
# PROTOCOL NKT-203

# A PHASE 2B DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF THE EFFICACY AND SAFETY OF NORKETOTIFEN IN THE TREATMENT OF ACUTE UNCOMPLICATED INFLUENZA-LIKE ILLNESS (ILI)

| | |
|---|---|
| **Investigational Product:** | Norketotifen |
| **Study Number:** | NKT-203 |
| **IND Number:** | 136899 |
| **Protocol Version:** | Original (Version 1) |
| **Protocol Version Date:** | 14 October 2020 |

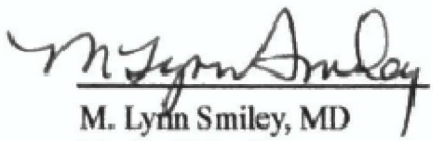
| | |
|---|---|
| **Sponsor:** | Emergo Therapeutics, Inc. |
| **Address:** | 6208 Fayetteville Rd, #104<br>Durham, NC 27713 |

# SPONSOR SIGNATURE PAGE

**Sponsor's Approval**

This protocol has been approved by Emergo Therapeutics, Inc.

**Sponsor's Authorized Officers:**



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# PROTOCOL SYNOPSIS

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Emergo Therapeutics, Inc. | | |
| **Name of Investigational Product:** Norketotifen | | |
| **Name of Active Ingredient:** Norketotifen | | |
| **Protocol Number:** NKT-203 | **Phase:** 2b | **Country:** US |
| **Title of Study:** A Phase 2b double-blind, randomized, placebo-controlled, parallel-group study of the efficacy and safety of norketotifen (NKT) in the treatment of acute uncomplicated influenza-like illness (ILI) | | |
| **Study centers:** Multi-center (approximately 30 sites in the US) | | |
| **Studied period (estimated):** First subject enrolled: Nov 2020; Last subject completed: May 2021 | | |
| **Objectives:**<br>• To evaluate the efficacy of NKT versus placebo on alleviation of symptoms in subjects with uncomplicated ILI<br>• To evaluate the safety and tolerability of NKT in subjects with uncomplicated ILI | | |
| **Study Design:**<br>This is a Phase 2b, multi-center, double-blind, randomized, placebo-controlled, parallel-group study of NKT versus placebo in otherwise healthy adults presenting with acute uncomplicated ILI due to influenza or other respiratory viruses in a community setting. The study will enroll subjects with symptom onset within ≤48 hours prior to the predose examinations (Screening). Each subject will complete Screening/Baseline, Treatment, and Follow-up Phases as follows.<br>Screening/Baseline Phase: The Screening/Baseline Phase will occur on Day 1 and will consist of assessing subject eligibility to participate in the study and completing predose study assessments.<br>Treatment Phase: Subjects who satisfy all entry criteria will be randomized to receive NKT or matching placebo in a 1:1 ratio. Starting on Day 1, subjects will administer their assigned study drug twice daily for a total of 7 days (Day 1 through Day 7). Subjects will also be provided with an electronic diary (eDiary) to record their symptom scores, body temperature, study drug dosing, rescue medication use, and ability to perform activities of daily life. Subjects will return to the clinic on Day 7 to complete safety assessments. Subjects will continue to record their symptom scores, body temperature, study drug dosing, rescue medication use, and ability to perform activities of daily life at home in the eDiary until they return to the clinic for the Day 14 Follow-up Visit.<br>Follow-up Phase: Subjects will return to the clinic for a Follow-up Visit on Day 14 to complete safety assessments. Clinic staff will then contact the subjects by phone for a final follow-up on Day 28 to check-in on the subject's health status and to collect information regarding adverse events (AEs) and concomitant medications (if any). Subjects experiencing any ILI-related complication (hospitalization, sinusitis, otitis media, bronchitis, or pneumonia) will be followed until resolution of the event or for at least 30 days after the last dose of study drug. | | |
| **Number of subjects (planned):** Approximately 320 subjects are planned for enrollment. | | |
| **Diagnosis and main criteria for inclusion:** Males and females aged 18 to 64 years; otherwise healthy with no history of significant medical disorders; symptoms of ILI including fever ≥38ºC (100.4ºF), total symptom severity score (sum of the scores of all 7 individual symptoms) of ≥11, at least one general systemic ILI symptom (headache, feverishness/chills, muscle/joint pain, or fatigue) with a severity of moderate or greater, and at least one respiratory ILI symptom (cough, sore throat, or nasal congestion) with a severity of moderate or greater; onset of symptoms within ≤48 hours (as defined in | | |

Section 4). Subjects with known or suspected infection with Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV2) or Coronavirus Disease 2019 (COVID-19) illness will be excluded.

