performed and patient is prior to Day 60 post-transplant.

4.1.2 Able to begin study treatment between Day 42 and Day 60 after the transplant and meets the following transplant related requirements:

- Sustained neutrophil (ANC > 1000/mcL for 3 consecutive days without growth factor) and platelet (> 30,000/ mcL without growth factors or transfusions) engraftment
- >50% donor myeloid and lymphoid chimerism in blood or bone marrow on most recent bone marrow (BM) evaluation
- No morphologic evidence of relapse (< 5% bone marrow blasts) on most recent BM evaluation (Day 21 or 28 post-transplant is acceptable)
- Being followed in the outpatient setting (not an inpatient)
- No plan of giving other anti-cancer treatment directed at the diseases under study (i.e. maintenance therapy [e.g. sorafenib for FLT3m+ AML or hypomethylating therapy], additional therapy for MDS)

4.1.3 If acute GVHD is present it must be clinically improving on topical steroids and/or on low dose systemic steroids (≤ 0.3 mg/kg/day prednisone) and with clinical stability for at least 1 week prior to determination of eligibility. GVHD prophylaxis will be continued per individual institutional standard practice

4.1.4 One of the following donor graft sources used for the transplant:
- sibling donor
- haploidentical donor [with post-transplant cyclophosphamide]
- unrelated donor
- unrelated umbilical cord blood

4.1.5 ≥ 18 years of age

4.1.6 Karnofsky performance status ≥ 70% (Appendix I)

4.1.7 Adequate organ function within 14 days of study enrollment defined as:
- Renal: serum creatinine: ≤ 2.0 mg/dL
- Hepatic: SGOT ≤ 3 x upper limit of institutional normal (ULN)

4.1.8 Sexually active females of child-bearing potential and males with partners of child bearing potential must agree to use effective contraception during therapy and for 4 months after completion of therapy

4.1.9 Voluntary written consent prior to the performance of any research related procedures

4.2 Exclusion Criteria

4.2.1 Prior N-803 (previously known as ALT-803)

4.2.2 Pregnant or breastfeeding – N-803 is an investigational agent. Women of child-bearing potential must have a negative pregnancy test at screening

4.2.3 Class II or greater New York Heart Association Functional Classification criteria (Appendix I) or serious cardiac arrhythmias likely to increase the risk of cardiac complications of cytokine therapy (e.g. ventricular tachycardia, frequent ventricular ectopy, or supraventricular tachyarrhythmia requiring chronic therapy)

4.2.4 Marked baseline prolongation of QT/QTc interval (e.g. demonstration of a QTc interval > 500 milliseconds)

4.2.5 Active uncontrolled bacterial, fungal, or viral infections – all prior infections must be under control following therapy and must be afebrile for at least 24 hours at time of enrollment

4.2.6 Active autoimmune disease requiring systemic immunosuppressive therapy (GVHD prophylaxis is permitted per institutional practice)

4.2.7 History of severe asthma and currently on chronic systemic medications (mild asthma requiring inhaled steroids only is eligible)

4.2.8 Received any investigational agent within the 14 days before the start of study treatment (1st dose of N-803)

5 Patient Screening and Enrollment

Depending on institutional practices, the patient may be presented with the study consent prior to transplant; however, final eligibility cannot be established until post-transplant.

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

5.1 Enrollment with the University of Minnesota Clinical Trials Office

Any patient who is consented is to be entered in OnCore by the site Study Coordinator or designee.

If a patient is consented but is not enrolled in the study treatment (i.e. is found to be ineligible), the patient's record is updated in OnCore as a screen failure and reason for exclusion recorded.

Complete enrollment information is found in the study's Procedures Manual for Participating Sites.

In addition, participating institutions are responsible for fulfilling any local study registration requirements.

5.2 Patient Enrollment to Study Treatment in OnCore

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

5.3 Patients Who Do Not Begin Study Treatment

If a patient is enrolled in the study (i.e. assigned a sequence number) and is later found unable to begin N-803 by Day 60, the patient will be removed from study and treated at the physician's discretion. The study staff will update OnCore of the patient's non-treatment status (off study) with the reason for removal from study prior to starting study treatment clearly indicated. The patient will be replaced to complete enrollment.

6 Treatment Plan

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

The use of systemic steroid medications may result in loss of therapeutic effects of the study drug and should be avoided. Standard of care GVHD prophylaxis is permitted per institutional practice. Topical steroid cream is permitted.

CMV and other viral prophylaxis/management will be per institutional practice.

6.1 N-803 Administration

Treatment is given as an outpatient.

N-803 at 6 mcg/kg is administered subcutaneously on Day 1 of a 28 day cycle for a maximum of 10 doses, or until relapse, unacceptable toxicity, or patient refusal, whichever comes earlier.

A window of ±1 week is permitted for each "monthly" N-803 injection in the event of scheduling issues (i.e. holiday, bad weather or other scheduling issues) but the first dose must be given by Day 60. There is no resetting of the treatment calendar when a treatment window is used as the recommended schedule for N-803, in general is every 3 to 4 weeks. At minimum of 3 weeks must separate each injection.

N-803 dosing is calculated using a weight obtained within 7 days prior to the first dose. For patients > 100 kilograms weight, the N-803 dose is calculated using a weight capped at 100 kg. The patient's weight is re-checked prior to each dose (within 7 days) and the dose re-calculated if ≥ 10% change from the weight used for the previous dose calculation. Rounding of a dose is permitted per institutional policy.

If the total subcutaneous dose is greater than 1.5 mL volume, the dose will be divided by the pharmacist into 2-3 subcutaneous injections as needed. Injections are given in the abdominal area. The injection site should be rotated per institutional guidelines and each injection site separated by at least 1 inch.

Pre-medication
Use of pre-medications is at the discretion of the treating physician on an individual patient basis. Acetaminophen may be given prior to the injection to reduce the intensity of the fever that often occurs a few hours later.

Required post N-803 dose monitoring
Patients will be observed for **a minimum of 2 hours after the 1st dose of N-803** for immediate adverse events. Vital signs (heart rate, blood pressure, respiration, temperature, and oxygen saturation) will be documented prior to the N-803 injection and then at 30, 60 and 120 minutes with a ± 20 minute window for each time point.

If the 1st dose of N-803 is well tolerated, subsequent doses may be administered with a 30 minute post dosing observation period. Vital signs (heart rate, blood pressure, respiration, temperature, and oxygen saturation) will be documented prior to each N-803 injection and then at 30 minutes ± 10 minutes.

6.1.1 Provider's Assessment Prior to Each N-803

In order to proceed with a planned N-803 injection, a provider must assess the patient prior to administration to rule-out any of the following contraindications for dosing:

- the previous injection site reaction is not showing signs of resolving (improving) based on measurement or intensity
- signs or symptoms of a new infection
- fever > 101°F (38.3 °C)
- there are signs or symptoms of new acute GVHD as evidenced by new skin rash outside of the injection reaction area
- there is clinical progression of existing acute GVHD
- there are signs or symptoms of relapse

The N-803 dose will be delayed for 1 week if one or more of the above conditions are present. Refer to Section 6.2 GVHD Management Guidance in the event of new (or suspected) aGVHD or worsening of existing aGVHD.