**Investigational product, dosage and mode of administration:** NKT oral capsules are provided at a strength of 33.3 mg (equivalent to 46.4 mg NKT hydrogen fumarate). Subjects will receive 3 capsules (NKT 100 mg, equivalent to 139.3 mg NKT hydrogen fumarate) administered twice daily for 7 days.

**Duration of participation:** The total duration of study participation for each subject (from Screening through the last Follow-up contact) is approximately 28 days.

**Reference therapy, dosage and mode of administration:** Placebo oral capsules identical in appearance to NKT capsules. Subjects will receive 3 capsules administered twice daily for 7 days.

**Criteria for evaluation:**

**Efficacy:**

ILI Symptom Severity: The subject will self-assess 7 symptoms associated with ILI (headache, feverishness or chills, muscle or joint pain, fatigue, cough, sore throat, and nasal congestion) on a 4-point rating scale (0=None; 1=Mild; 2=Moderate; 3=Severe).

Body Temperature: The subject will self-measure axillary temperature with an electronic thermometer.

Assessment of Ability to Perform Normal Daily Activities: The subject will self-assess his or her ability to perform normal daily activities on a scale of 0 to 3 (0=No difficulty performing normal daily activities; 1=Some difficulty performing normal daily activities; 2=Moderate difficulty performing normal daily activities; 3=Great difficulty performing normal daily activities).

**Safety:**

Safety and tolerability assessments include: AEs, vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation [by pulse oximetry], and body temperature), physical examination, 12-lead electrocardiograms (ECGs), laboratory tests (hematology/coagulation, blood chemistry, and urinalysis), and the incidence of ILI-related complications (hospitalization, death, sinusitis, otitis media, bronchitis, or pneumonia).

**Statistical methods:**

Sample size: The primary endpoint analysis is based on time to alleviation of symptoms (TTAS), defined as the time when all of the 7 symptoms of ILI (headache, feverishness or chills, muscle or joint pain, fatigue, cough, sore throat, and nasal congestion) have been assessed by the subject as 0 (None) or 1 (Mild) in the subject diary for a duration of at least 21.5 hours. Response must occur within 13 days, to be confirmed on the $14^{th}$ day of follow-up. A total of 320 subjects randomized to NKT and placebo groups on a 1:1 randomization ratio with the assumption of nominal drop-outs provides 80% power using a two-sided 0.05 log-rank test to test the hypothesis of equal TTAS between the two treatment groups assuming the median TTAS is 85 hours for NKT and 120 hours for placebo.

Subjects who return a positive result on the central lab confirmatory SARS-CoV2 test after randomization will be discontinued and replaced.

Analysis populations: Data will be analyzed using two analysis data sets as follows.

Intent-to-Treat (ITT) Population: all non-COVID subjects who are randomized to study drug.

Safety Population: all non-COVID subjects who receive at least 1 dose of study drug (NKT or placebo).

COVID Population: The COVID population consists of randomized subjects who take at least 1 dose of study drug (NKT or placebo) but are subsequently confirmed to have COVID-19. These subjects will be included in listings, and AEs for these subjects will be reported separately from the Safety Population.

Statistical analysis: The primary efficacy endpoint, TTAS, will be compared between the NKT group and the placebo group with the use of a generalized Wilcoxon test (log-rank test). Data from subjects whose symptoms have not resolved by the last observation time point will be censored at that time point.

Kaplan-Meier curves will be plotted for each treatment group, and the median TTAS and its 95% confidence interval (CI) will be calculated. In addition, the group difference in median TTAS and its 95% CI will also be calculated.

All numerical background and safety data will be summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum). Categorical data will be summarized using counts and percentages.

Subject listings will be provided to present the data collected in this study.

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ADL | activities of daily living |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| $AUC_{inf}$ | area under the plasma concentration time curve from time 0 extrapolated to infinity |
| $AUC\tau$ | area under the plasma concentration time curve over the dosing interval |
| BMI | body mass index |
| CI | confidence interval |
| COVID-19 | Coronavirus Disease 2019 |
| $C_{max}$ | maximum plasma concentration |
| $C_{min}$ | minimum plasma concentration |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eDiary | electronic diary |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HDPE | high density polyethylene |
| HIV | human immunodeficiency virus |
| ICH | International Council on Harmonisation |
| IEC | Independent Ethics Committee |
| ILI | influenza-like illness |
| IRB | Institutional Review Board |
| KT | ketotifen |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NKT | norketotifen |
| OTC | over the counter |
| PD | pharmacodynamic(s) |
| PI | Principal Investigator |
| PK | pharmacokinetic(s) |
| PT | preferred term |
| RDT | rapid diagnostic test |

| Abbreviation | Definition |
|---|---|
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SARS-CoV2 | Severe Acute Respiratory Syndrome-Coronavirus 2 |
| SD | standard deviation |
| SOC | system organ class |
| SRC | Safety Review Committee |
| $t_{½}$ | elimination half-life |
| TEAE | treatment-emergent adverse event |
| $T_{max}$ | time to maximum plasma concentration |
| TTAS | time to alleviation of symptoms |
| ULN | upper limit of normal |