In addition, N-803 may be delayed for 1 week on the day of a planned dose for either of the following situations:

- any Grade 3 or greater ongoing N-803 treatment related toxicity (injection site reaction, neurologic, increased liver function tests)
- if in the opinion of the treating physician, holding N-803 would be of benefit to the patient

If after a 1 week rest:

- The patient meets the criteria for treatment, the patient may receive N-803. The patient calendar would not be adjusted (reset)
- The patient does not meet the criteria for treatment or the investigator feels holding treatment would be of benefit to the patient, the dosing may be skipped with treatment resumed at the next planned date.

There is no resetting of the treatment calendar in OnCore for either scheduling issues or delays due to toxicities. Cycle 1 Day 1 is the anchor for all subsequent injections spaced every 4 weeks. A ± 1 week window is associated with each injection date; however injections should be no closer than 3 weeks apart.

6.1.2 Dose Reduction

A one-time dose decrease to 4 mcg/kg is allowed for recurrent N-803 related constitutional symptoms (e.g. fever, fatigue, muscle aches) interfering with activities of daily living (ADL) despite pre-medication. Patients unable to tolerate the reduced dose will be discontinued from further N-803. Re-escalation of the dose is not permitted.

6.1.3 Inadequate Dosing

If a patient receives only one dose of N-803, the patient will be taken off treatment and followed per Section 8.1. The patient will be fully evaluable for safety and toxicity, but replaced in the evaluation of efficacy.

6.2 GVHD Management Guidance

New or worsening skin rash outside of injection site area (whether GVHD clinically suspected or previously diagnosed) and other GVHD manifestations should be managed as described in this section. Refer to Section 7.1 for management of skin rash/injection site reaction within the vicinity of the injection.

The following guidance is based on GVHD grading criteria using the University of Minnesota aGVHD Grading Scale (Appendix III).

If new GVHD Grade I or Grade II is clinically suspected or definitive, hold N-803 until the next planned dose. N-803 may resume with the next planned dose if GVHD is clinically improving with topical steroids and/or low dose systemic steroids (prednisone ≤ 0.3 mg/kg/day or equivalent) with clinical stability for at least 1 week prior to the planned N-803 injection (and other criteria for treatment in Section 6.1 is met).

If new or worsening GVHD Grade III is clinically suspected or definitive, hold N-803 until the next planned dose. If the GVHD flare was in the context of tapering immunosuppressive medications, one could consider subsequent cycles if GVHD is controlled with systemic steroids (≤ 0.3 mg/kg/day) with clinical stability for at least 1 week prior to the planned N-803 injection. If GVHD flare was not in the context of tapering immunosuppressive medications, one should consider permanently discontinuing N-803. If prednisone > 0.3 mg/kg/day (or equivalent) is required, N-803 will be permanently discontinued.

If new or worsening GVHD Grade IV, N-803 will be permanently discontinued.

6.3 Supportive Care

Supportive care will be provided per institutional guidelines and standard of care. Guidelines may be updated based on current data/drugs without requiring a protocol amendment or be considered a protocol deviation.

At study enrollment, GVHD prophylaxis will be continued according individual institutional standard practice.

Supportive care may be given as needed on an individual patient basis including, but not limited to:
Fever - acetaminophen
Chills - meperidine or morphine sulfate
Nausea and vomiting - anti-emetics and IV fluids
Diarrhea - loperamide and fluids after stool testing

6.4 General Concomitant Medications Guidelines

Administration of additional glucocorticoids is discouraged during the N-803 treatment period as the use of systemic steroid medications may result in loss of therapeutic effects of the study drug. Sustained use of steroids at a prednisone dose > 0.3 mg/kg/day or equivalent (other than standard GVHD prophylaxis per institutional practice) or steroid use to treat related toxicity will

be an indication to stop N-803. Transient use is permitted as needed per standard of care. Topical steroid cream is permitted.

CMV prophylaxis/management will be per institutional practice.

The use of anti-cancer therapies including maintenance therapy, agents that affect immunity, and investigational agents, are prohibited while a patient is receiving study treatment.

Refer to Section 6.2 for guidelines in the management of GVHD.

6.5 Duration of Treatment

N-803 post-transplant may continue for a maximum of 10 doses unless one of the following occurs:

- unacceptable toxicity
- development of Grade IV aGVHD (refer to Appendix III) or GVHD requires steroid dose > 0.3 mg/kg/day prednisone or equivalent
- initiation of new anti-cancer therapy or other prohibited therapy (including approved therapies, investigational agents, agents that affect immunity)
- consent is withdrawn or patient is not compliant

An End of Treatment (EOT) visit occurs 4 weeks (± 1 week) after the last dose of N-803 to assess for signs of acute GVHD and N-803 related toxicity.

All patients will be followed per Section 8.1 and evaluable per Section 13.1.

6.6 Duration of Study Participation

Patients are followed for late toxicity, disease status, and survival for 2 years from the date of transplant, unless one of the following occurs:

- consent is withdrawn
- patient is discharged to hospice and/or not returning to the study site for routine post-transplant follow-up – in these cases, follow-up information including date and cause of death may be obtained, as available from other sources (i.e. BMT database).

7 Management of Injection Site Reactions/Skin Rash in Association with N-803

Based on current experience, localized skin rashes are common with subcutaneous administration. If a rash occurs and the rash area surrounding the N-803 injection site is > 6 cm or symptomatic (painful and/or itchy), it may be treated with topical 0.05% clobetasol propionate (i.e. 0.05% Cormax) or 0.1% triamcinolone (i.e., Kenalog) cream. Diphenhydramine may be administered pre- and post-dosing (25-50 mg TID orally x 2 days) of N-803 at the discretion of the treating physician.

Usually the rash associated with an N-803 starts small at the site of the injection and spreads outwardly sometimes covering a large area of the abdomen. It generally resolves within 7 days of treatment. Patients will be instructed to contact a member of the study team for rashes outside of the injection site area and/or lasting more than 7 days.

8 Clinical Evaluations and Procedures

Scheduled evaluations during the treatment cycles may be performed up to 3 days before (-3 days) the targeted date with the additional visits during Cycle 1 having a ±1 day window.

A window of ±1 week for the N-803 dosing is allowed in the event of scheduling issues. Treatment may be delayed for 1 week for toxicity related reasons as detailed in Section 6.1.1; however, if treatment cannot be given after a 1 week delay, treatment will be held until the next planned dose.

The End of Treatment (EOT) visit (4 weeks after the last dose of N-803) may be scheduled using a ±1 week. After the EOT visit, follow-up for this study will coincide with the standard of care transplant follow-up schedule through 2 years post-transplant. In addition, targeted days may be altered as clinically appropriate.