# 1. INTRODUCTION

## 1.1. Background

Norketotifen (NKT) is the principal demethylated active metabolite of ketotifen (KT), a selective, non-competitive antagonist of the histamine $H_1$ receptor. KT has been approved in the US since 1999 as a fumarate salt for topical ophthalmic use (0.025%) in allergic conjunctivitis and is currently available over the counter (OTC) under the brand names Zaditor® and Alaway®. Oral formulations of KT (capsules, tablets, and/or syrup) were initially approved in Europe in 1977 and are currently approved in over 95 countries worldwide for the treatment of asthma and/or allergic conditions in children and adults (under the brand names Zaditor® and Zaditen®). Oral KT is not currently approved in the US but has been available through compounding pharmacies that supply KT fumarate as a compounded product for oral administration. Oral KT was approved in 2006 as a switch OTC medication for the treatment of allergic rhinitis in Japan under the brand name Pabron®. To the sponsor's knowledge this is the only jurisdiction where oral KT is available as an OTC treatment. The metabolite, NKT, is not approved in the US or anywhere else for any indication.

In addition to antagonism of the histamine $H_1$ receptor, KT also exhibits mast cell stabilizing activity, which is not a general property of anti-histamines. These properties have been extensively studied recently. KT has been shown to inhibit degranulation of mast cells by activating the phosphorylation of Annexin-A1, initiating a cascade of molecular events that reduces the influx of calcium into mast cells (Yazid et al, 2013). Thus, KT acts directly on mast cells to reduce the release of cytokines from a wide variety of stimuli.

The mast cell stabilizing properties of KT and its active metabolite, NKT, form the scientific rationale for the development of NKT for the treatment of influenza and influenza-like illness (ILI) by Emergo Therapeutics, Inc. There is extensive agreement that the symptoms and pathology of influenza and many other respiratory viral infections are due to an excess release of pro-inflammatory cytokines (Liu et al, 2016; Tisoncik et al, 2012; Peiris et al, 2010). This has been clearly demonstrated in human studies where healthy subjects who were exposed to influenza A and went on to become symptomatic showed characteristic cytokine expression patterns, while subjects who remained asymptomatic had a significant early down-regulation of their cytokine response (McClain et al, 2016). The link between cytokine expression and mast cells was further demonstrated in mouse infection models where mice lacking mast cells were found to be resistant to lung pathology and physiological impacts of influenza infection (Graham et al, 2013). Providing further support for the role of mast cells in influenza infection is a study by Hu et al (2012), which showed that pretreatment of mice with KT significantly reduced lung pathology after infection with the influenza virus. Mice not treated with KT showed severe bronchiolitis, peribronchiolitis, and bronchopneumonia characterized by necrosis of the epithelial cells, infiltration of inflammatory cells, and interstitial edema. In contrast, lungs of mice treated with KT showed only mild pathological lesions.

## 1.2. Completed Clinical Studies with NKT

Emergo has completed three clinical studies with NKT to date; the results of these studies are summarized briefly in the sections that follow. Refer to the NKT Investigator's Brochure for a detailed summary of completed nonclinical and clinical studies with NKT.

### 1.2.1. NKT-101 (Phase 1)

NKT-101 was a Phase 1 clinical study assessing the safety and pharmacokinetics (PK) of NKT compared with placebo in healthy subjects. NKT was safe and well-tolerated when administered at single doses of 2, 6, 12, 24, 72, or 200 mg and multiple doses of 100 or 200 mg administered once daily for 5 days. There were no deaths, serious adverse events (SAEs), or adverse events (AEs) leading to withdrawal reported in this study. Following single doses of NKT, the incidence of AEs overall ranged from 12.5% to 50% in subjects receiving single doses of NKT compared with 41.7% in those receiving placebo. No AEs occurred in more than one subject in any individual NKT dose group and there was no pattern of increasing incidence of any AEs with increasing dose. AEs reported following single dose NKT treatment that were not observed with placebo included: diarrhea, fatigue, blood phosphorus decreased, blood sodium increased, platelet count decreased, decreased appetite, dysgeusia, headache, and dermatitis contact. Four subjects treated with NKT and 3 subjects treated with placebo experienced severe/Grade 3 AEs following single doses, all of which were in the System Organ Class of Investigations: blood cholesterol increased (1 subject each the NKT 24 mg and 72 mg groups and 2 subjects in the placebo group); blood creatine phosphokinase increased (1 subject in the NKT 12 mg group and 1 subject in the placebo group); and platelet count increased (1 subject in the NKT 2 mg group). None of these events were considered related to study drug by the investigator.