8.1 Required Clinical Care Evaluations

	Optional Pre-Screening (prior to transplant or later)	Screening[1] within 30 days unless o/w noted	Day of N-803 dosing Day 1 (-7 days)	With 1st Dose only		Cycle 3 and 6 only Day 8 (±1 day)	End of Treatment (EOT) Visit (4 weeks ±1 week after final N-803 dose)	Follow-up for 2 year post HCT[5]
				Day 8 (±1 day)	Day 15 (±1 day)			
Initial Presentation of Study	optional							
Consent	optional	X						

Screening Assessment		X						
Medical History		X						X
Concomitant Medications associated with treating an injection site reaction per Section 7.1			X	X	X		X	
Late Toxicity Assessment							X	X
Physical Exam		X	X					X
Provider Assessment per Section 6.1.1		X	X	X	X			
Assess for GVHD		X	X				X	
Weight		X	X				X	
Vitals, Pulse Oximetry		X	X	X	X		X	
Performance Status		X		X			X	
CBC, diff, plt		X	X	X	X	X	X	
CMV surveillance		Weekly through Day 100						
EBV and other viral monitoring		Per individual institutional usual practice						
Comprehensive Metabolic Panel (CMP) or equivalent[2]		X	X	X	X		X	
Pregnancy Testing[3]		X						
Peripheral Blood Chimerism		X						
Bone Marrow Biopsy	Day -21 or -28 bx acceptable	At time of post-transplant SOC BM bx (i.e. Day +100, Day +180, 1 year, 2 year)[4]						
Bone Marrow Chimerism	Day -21 or -28 bx acceptable	At time of post-transplant SOC BM bx (i.e. Day +100, Day +180, 1 year, 2 year)[4]						
MRD by flow pf BM aspirate	Day -21 or -28 bx acceptable	At time of post-transplant SOC BM bx (i.e. Day +100, Day +180, 1 year, 2 year)[4]						
Disease Staging								X
Survival Status								X

1 –within 14 days for labs required for eligibility per Section 4.1.7, if consent signed during pre-screening, patient must sign a new consent or initial and date prior consent if it is still the current IRB approved consent

2– comprehensive metabolic panel consists of albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, creatinine, glucose, lytes (CO2, Cl, Na, K), total bilirubin, and total protein

3- women of child bearing potential – urine or serum

4-for UMN only: at the time of SOC bm bx collect an additional 30 ml aspirate for TTL

5–unless unevaluable, withdraws consent, or is discharged to hospice/not returning to study site per Section 6.6; death should be recorded upon knowledge per Section 10.5

8.2 Research Related Tests and Procedures

	Lead Lab Study Section	Baseline	All Doses	Cycle 1, 3, 6	Cycle 1 only	At the End of Treatment (EOT) visit
			Day 1 (day of planned dose)[2] before N-803 is given	Day 8	Day 15	
ECG		X				

50 ml of heparinized blood (5 green top tubes) [1]	Masonic Cancer Center TTL Section 8.2.1		X	X	X	X
10 ml of serum (1 red top tube) [1]			X	X	X	X
Immunogenicity: 5 ml of serum (1 red top tube)[3]	Site batch ships to ImmunityBio, Inc per, Section 8.2.2		X	X	X	X
UMN Only: 30 ml or lesser based on the amount of aspirate that can be obtained		At time of each BM biopsy and aspirate done for clinical purposes				
Toxicity Notation		Refer to Section 10.2 for documentation requirements				
Targeted Toxicities		Refer to Section 10.2 for documentation requirements				
Completion of the Infection CRF		On day of planned dose and EOT visit				
Review of Patient Diary of Injection Reactions			At each treatment visit and the EOT visit			

1 Samples, other than for immunogenicity, are shipped the day of collection (Monday-Thursday) for next day delivery to the Masonic Cancer Center's Translational Therapy Lab (TTL).
2 Collect research samples as scheduled even if N-803 dose is delayed, but do not collect a 2nd of samples if patient is treated 1 week later
3 Immunogenicity samples are stored frozen at the study site until the time of batch shipping directly to ImmunityBio, Inc's central laboratory.

Refer to the Laboratory Manual for additional details.

Note: if a patient is not abiding by the required clinical care calendar (Section 8.1), the collection schedule of the toxicity (adverse event) data and research related samples schedule may be altered or discontinued on an individual patient basis, as appropriate. It will not be a protocol deviation if a research related sample collection is not done because the patient did not comply with the standard of care visit.

It is recognized that with novel therapies as used in this study, the timing of protocol directed research samples may miss important patient specific events. For this reason, up to 3 extra samples of 60 ml of blood each may be drawn at additional relevant time points (i.e. development of GVHD, relapse, change in blood counts (lymphocytosis)) as per the PI's opinion, and are not specified above.

8.2.1 Assessment of Immune Activation (TTL)

Samples to evaluate lymphocyte number, phenotype and function will be collected as detailed above for the Masonic Cancer Center Translational Therapy Lab (TTL) along with serum (red top tubes) for measure of cytokines that can reflect immune activation.

Flow cytometry analysis of a fraction of the PBMC will detect surface markers that define lymphocyte subsets (NK, NKT, B, and T cells, both CD4 and CD8), as well as intracellular markers that define regulatory T cells (Foxp3) and proliferating cells (Ki67). All remaining PBMC will be cryopreserved in 10%

DMSO and stored in liquid nitrogen for future testing, if subject agreed to future storage at the time of initial consent.

8.2.2 Immunogenicity (ImmunityBio, Inc)

Immunogenicity assays will be performed at ImmunityBio, Inc. Serum samples for immunogenicity testing will be collected for all. The collection schedule is specified in the Study Calendar. One 5 mL silicone coated (red top) tube per time point will be collected.

The collected blood samples will be processed (centrifuge at 1000-1500 x g for 10 minutes) at the study site and the serum portion will be frozen and shipped to ImmunityBio, Inc in batches upon request for evaluation using validated ELISA methods.

In these tests, human anti-N-803 antibodies are detected in patient serum samples using a direct sandwich ELISA method with plates coated with N-803. After the appropriate wash conditions, biotinylated N-803 is used for detection with standard HRP-labeled streptavidin reagents. For analysis of clinical samples, anti-IL-15 antibody serve as reference standard and serum from N-803 immunized mice serve as a positive control. The level of anti-N-803 antibody in patient samples is determined based on the anti-IL-15 antibody standard curve.

9 N-803 Formulation, Supply, and Potential Toxicity

N-803 (previously known as ALT-803 - Altor BioScience is now a wholly owned subsidiary of ImmunityBio, Inc.) is a recombinant human superagonist IL-15 complex. Its active ingredient is N-803 and its pharmacologic class is an anti-cancer and anti-viral immunotherapeutic.

N-803 has been referred to as IL-15N72D:IL-15RαSu/IgG1 Fc complex in various preclinical study reports, publications, and other related documents.

N-803 is an IL-15-based immunostimulatory protein complex that acts as a growth and activation factor for NK cells and effector and memory T cells. Based on the results of animal tumor models, N-803 stimulated cellular immune responses are expected to exhibit potent activity against human tumor cells. Due to the higher affinity single amino acid substituted IL-15 variant and the presentation of IL-15 with IL-15RαSu, N-803 is likely to be effective at low concentrations. Owning to its longer half-life as a result of fusion with Fc, N-803 is likely to be effective using a practical regimen of every 4 week injections in this patient

population. It is likely that low concentrations of N-803 will increase the peripheral blood T cell and NK cell counts to predictable levels with a safety profile appropriate for outpatient use.

9.1 Structural Formula

N-803 is a soluble complex consisting of 2 protein subunits of a human IL-15 variant associated with high affinity to a dimeric IL-15R sushi domain/human IgG1 Fc fusion protein. The IL-15 variant is a 114 aa polypeptide comprising the mature human IL-15 cytokine sequence with an Asn to Asp substitution at position 72 of helix C (N72D).6. The human IL-15R sushi domain/human IgG1 Fc fusion protein comprises the sushi domain of the IL-15R subunit (aa 1-65 of the mature human IL-15Rα protein) linked with the human IgG1 CH2-CH3 region containing the Fc domain (232 amino acids). Aside from the N72D substitution, all of the protein sequences are human. Based on the amino acid sequence of the subunits, calculated molecular weight of the complex comprising 2 IL-15N72D polypeptides and a disulfide linked homodimeric IL-15RαSu/IgG1 Fc protein is 92.4 kDa. Each IL-15N72D polypeptide has a calculated molecular weight of approximately 12.8 kDa and the IL-15RαSu/IgG1 Fc fusion protein has a calculated molecular weight of approximately 33.4 kDa. Both the IL-15N72D and IL-15RαSu/IgG1 Fc proteins are glycosylated resulting in an apparent molecular weight of N-803 as approximately 114 kDa by size exclusion chromatography. The isoelectric point (pI) determined for N-803 range from approximately 5.6 to 6.5. Thus, the fusion protein is negatively charged at pH 7. The calculated molar extinction coefficient at A280 for N-803 is 116,540 M-1, or 1.26 OD280 for a 1 mg/mL solution of ALT-801, or one OD280 is equivalent to 0.79 mg/mL solution of N-803.

9.2 Formulation

The biological drug product, N-803, is formulated in a phosphate buffered saline (PBS) solution. The solution appears as a clear and colorless liquid. The drug substance is produced by a recombinant mammalian cell line and is manufactured using a protein free media.

9.3 Packaging

Vials are packaged in cartons and shipped to the clinical site.

9.4 Storage

N-803 is supplied in a 2-mL single-dose/single-use vial containing 0.6 mL of N-803 (extractable volume is 0.5 mL) at a concentration of 1 mg/mL or 2 mg/mL.

N-803 will be stored at the site in a secured area at 2°C to 8°C with limited access and protection from excess light and heat.

9.5 Study Drug Preparation

N-803 dosing is calculated using a weight obtained within 7 days prior to the first dose. For patients > 100 kilograms weight, the N-803 dose is calculated using a weight capped at 100 kg. The patient's weight is re-checked prior to each dose (within 7 days) and the dose re-calculated if ≥ 10% change from the weight used for the previous dose calculation. Rounding of a dose is permitted per institutional policy.

The appropriate volume of N-803 is withdrawn.

If the total subcutaneous dose is greater than 1.5 mL, the dose will be divided into 2-3 subcutaneous injections as needed.

N-803 can be stored in a syringe for up to 24 hours at 4°C.

9.6 Agent Inventory Records

The investigator, or a responsible party designated by the investigator (e.g. institutional investigational pharmacy), must maintain a record of the inventory and disposition of all agents received from ImmunityBio, Inc using the Study Agent Drug Accountability Record.

9.7 Toxicity

The most common side effects seen in studies with subcutaneous (under the skin) injections have been fever, chills, hypoalbuminemia, and injection site reaction, and skin rash, which at times has been widespread. These localized skins reactions are common (occurring in more than 50% of patients).

In June 2020 an SAE was filed on a study participant who developed atrial fibrillation (a-fib) with no prior history resulting in a hospitalization. We identified a previous case of a patient who developed a-fib while on treatment from a different clinical trial that used N-803 weekly to treat relapse. In both cases of a-fib, there were other potential explanations that could have triggered the arrhythmia. While we cannot directly attribute causality between N-803 and a-fib, it is at least possible that they are related, directly or indirectly. A-fib may be indirectly triggered in susceptible patients by fevers and/or use of diuretics for fluid retention that can be observed with some N803 regimens. Based on this information, we decided to add the development of a-fib as a possible rare side effect from N-803 in the consent form.

Risks of N-803 when given as a subcutaneous injection		
Very common (more than 1 in 10 patients experience)	Common (between 1 in 30 and 1 in 10 patients experience)	Rare (fewer than 1 in 30 patients experience)
• injection site reaction (skin rash), which may be large (> 2 inches), itchy, and/or painful • fever • chills • anemia • change in blood pressure • nausea • swelling of hands or feet • temporary changes in routine lab results including decreased albumin and decreased lymphocytes	• flu-like symptoms, including headache, muscle, or joint pain • fatigue • decreased appetite • diarrhea, vomiting • abdominal pain • itchy skin and/or skin irritation • shortness of breath • high blood sugar (hyperglycemia) • changes in electrolytes on routine lab work	• inflammatory reaction • infection including upper respiratory infection • atrial fibrillation (a-fib) – may be asymptomatic, but when symptoms do appear they may include irregular and often rapid heartbeat, shortness of breath, and fatigue

Tuberculosis is a potential risk of N-803. One instance of tuberculosis has been reported in a participant receiving N-803 in combination with BCG (a live, attenuated strain of *Mycobacterium bovis*) administered into the bladder by a urinary catheter. A causal relationship between N-803, in combination with BCG, and tuberculosis infection cannot be definitely ruled out.

Anti N-803 antibodies have been detected in subjects receiving N-803. The impact of anti-N-803 antibody formation on clinical efficacy and safety of N-803 is unknown.

Previous editions of the ALT-803 Investigator's Brochure prior to 2019 relied heavily on clinical experience with the related cytokine therapeutic Proleukin® Interleukin-2 to anticipate potential risks associated with ALT-803 (N-803) administration. This approach was based on the fact that N-803 and IL-2 are both γ chain cytokines and thus could reasonably be predicted to have similar immunostimulatory properties. However, the substantial accumulated information on N-803 effects in humans indicates that many side effects of IL-2 are not observed in patients treated with N-803 at the doses being used clinically. For this reason, side effects observed in subjects treated with IL-2 but not N-803, such as capillary leak syndrome, pulmonary dysfunction, acidosis, and gastritis, have been removed from the IB and are reflected in this protocol and its consent form.

Refer to the current Investigator Brochure (April 2020 version 7) for additional information.

9.8 Agent Ordering

N-803 will be shipped by cold chain from ImmunityBio, Inc directly to the study site.