Following treatment with NKT 100 or 200 mg administered once daily for 5 days in the same study, the incidence of AEs overall was higher in subjects receiving NKT 200 mg (100%) compared with those receiving NKT 100 mg or placebo (50% each). AEs reported in more than one subject across the two NKT groups that were not reported with placebo included: anemia, constipation, lymphocyte count decreased, and somnolence. One subject in the NKT 200 mg group and 1 subject in the placebo group reported severe/Grade 3 AEs following multiple doses: hypotension (NKT 200 mg) and blood cholesterol increased (placebo); the event of hypotension was considered by the investigator to be possibly related to study drug.

PK analyses in the Phase 1 study showed that, following single doses of NKT, maximum plasma concentration ($C_{max}$) values increased generally in proportion to dose with geometric means ranging from 2.12 h•ng/mL at 2 mg to 348 h•ng/mL at 200 mg. The median time to $C_{max}$ ($T_{max}$) ranged from 1 to 2 hours and was independent of dose. Geometric mean area under the plasma concentration time curve from 0 extrapolated to infinity ($AUC_{inf}$) values ranged from 22.6 h•ng/mL at 2 mg to 3880 h•ng/mL at 200 mg. Terminal phase half-life ranged from 12.5 to 16.6 hours. Following multiple dosing with NKT once daily for 5 days, the Day 5 geometric mean $C_{max}$ values were 201 and 453 ng/mL at 100 and 200 mg, respectively, respectively, with minimum plasma concentration ($C_{min}$) values of 23.1 and 76.5 ng/mL, respectively. Geometric mean AUCs during the dosing interval ($AUC\tau$) on Day 5 were 1640 and 4920 h•ng/mL at 100 and 200 mg, respectively. Terminal phase half-life was 14.7 and 17.2 hours for the 100 and 200 mg doses, respectively.

### 1.2.2. NKT-201 (Phase 2a)

Emergo has also completed a Phase 2a clinical study assessing the efficacy and safety of single doses of NKT compared with placebo in subjects with allergic rhinitis following allergen exposure in an allergen challenge chamber (ACC) (NKT-201). Subjects completed a total of three Treatment Periods; each Treatment Period consisted of an 8-hour ACC exposure to

mountain cedar pollen, with a single dose of study drug administered at 2 hours after the start of the ACC exposure. Subject were randomized to receive single doses of the 3 treatments (NKT 10 mg, NKT 100 mg, or placebo) in a crossover manner across the 3 periods. A total of 36 subjects were randomized in the study; 35 of these subjects completed all 3 Treatment Periods and 1 subject chose to withdraw from the study after her first Treatment Period during which she received placebo. The primary efficacy endpoint of the study was the change in the total nasal symptom score (TNSS) from predose to 6 hours post-dose analyzed using a mixed model with treatment sequence, period, and treatment as fixed effects, and the subjects within sequence as random effect. Treatment with a single dose of NKT 100 mg resulted in a statistically significant reduction in TNSS compared with placebo (least squares mean difference of -1.6; 95% confidence interval [CI] -2.8, -0.4; p=0.012). NKT 10 mg also resulted in a numerical reduction in TNSS compared with placebo, but the difference was not statistically significant (least squares mean difference of -0.9; 95% CI -2.1, 0.4; p=0.158).

The incidence of AEs overall in this study was higher following treatment with NKT 100 mg (31.4%) compared with NKT 10 mg (5.7%) and placebo (13.9%). This was primarily due to the higher incidence of somnolence with NKT 100 mg treatment (10 subjects [28.6%]) compared with NKT 10 mg (no subjects) and placebo (1 subject [2.8%]). The only other AEs reported following NKT treatment included: dry eye (1 subject each following 10 mg and 100 mg), eye irritation (1 subject, 10 mg), nausea (1 subject, 100 mg), and tongue disorder (1 subject, 100 mg). There were no deaths, SAEs, or AEs leading to withdrawal reported in this study. Severe AEs occurred in 2 subjects: dry eye in 1 subject following NKT 100 mg and elevations in alanine and aspartate aminotransferase (AST, ALT), creatine kinase, and lactate dehydrogenase in 1 subject following placebo.

### 1.2.3. NKT-202 (Phase 2b)

NKT-202 was a multi-center, randomized, double-blind, placebo controlled, parallel group study of NKT versus placebo in otherwise healthy adults presenting with acute uncomplicated ILI due to influenza or other respiratory viruses in a community setting. To be eligible to participate in the study, subjects were required to have symptoms of ILI including fever ≥38ºC (100.4ºF), at least one general systemic symptom (headache, feverishness/chills, muscle/joint pain, or fatigue) and at least one respiratory symptom (cough, sore throat, or nasal congestion) with a severity of moderate or greater. Onset of symptoms was required to be within ≤96 hours. Eligible subjects were randomized to receive NKT 100 mg or placebo (1:1 ratio) administered once daily for 5 days with randomization stratified by time since symptom onset of symptoms (≤48 hours vs >48 to ≤96 hours). Each subject completed in-clinic visits on Day 1, Day 3, Day 5, and Day 14, and phone call visits on Day 8 and Day 28.

In the primary efficacy analysis, no difference between NKT and placebo was observed in the median time to alleviation of symptoms (TTAS) in the overall population (118 vs 116 hrs, respectively; difference of 2 hrs). However, in the ≤48 hr stratum, NKT showed a clinically meaningful reduction in median TTAS compared with placebo (122 vs 141 hrs; difference of -19 hrs). A similar pattern was not observed in the >48 hr stratum, likely due to shorter median TTAS in both the NKT and placebo treatment groups (108 and 99 hrs, respectively), reflecting a faster resolution of illness for subjects in this stratum. NKT showed clinically meaningful reductions in median TTAS compared with placebo in both influenza (122 vs

141 hrs; difference of -19 hrs) and non-influenza infected subjects (118 vs 132 hrs; difference of -14 hrs) in the ≤48 hr stratum.

NKT showed a clinically meaningful and statistically significant reduction in median time to resolution of fever compared with placebo in the overall population (23 vs 47 hrs; difference of -23 hrs; p=0.036). The magnitude of improvement for NKT vs placebo was similar in the ≤48 hr stratum (26 vs 50 hrs; difference of -24 hrs) but less pronounced in the >48 hr stratum, primarily due to a substantial decrease in the time to resolution of fever in the placebo group in this stratum (23 vs 30 hrs; difference of -7 hrs). NKT showed clinically meaningful reductions in median time to resolution of fever compared with placebo in both influenza (22 vs 50 hrs; difference of -28 hrs) and non-influenza infected subjects (28 vs 49 hrs; difference of -21 hrs) in the ≤48 hr stratum.

The incidence of AEs overall was similar in the NKT 100 mg and placebo groups (17.8% vs 19.2%, respectively), and there were no notable differences in the incidences of drug-related AEs (5.0% vs 4.1%, respectively), CTCAE Grade 3 AEs (0.8% vs 0, respectively), or AEs that led to withdrawal of study drug (0.8% vs 1.7%, respectively). No SAEs, CTCAE Grade 4 AEs, or deaths were reported in the study. The incidences of individual AEs were low and generally similar in the NKT and placebo groups. The most commonly reported AE in the NKT group was diarrhea, occurring in 5 (4.2%) subjects compared with 3 (2.5%) subjects for placebo. All other AEs occurring in 2 or more subjects in the NKT group had a similar incidence compared with the placebo group: nausea 1.7% vs 2.5%, vomiting 1.7% vs 4.2%, pneumonia 1.7% vs 0, sinusitis 1.7% vs 3.3%, and urinary tract infection 1.7% vs 2.5%, respectively. Notably, there was only a single report of somnolence (0.8%) following treatment with NKT 100 mg.

The purpose of the current study is to confirm the preliminary trends in efficacy observed in Study NKT-202 in subjects with symptom onset within ≤48 hours and explore whether a higher dose could improve the potential efficacy of NKT in ILI. Similar to NKT-202, NKT-203 will evaluate the efficacy and safety of NKT compared with placebo in otherwise healthy adults presenting with acute uncomplicated ILI due to influenza or other respiratory viruses in a community setting.