10 Adverse Event Monitoring, Documentation, and Reporting

Toxicity and adverse events will be classified and graded according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from the CTEP home page:
(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

The following definitions of adverse events (AEs) and serious adverse events (SAEs) will determine whether the event requires expedited reporting via the OnCore SAE Report Form in addition to routine documentation in the OnCore AE case report form (CRF).

The reporting timeframes for SAEs, product related issues, and other reportable events are located in Section 10.6.

Note: Throughout this section the generic term “study drug” refers to the study related treatment (N-803 injections).

10.1 Adverse Event Terminology

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

Serious Adverse Event: An adverse event is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject

and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

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

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

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

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

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

10.2 AE Documentation Requirements

Adverse event collection for the purposes of this study will focus on events felt to be related to N-803 or events that cannot be attributed to other causes (i.e. transplant-related, co-morbidities).

At visits through the End of Treatment visit a targeted toxicity worksheet (Appendix IV) will be completed to document select expected toxicities associated with N-803 as follows:

- Prior to each planned N-803 injection

- At the end of dose monitoring period (as described in Section 6.1) with ±20 minute window for 2 hour monitoring or ±10 minute window for 30 minute monitoring
- Day 8 and Day 15 visits after 1st dose only
- At the End of Treatment visit

In addition, unexpected events and expected events that are not listed in Section 9.7 or the consent form or the IB must also be documented.

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

After the End of Treatment visit, monitoring for adverse events will become less frequent based on the schedule in Section 8.1 and only events that are unexpected and at least possibly related to N-803 will be documented upon knowledge.

10.3 SAE Documentation and Reporting

Any event meeting the definition of an SAE must be documented using the paper MCC SAE Report Form.

Any event meeting the definition of serious must be reported to Masonic Cancer Center Multisite Program Manager within 24 hours of knowledge. Refer to Section 10.6.

10.4 Early Stopping Rule Event Documentation and Reporting Requirements

The following event counts toward an early study stopping rule and must be reported to the MCC Multisite Program Manager using the Event Form found OnCore under the reports tab:

- Grade III or IV acute GVHD from the day of first dose of N-803 through Day 120 after alloHCT (refer to Appendix III for grading)
- Grade 4 and 5 non-relapse toxicity from the day of first dose of N-803 through Day 120 after alloHCT

An event that counts toward an early stopping rule does not necessarily constitute a SAE and should be reported as such only if it meets the criteria for reporting as defined in Section 10.3.

10.5 Documentation of Death and Reporting Requirements

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

In addition, the death date and cause must be documented in the patient follow-up tab in OnCore upon knowledge using the comment field in the survival status section to record the cause.

10.6 Institutional Event Reporting Table

Event Type	Reporting Timeframe	Form in OnCore to Use	Report to
Any event meeting the definition of serious and all patient deaths	Within 24 hours of knowledge	SAE Report Form	For Participating Sites: Masonic Cancer Center (MCC) Multisite Program Manager affilates@umn.edu. Local institutional IRB or other entities per institutional policies and guidelines
Stopping Rule Events	Within 24 hours of knowledge	Stopping Rule Event Form	
Major Deviations, as defined in Section 10.1.	Within 5 working days of knowledge	Deviation Report Form	
Minor Deviations, as defined in Section 10.1.	Per Institutional Policy	n/a (record in Deviations Tab)	For UMN MCC: Report to the study's regulatory specialist For Participating Sites: minor deviations are not reportable to the MCC Multisite Program Manager. Report to local institutional IRB or other entities per institutional policies and guidelines.

*events occurring at the University of Minnesota are reported to the study's Regulatory Specialist and to the MCC Multisite Program Manager, who will submit to ImmunityBio, Inc and other entities as usual

Individual institutional sites are responsible for reporting any event meeting local reporting requirements to their institutional IRB and/or other research oversight committees.

10.7 Expedited MCC Reporting Requirements (MCC)

As the study sponsor, the Masonic Cancer Center has the following expedited reporting responsibilities for select events reported in Section 10.6:

Agency reporting to	Criteria for reporting	Timeframe	Form to Use	Submission address/email address
U of MN IRB (for UMN patients only)	Unanticipated death of a locally enrolled subject(s); New or increased risk; Any adverse event that requires a change to the protocol or consent form – refer to the IRB website for complete details	5 Business Days	RNI	ETHOS
	Deviations that occur at MCC as defined in Section 10.1.	Per current IRB requirements	OnCore Deviation Form and IRB Report Form	
FDA	Unexpected and fatal or unexpected and life threatening suspected adverse reaction	no later than 7 Calendar Days	MCC SAE Report Form	Submit to FDA as an amendment to IND with a copy to ImmunityBio, Inc and each participating site
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	no later than 15 Calendar-Days		
	All other events per CFR 312.33	At time of annual report	Annual report	
Masonic Cancer Center SAE Coordinator	Events that meet the definition of an early study stopping rule event	At time of reporting	Stopping Rule Event Form	mccsaes@umn.edu
Nant Inc.	Any event meeting the definition of an SAE	Within 24 hours of study team knowledge	MCC SAE Report Form	SAE.Reporting@NantBio.com Cc: Dawn.Camden@Immunitybio.com.

11 Study Data Collection and Monitoring

11.1 Data Management

This study will collect regulatory and clinical data using University of Minnesota CTSI's instance of OnCore® (Online Enterprise Research Management Environment).

The OnCore database resides on dedicated secure and PHI compliant servers. All relevant AHC IS procedures related for PHI compliant servers (as required by the Center of Excellence for HIPAA Data) apply to OnCore databases.

Additional immune monitoring data about correlative laboratory samples generated by the Masonic Cancer Center Translational Therapy Laboratory (TTL) from the protocol-directed correlative research samples is stored in their

Laboratory Information Management System (LIMS). The LIMS database application is also stored on a production server located in the UMN datacenter (WBOB) and is managed by the Academic Health Center

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

11.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRFs) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into OnCore at time of study entry, completing e-CRFs based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

11.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which may be accessed at http://z.umn.edu/dmsp.

For the purposes of data and safety monitoring, this study is classified as high risk (under a locally held IND). Therefore, the following requirements will be fulfilled at the University of Minnesota and at participating sites:

- At least quarterly review of the study's progress by the Masonic Cancer Center Data and Safety Monitoring Council (DSMC).
- The University of Minnesota (lead site) Principal Investigator will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The local site PIs will comply with at least twice yearly monitoring of the project by each site's internal monitoring staff.
- The University of Minnesota (lead site) Principal Investigator will oversee the submission of all reportable adverse events per Section 10.7 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB; and oversee the submission of all reportable adverse events to the FDA and to ImmunityBio, Inc.
- The University of Minnesota (Sponsor) and the MCC CTO have oversight responsibility for trial monitoring at participating sites.

IND Annual Reports

In accordance with regulation 21 CFR § 312.33, the IND sponsor (Dr. Miller) will submit a progress report annually. The report is submitted within 60 days of the anniversary date that the IND went into effect. A copy of the report will be provided to ImmunityBio, Inc.