# 2. STUDY OBJECTIVES

The objectives of this study are:

- To evaluate the efficacy of NKT versus placebo on alleviation of symptoms in subjects with uncomplicated ILI
- To evaluate the safety and tolerability of NKT in subjects with uncomplicated ILI

# 3. INVESTIGATIONAL PLAN

## 3.1. Overall Study Design

This is a Phase 2b, multi-center, double-blind, randomized, placebo-controlled, parallel-group study of NKT versus placebo in otherwise healthy adults presenting with acute uncomplicated ILI due to influenza or other respiratory viruses in a community setting. The study will enroll

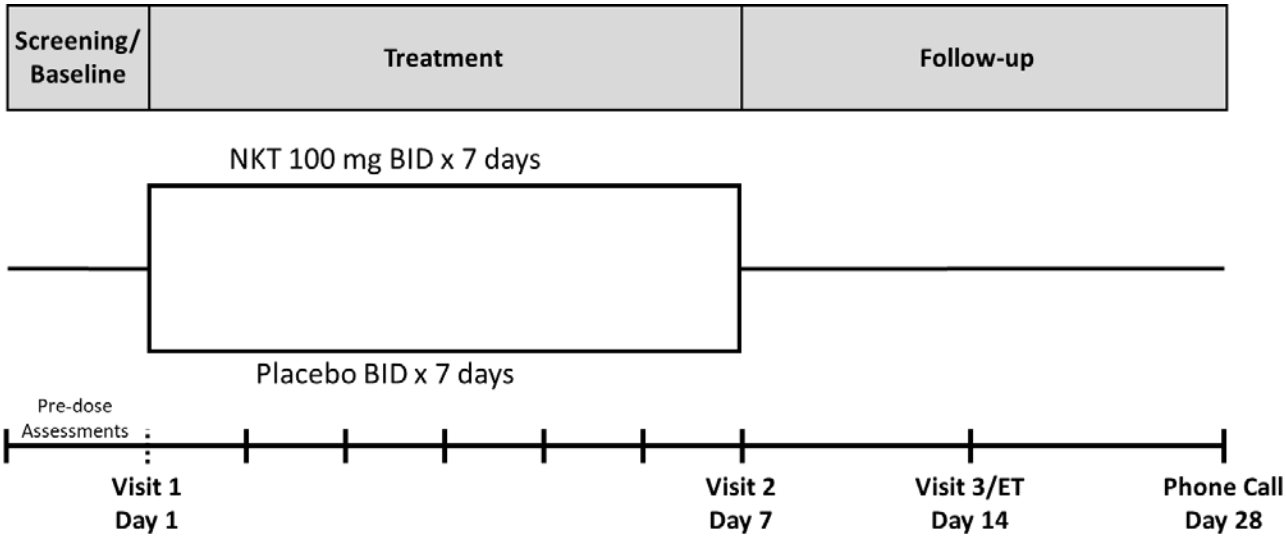
subjects with symptom onset within ≤48 hours prior to the predose examinations (Screening). Each subject will complete Screening/Baseline, Treatment, and Follow-up Phases as follows. A schematic of the study design is presented in Figure 1.

Screening/Baseline Phase: The Screening/Baseline Phase will occur on Day 1 and will consist of assessing subject eligibility to participate in the study and completing predose study assessments.

Treatment Phase: Subjects who satisfy all entry criteria will be randomized to receive NKT or matching placebo in a 1:1 ratio. Starting on Day 1, subjects will administer their assigned study drug twice daily for a total of 7 days (Day 1 through Day 7). Subjects will be provided with an electronic diary (eDiary) to record their symptom scores, body temperature, study drug dosing, rescue medication use, and ability to perform activities of daily life. Subjects will return to the clinic on Day 7 to complete safety assessments. Subjects will continue to record their symptom scores, body temperature, study drug dosing, rescue medication use, and ability to perform activities of daily life at home in the eDiary until they return to the clinic for the Day 14 Follow-up Visit.

Follow-up Phase: Subjects will return to the clinic for a Follow-up Visit on Day 14 to complete safety assessments. Clinic staff will then contact the subjects by phone for a final follow-up on Day 28 to check-in on the subject's health status and to collect information regarding AEs and concomitant medications (if any). Subjects experiencing any ILI-related complication (hospitalization, sinusitis, otitis media, bronchitis, or pneumonia) will be followed until resolution of the event or for at least 30 days after the last dose of study drug.

**Figure 1: Study Schematic**




### 3.1.1. Regions and Study Centers

The study will be conducted at approximately 30 sites in the United States.

### 3.1.2. Total Number of Subjects

A total of approximately 320 subjects are planned for enrollment into the study.

### 3.1.3. Total Duration of Participation per Subject

The total duration of study participation for each subject (from Screening through the last Follow-up contact) is approximately 28 days.