11.4 Participating Site Monitoring

The PI (Dr. Miller) with the CTO has oversight responsibility for trial monitoring at participating sites.

Participating sites must self-monitor following the University of Minnesota Masonic Cancer Center Data and Safety Monitoring Plan (DSMP - http://z.umn.edu/dmsp).

The investigator will permit study-related monitoring, audits, and inspections by the study's Principal Investigator and/or IND sponsor and/or any designees, the local IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

11.5 Teleconferences – Lead Site and Participating Sites

Regular teleconferences will be held to facilitate communication between participating sites regarding the study's progress, patient updates, summary of safety reports, case report form completion, and other issues for discussion. The University of Minnesota Multisite Program Manager is responsible for arranging these teleconferences and preparing the agenda. Meetings will occur every 2 weeks; however, these may be scheduled more or less frequently at the discretion of the lead institution. Participation of a minimum of one representative from each participating site is expected. These teleconferences are in addition to other previously described site interactions including centralized patient registration, institutional and MCC required reporting of safety related issues, case report form completion in the study's central database (OnCore) and participating site oversight through self-monitoring in compliance with the Masonic Cancer Center's Data and Safety Monitoring plan.

11.6 Record Retention

The investigator will retain study records including source data, copies of case report forms, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at least 6 years after the study file is closed with the IRB and FDA.

Please contact the CTO before destroying any study related records.

12 Study Endpoints

12.1 Primary Endpoint

The primary endpoint will be cumulative incidence of relapse evaluated between the day of the first dose of N-803 (approximately 42 days after alloHCT, but as late as 60 days) and two years after alloHCT.

12.2 Secondary Endpoints

Secondary endpoints include safety and efficacy outcomes listed below.

- Frequency of adverse and serious adverse events
- Description of N-803 dose intensity based on the number of doses given out of the number planned (10 doses)
- Incidence of relapse at two years after alloHCT stratified by number of doses of N-803 (1-3 or 4-10).
- Incidence of Grade II-IV and Grade III-IV acute/late acute graft-versus-host-disease (GVHD) at 100 and 180 days after alloHCT
- Incidence of chronic graft-versus-host disease (GVHD) at one year after alloHCT
- Incidence of cytogenetic and flow cytometry positive minimal residual disease (MRD) post-transplant (before and after N-803)
- Overall survival at two years after alloHCT
- Incidence of non-relapse mortality at two years after alloHCT

13 Statistical Considerations

13.1 Objectives and Study Design

This is a single-arm, open-label, multi-center phase II trial with discontinuation for futility using IL-15 super-agonist complex (N-803) maintenance after alloHCT for AML and MDS. The primary objective is to determine if post-transplant N-803 effectively reduces relapse from a historical estimate of 35% to 20% in the study cohort as measured by cumulative incidence of relapse

between the 1st dose of N-803 and 2 years after alloHCT. A total of 60 subjects will be enrolled if the trial reaches conclusion. An analysis for futility will be carried out after 40 patients have been enrolled (without pause in enrollment). A secondary aim is to achieve this goal without increasing the frequency or severity of graft-versus-host disease (GVHD).

Follow-up for disease status, toxicity, and survival will be done for 2 years from alloHCT (i.e., 22 months after 1st administration of N-803). Patients are considered evaluable if they receive the first dose of N-803.

13.2 Statistical Analysis

Analysis Population

The primary analysis will be intent-to-treat in that all patients receiving the first dose of study drug will be evaluable for relapse. This single arm study will compare the cumulative incidence of relapse of N-803 treated patients to an historical controls estimate of 35% at 2 years. This estimate is based on data of AML or MDS patients from the University of Minnesota as well as data from the Center for International Blood and Marrow Transplant Research (CIBMTR).

Analysis of the Primary Endpoint

Relapse and non-relapse mortality at 2 years and their respective 95% confidence intervals will be calculated using the cumulative incidence function, considering the other event as a competing risk[18]. For the final test, the incidence of relapse will be compared to the historical estimate of 35% using a one sample log-rank test with an assumed exponential distribution for the null hypothesis with one-sided alpha = 0.05. Interim analysis for futility will be carried out after 40 patients have been enrolled (without pause in enrollment). If the cumulative incidence of relapse is projected to be greater than 34%, enrollment will be suspended, otherwise enrollment will continue until 60 subjects have been accrued.

Secondary Analysis

Adverse events, tolerability, immunogenicity and MRD will be tabulated with frequencies and percentages. The function of NK cells, T cells, T regulatory cells and myeloid derived suppressor cells pre- and post N-803 therapy and cytokines will be correlated with response using the Wilcoxon rank-sum test. Overall survival at 2 years and its 95% confidence interval will be estimated by the Kaplan-Meier curve[19]. GVHD and their 95% confidence intervals will be calculated using the cumulative incidence function, with death as a competing risk[20].

Cumulative incidence of relapse at 2 years and 95% confidence intervals will be described for the following subgroups: patients who receive 1-3 doses of N-803, and patients who receive 4-10 doses of N-803.

All primary and secondary outcomes will be described overall and for each donor type. Comparison of relapse versus historical controls will be made for the pooled cohort only.

13.3 Sample Size and Power

This study is designed as a Phase II trial to estimate relapse from 42 days to 2 years post-transplant. We will potentially enroll a total of 60 patients with one interim analysis (without pause in enrollment) at 40 subjects to test for futility. Since the goal is to estimate the relapse at a long-term time-point (2 years), we ran a simulated exponential model 10,000 times based on complete follow-up and a one-sided log-rank test through 2 years with interim analysis based on accrual of 40 subjects with incomplete follow-up to generate sample size and power estimates.

Based on interim analysis of the first 40 patients, we will discontinue the trial if the projected cumulative incidence curve has an estimated 2 year relapse of >34%. Assuming the null hypothesis of 35% relapse is true, we have a 25-50% chance of stopping the trial early due to futility depending on the rate of initial accrual. Assuming the alternative hypothesis of 20% relapse from 42 days to 2 years, we have an overall power of approximately 80%.

Accrual

We expect to complete the study after 2 years of enrollment plus 2 years follow up after the last enrolled patient. The study was suspended in October 2018 to rewrite the protocol using every 4 week N-803 dosing. The study re-opened to accrual in May 2019, but was suspended in March 2020 due to COVID-19.

13.4 Stopping Rules

We hypothesize that risk of acute graft versus host disease (GVHD) and Grade 4-5 non-relapse toxicity following N-803 treatment could vary by donor type. Therefore, there will be separate stopping rules for each donor type (sibling, umbilical cord blood, unrelated, and haploidentical)[21]. If a stopping rule is met for one donor type, enrollment will be suspended for that group only. Enrollment for all other donor groups may continue until the maximum study size is reached. Note: overall enrollment is irrespective of donor type.

13.4.1 Grade III-IV acute GVHD

Grade III-IV acute GVHD between Day 42 and Day 60 has been near 10% in adult alloHCT for AML and MDS. We will stop for unacceptably high Grade III-IV acute GVHD when 2/4, 3/9, 4/14, or 5 patients at any time are diagnosed in a donor group, from the day of first dose of N-803 through Day 120 after allo-HCT. If the true acute GVHD incidence is 10% (expected), there is a 9% probability of stopping in a given group. If the true acute GVHD incidence is 30% (unacceptable), there is a 71% probability of stopping, with an expected number of 9 patients treated in that group. These expectations are based on an assumed group size of 15, but the group sizes will not be fixed.

13.4.2 Grade 4 and 5 Non-Relapse Toxicity

Grade 4 and 5 non-relapse toxicity between Day 42 and Day 60 is expected to be near 10% in adult alloHCT for AML and MDS. We will stop for unacceptably high Grade 4 and 5 non-relapse toxicity when 2/4, 3/9, 4/14, or 5 patients at any time have toxicity in a donor group, from the day of first dose of N-803 through Day 60 after alloHCT. If the true incidence of toxicity is 10% (expected), there is a 9% probability of stopping in a given group. If the true incidence is 30% (unacceptable), there is a 71% probability of stopping, with an expected number of 9 patients treated in that group. These expectations are based on an assumed group size of 15, but the group sizes will not be fixed.

14 Conduct of the Study

14.1 Good Clinical Practice

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

14.2 Ethical Considerations

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

safety updates, progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

15 References

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Appendix I – Karnofsky PS and NYHA Classification

Karnofsky Performance Status Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Ref: Karnofsky DA, Burchenal JH. (1949). "The Clinical Evaluation of Chemotherapeutic Agents in Cancer." In: MacLeod CM (Ed), *Evaluation of Chemotherapeutic Agents.* Columbia Univ Press. Page 196.

New York Heart Association Functional Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

Ref: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix II – Disease Specific Response Criteria

ACUTE MYELOGENOUS LEUKEMIA (AML) RESPONSE CRITERIA

Modified RECIST

Complete Remission (CR)

CR requires that all of the following be present.

- Peripheral Blood Counts
  - ANC count > 1,000/mm^3
  - Platelet count > 100,000/ mm^3
  - Reduced hemoglobin concentration or hematocrit has no bearing on remission status.
  - Leukemic blasts must not be present in the peripheral blood
- Marrow Aspirate and Biopsy
  - Bone marrow biopsy must demonstrate trilineage hematopoiesis with maturation of all cell lines.
  - < 5% blasts
- Extramedullary leukemia, such as CNS or soft tissue involvement, must not be present.

Morphological Remission (MR)

MR requires that the following be present:

- Patient meets all peripheral blood and bone marrow criteria for CR, except that platelet count is < 100,000/mm^3 but > 50,000/mm^3.

Relapse

Relapse following CR is defined as:

- Peripheral Blood Counts
  Presence of peripheral blasts. A bone marrow examination must be performed to confirm relapse. However, please note that the date of relapse is the first date at which the relapsed patient had: leukemic blasts in the peripheral blood smear, **or** >5% blasts in the bone marrow.
- Bone Marrow Aspirate or Biopsy
  Presence of more than 5% blasts, not attributable to another cause (e.g., bone marrow regeneration).

MYELODYSPLASTIC SYNDROMES (MDS) RESPONSE CRITERIA

Based on International Working Group 2006 Modified Criteria

- Complete Remission (CR): < 5% myeloblasts with normal maturation of all cell lines
  - Persistent dysplasia will be noted
  - Peripheral Blood:
    - Hgb ≥ 11g/dl
    - Platelets ≥ 100 X 10^9 /L
    - Neutrophils ≥ 1000
    - Blasts = 0%
- Partial Remission (PR): all CR criteria if abnormal before except:
  - BM blasts decreased by ≥ 50% over pre-treatment but still >5%
- Marrow CR: Bone marrow with ≤ 5% myeloblasts and decrease by ≥50% over pretreatment with incomplete peripheral blood count normalization
- Hematologic Improvement (HI):
  - Hgb: Increase by ≥ 1.5g/dl or decreased PRBC transfusions by at least 4/8 week period (only PRBC given for Hgb<9.0g/dl)
  - Platelet Response: Absolute increase of ≥ 30 X 10^9/L for those starting at >20 X 10^9/L For those < 20 X 10^9/L at baseline increase by 100%.
  - Neutrophil Response: at least 100% increase and an absolute increase of >0.5 X 10^9/L
- Stable Disease: Failure to achieve at least a PR but no evidence of disease progression for >8 weeks
- Failure: Death during treatment or disease progression characterized by worsening cytopenias, increase percentage of marrow blasts, or progression to a more advanced MDS FAB subtype
- Cytogenetic Response:
  - Complete: Disappearance of any pre-treatment chromosomal abnormalities without the appearance of new ones
  - Partial: At least 50% reduction of chromosomal abnormality
- Disease Progression: Compared to pre-treatment values
  - Less than 5% blasts: greater than 50% increase to >5% blasts
  - 5-10% blasts: greater than 50% increase to >10% blasts
  - 10-20% blasts: greater than 50% increase to >20% blasts

Appendix III– GVHD Grading Scales

Acute GVHD:

Consensus Clinical Stage and Grade of Acute GVHD (Glucksberg *et al*, 1974; Thomas *et al*, 1975, Przepiorka *et al*, 1995)

Stage	Skin	Liver	Lower Gastrointestinal Tract	Upper Gastrointestinal Tract
1	Maculopapular rash <25% of body surface	Bilirubin 2.0 – 3.0 mg/dl	Diarrhea 500 – 1000 mL/day or 280 – 555 mL/m^2	No protracted nausea and vomiting
2	Maculopapular rash 25-50% body surface	Bilirubin 3.1 – 6.0 mg/dl	Diarrhea 1000 – 1500 mL/day or 556 – 833 mL/m^2	Persistent nausea, vomiting or anorexia
3	Generalized erythroderma	Bilirubin 6.1 – 15.0 mg/dl	Diarrhea >1500 mL/day or >833 mL/m^2	
4	Generalized erythroderma with bullous formation and desquamation	Bilirubin > 15 mg/dl	Severe abdominal pain, with or without ileus, or stool with frank blood or melena	

University Of Minnesota Acute GVHD Grading

Acute GVHD Grade	Skin Stage	Liver Stage	Lower GI Stage	Upper GI Stage
I	1-2	0	0	0
II	3	1	1	1
III	-	2-4	2-3	
IV	4	-	4	

- Each column identifies minimum criteria for organ grade.
- Each grade is based on maximum stage for each individual organ involved

e.g. Grade II = skin stage 3 and/or liver stage 1 and/or gut stage 1 and/or UGI stage 1

Late Acute and Chronic GVHD:
Late acute and chronic GVHD will be assessed using the National Institutes of Health (NIH) Consensus Criteria.