## 3.2. Safety Review Committee

A Safety Review Committee (SRC), consisting of the Medical Monitor, an independent Safety Physician, and representatives of the Sponsor, will review all available safety data in a blinded manner on an ongoing basis throughout the study to determine if any of the pre-defined stopping rules have been met and, if so, to implement appropriate actions (see Section 3.3).

## 3.3. Safety Stopping Rules

Subject safety data will be monitored continuously throughout the study to determine if any of the following treatment-emergent events occur and are attributable to active drug:

- Systolic blood pressure < 80 mmHg
- Heart rate > 130 beats per minute
- QT interval corrected for heart rate (QTc) > 500 msec or > 60 msec change from baseline
- Post-baseline elevation of ALT or AST ≥ 3 x the upper limit of normal (ULN) and/or bilirubin ≥ 2 x ULN
- Subject is hospitalized due to any serious sequalae of ILI (e.g., pneumonia)

**If ≥ 3 subjects develop any one of the above qualifying events**, the SRC will conduct a full safety review for each subject experiencing the relevant events to determine if the events are attributable to active drug. The SRC will unblind the treatment for these subjects in order to complete their review. If the SRC confirms that the events are attributable to active drug, the Sponsor will notify the Food and Drug Administration (FDA). Enrollment into the study may proceed under continued careful monitoring, unless it is deemed unsafe to do so by the SRC, the Sponsor, or the FDA.

**If ≥ 5 subjects develop any one of the above qualifying events**, enrollment into the study will be paused and the SRC will again conduct a full safety review as described above. If the SRC confirms that the events are attributable to active drug, enrollment into the study will remain paused and the Sponsor will immediately notify the FDA for further consultation.

The Sponsor may also choose to stop the study at any time based on any other safety concerns that arise from ongoing review of AEs, SAEs, and all other safety data.

## 3.4. Rationale for Study Design and Selection of Doses

A randomized, double-blind, placebo-controlled, parallel group design is appropriate for the evaluation of the efficacy and safety of NKT compared with placebo in otherwise healthy subjects with uncomplicated ILI.

The dose of NKT to be evaluated in this study was selected based on the results of three completed Phase 1 and 2 studies with NKT. NKT has been shown to be safe and well-tolerated when administered at single doses of up to 200 mg and at multiple doses of up to 200 mg administered once daily for 5 days. Treatment of subjects with uncomplicated ILI whose symptoms started within ≤48 hours with NKT 100 mg once daily for 5 days in Study NKT-202 resulted in a clinically meaningful reduction in median time to alleviation of symptoms compared with placebo; however, this difference did not reach statistical significance. Post-hoc analyses of data from this study suggested improved efficacy for subjects who received a higher dose on a mg/kg basis. Based on these findings, an NKT dose of 200 mg/day (100 mg taken twice daily) for 7 days was selected for the current study.

Refer to Section 1.2 for a summary of the results of these clinical studies.

## 3.5. Considerations for Trial Conduct During COVID-19 Public Health Emergency

This study is being conducted during the Coronavirus Disease 2019 (COVID-19) public health emergency caused by Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV2). Public health infection control measures implemented during the outbreak may cause challenges to the conduct of this study including site closures, staff availability limitations, travel restrictions, interruptions to supply chains, etc., and these challenges may lead to difficulties in adhering to protocol-mandated visits/procedures and laboratory/diagnostic testing. The Sponsor has implemented the following measures to ensure the safety and welfare of subjects participating in this study:

- Subjects with known or suspected infection with SARS-CoV2 or COVID-19 illness will be excluded from participation in the study (see Section 4.2).
- Subjects who return a positive result on central laboratory SARS-CoV2 diagnostic testing after being randomized will be immediately discontinued from study drug and referred to their primary care provider for further evaluation and care; discontinued subjects should complete all follow-up safety assessments (Section 4.3).
- In the event that subject in-clinic visits cannot be performed, a number of alternative methods for performing safety assessments may be considered as alternatives when necessary (e.g., phone contact, virtual visit, drive-through limited contact visit, home health visit).
- The following safety parameters are considered critical to ensure subject safety in the study and all efforts should be made to ensure they are performed/collected as scheduled:
  - Vitals signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, oxygen saturation [by pulse oximetry], and body temperature)

  - Blood samples for chemistry and hematology assessments
  - Nasopharyngeal swab samples for respiratory virus testing
  - Adverse event collection
  - ILI-related complications
- Missing safety assessments and/or visits related to COVID-19 restrictions must be reported as protocol deviations and the Sponsor and IRB notified, as appropriate.
- To limit on-site visits by the Sponsor, remote monitoring will be performed regularly throughout the trial to maintain oversight of clinical site activities and adherence to protocol requirements. Clinical sites will be asked to provide the appropriate materials to facilitate these monitoring activities.
- The Sponsor, in consultation with Investigators and the Institutional Review Board (IRB), may at any time determine that the protection of subjects' safety, welfare, and rights is best served by discontinuing the administration of study drug and/or stopping enrollment in the trial.