Patient ID: _____

Date of late acute or chronic GVHD diagnosis (mm/dd/yyyy) ☐☐/☐☐/☐☐☐☐

Onset of chronic GVHD was:

- ○ Progressive (acute GVHD progressed directly to chronic GVHD)
- ○ Interrupted (acute GVHD resolved, then chronic GVHD developed)
- ○ De novo (acute GVHD never developed)
- ○ Chronic GVHD flare (symptoms reactivated within 30 days of drug tapering or discontinuation)

Karnofsky Performance status:

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

Diagnosis was based on:

- ○ Histologic evidence / biopsy proven
- ○ Clinical evidence
- ○ Both
- ○ Unknown

Maximum grade of chronic GVHD

- ○ Limited
- ○ Extensive

Overall severity of chronic GVHD

- ○ Mild
- ○ Moderate
- ○ Severe

Organ/System Involvement (check if yes)

- ○ Sclerosis of skin
- ○ Other skin or hair involvement (rash, ulcers, pruritus or itching, dyspigmentation, alopecia, lichenoid skin changes, etc)
- ○ Eyes (xerophthalmia (dry eyes), abnormal Schirmer's test, abnormal slit lamp, corneal erosion / conjunctivitis, etc)
- ○ Mouth (lichenoid changes, mucositis / ulcers, erythema, etc)

- ○ Bronchiolitis obliterans
- ○ Other lung involvement

Organ/System Involvement (check if yes)

- ○ Gastrointestinal tract (esophageal involvement, chronic nausea / vomiting, chronic diarrhea, malabsorption, abdominal pain / cramps, etc)
- ○ Liver
- ○ Genitourinary tract (vaginitis / stricture, etc)
- ○ Musculoskeletal (arthritis, contractures, myositis, myasthenia, etc)
- ○ Thrombocytopenia (< 100 x 10^9/L)
- ○ Eosinophilia
- ○ Autoantibodies
- ○ Other hematologic involvement
- ○ Serositis
- ○ Weight loss
- ○ Other organ involvement from chronic GVHD

Specify other organ:

Ref: Jagasia MH, Greinix HT, Arora M. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant. 2015 March; 21(3): 389–

Appendix IV - N-803 Targeted Toxicity Worksheet

MT2016-07 CTCAE v4 Refer to Section 10.2 for time points

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

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
N-803 Injection site reaction	None	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Dyspnea	None or no change	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Hypoxia	None	……	Decreased O_2 saturation with exercise (e.g., pulse oximeter < 88%) intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter < 88% or PaO_2 ≤ 55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Fever	None	38.0 - 39.0◦ C (100.4 - 102.2◦ F)	> 39.0 - 40.0◦C (102.3 - 104.0◦F)	> 40.0 ◦ C (>104.0◦ F) for ≤ 24 hrs	> 40.0 ◦ C (>104.0◦ F) for > 24 hrs
Chills	None	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	……
Hypertension	None	Pre-hypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent ≥ 24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated.	Stage 2 hypertension (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated.	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated.
Hypotension	None	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated
Edema	None	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	……
Pneumonitis	None	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g. intubation or tracheotomy)
Headache	None	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	……
Confusion (Altered Mental Status)	None	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Rash (outside of the injection site reaction)	None	Covering < 10% body surface area (BSA)	Covering 10-30% body surface area (BSA)	>30% body surface area (BSA)	Generalized exfoliative, ulcerative, or bullous dermatitis
Gait Disturbance	None	Mild change in gait (eg, wide-based, limping or hobbling)	Moderate change in gait (eg, wide-based, limping or hobbling); assistance device indicated; limiting instrumental ADL	Disabling; limiting self care ADL	……

Person Completing Form: _____ ADL = activities of daily living

Appendix V – N-803 Injection Site Reactions Diary

The Diary is to be completed by the patient as a self-assessment in association with each dose of N-803.

A new diary must be started for each N-803 injection.

If the injection reaction has not resolved by Day 6 post-injection, continue to collect information on page 2 based on the days from that injection.

For inpatients, the diary is completed by study personnel.

Patient Number*		Date of Study Drug Injection*	_____/_____/_____	*To be completed by the site.

Please answer all questions below <u>daily</u> for 7 days, beginning with day of treatment. Be sure to bring back this completed diary to your next clinic visit.

	Instructions	Day of Study Drug Injection ___/___/_____	Day 1 Post Injection ___/___/_____	Day 2 Post Injection ___/___/_____	Day 3 Post Injection ___/___/_____	Day 4 Post Injection ___/___/_____	Day 5 Post Injection __/__/_____	Day 6 Post Injection ___/___/_____
1. Is there redness at the injection site?	Check: Yes or No If yes, measure longest diameter in cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm
2. Is there firmness or swelling at the injection site?	Check: Yes or No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
3. Have you experienced any pain or itching at the injection site?	Check the pain and/or itch box if present Indicate if the pain and/or itching is mild, moderate or severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe
4. Have you taken or applied any medication for injection site pain or itching?	Check: Yes or No Provide name of medication(s)	☐Yes ☐No Name(s):	☐Yes ☐No Name(s):	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:
5. Have you experienced any chills?	Check: Yes or No If yes, circle the worse severity of the chills: mild, moderate or severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe
6. Record your daily temperature upon waking (do not drink anything 5 minutes before taking your temperature)	Check: Yes or No If your temperature is 101°F for more than 24 hours notify your study doctor or research staff.	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM

Grading Injection Site Pain or Itching
Mild – Noticeable, does not interfere with activity
Moderate – Interferes with activity, limiting activities of daily living
Severe – Severely limiting self-care activities of daily living, incapacitating

Grading Chills
Mild – Mild sensitive of cold, shivering, chattering of teeth
Moderate – Moderate tremor of entire body, medication taken
Severe – Prolonged or severe, does not respond to medication

Page 2 – Please continue to complete for Injection Site Reaction if ongoing after page 1 has been filled out.

Patient Number*		**Date of Study Drug Injection***	_____/_____/_____	*To be completed by the site.

Complete <u>daily</u> for 7 days or until the injection site has resolved (returned to normal) . Please bring back this completed diary to your next clinic visit.

	Instructions	**Day 7 Post Injection** ___/___/_____	**Day 8 Post Injection** ___/___/_____	**Day 9 Post Injection** ___/___/_____	**Day 10 Post Injection** ___/___/_____	**Day 11 Post Injection** ___/___/_____	**Day 12 Post Injection** __/__/_____	**Day 13 Post Injection** ___/___/_____
1. Is there redness at the injection site?	Check: Yes or No If yes, measure longest diameter in cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm
2. Is there firmness or swelling at the injection site?	Check: Yes or No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
3. Have you experienced any pain or itching at the injection site?	Check the pain and/or itch box if present Indicate if the pain and/or itching is mild, moderate or severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe
4. Have you taken or applied any medication for injection site pain or itching?	Check: Yes or No Provide name of medication(s)	☐Yes ☐No Name(s):	☐Yes ☐No Name(s):	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:

Grading Injection Site Pain or Itching
Mild – Noticeable, does not interfere with activity
Moderate – Interferes with activity, limiting activities of daily living
Severe – Severely limiting self-care activities of daily living, incapacitating