# 4. SELECTION AND WITHDRAWAL OF SUBJECTS

## 4.1. Subject Inclusion Criteria

Subjects must meet all of the following criteria to enter the study:

1. Able to understand the study and comply with all study procedures, and willing to provide written informed consent prior to the predose examinations
2. Age 18 to 64 years, inclusive
3. Symptoms of ILI including **all** of the following:
   a) Fever ≥38ºC (100.4ºF) in the predose examinations (Screening)

   **Note:** If the subject took an antipyretic within 4 hours prior to the predose examinations (Screening), a self-measured temperature of ≥38ºC (100.4ºF) (by any route) obtained by the subject within 6 hours prior to Screening will be acceptable in lieu of an in-clinic measurement. The self-measured temperature must be documented in the electronic case report form (eCRF).

   **AND**

   b) At least one of the following general systemic symptoms associated with ILI are present with a severity of moderate or greater (as reported by the subject):
      - Headache
      - Feverishness or chills
      - Muscle or joint pain
      - Fatigue

**AND**

c) At least one of the following respiratory symptoms associated with ILI are present with a severity of moderate or greater (as reported by the subject):

- Cough
- Sore throat
- Nasal congestion

4. Total symptom severity score (sum of the scores of all 7 individual symptoms) of ≥11 in the predose examinations (Screening)
5. The time interval between the onset of symptoms and the predose examinations (Screening) is ≤48 hours. The onset of symptoms is defined as either:
   - Time of the first increase in body temperature (an increase of at least 1ºC [1.8ºF] from normal body temperature)
   - Time when the subject experiences at least one general or respiratory symptom
6. Females of childbearing potential and males will agree to use an appropriate method of contraception as detailed in Section 5.7.3. Females of nonchildbearing potential are defined as permanently sterile (i.e., due to hysterectomy) or post-menopausal (defined as more than 1 year since last menstrual period).

## 4.2. Subject Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Known or suspected infection with Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV2) or Coronavirus Disease 2019 (COVID-19) illness, including **any** of the following:
   - A positive result on a rapid diagnostic test (RDT) for SARS-CoV2 during the predose examinations (Screening) (if an RDT is available at the time of enrollment), or a positive result on any SARS-CoV2 diagnostic laboratory test performed by any facility within the 4 weeks prior to Screening
   - COVID-19 illness within the 4 weeks prior to Screening
   - Exposure to someone with a positive SARS-CoV2 diagnostic laboratory test or COVID-19 illness within the 2 weeks prior to Screening
   - Oxygen saturation (by pulse oximetry) of <95% during the predose examinations (Screening)
   - Symptoms suggestive of COVID-19 illness including difficulty breathing, tightness in chest, or loss of sense of smell or taste reported during the predose examinations (Screening) or within the 2 weeks prior to Screening
2. Female subjects who are pregnant, 2 weeks post-partum, or breastfeeding
3. Severe ILI requiring inpatient treatment

4. Any of the following risk factors (according to the CDC's list of People at High Risk for Developing Serious Flu–Related Complications):
    - Extreme obesity (body mass index [BMI] ≥40 kg/$m^2$)
    - Residents of nursing homes or other long-term care facilities
    - American Indians and Alaska natives
    - Asthma
    - Chronic lung disease (such as chronic obstructive pulmonary disease or cystic fibrosis)
    - Neurological and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
    - Heart disease (such as congenital heart disease, congestive heart failure, or coronary artery disease)
    - Blood disorders (such as sickle cell disease)
    - Endocrine disorders (such as diabetes mellitus)
    - Kidney disorders
    - Liver disorders
    - Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
    - Compromised immune system due to disease or medication (such as subjects with human immunodeficiency virus [HIV] or cancer, or those on chronic steroids)
5. Presence of any severe or uncontrolled medical or psychiatric illness
6. History of or current autoimmune disease
7. History of recurrent lower respiratory tract infection
8. Any concurrent infection requiring systemic antimicrobial and/or antiviral therapy
9. Any clinically significant electrocardiogram (ECG) test
10. Received baloxavir, oseltamivir, peramivir, zanamivir, rimantadine, or amantadine within 30 days prior to the predose examinations
11. Received an investigational monoclonal antibody for a viral disease in the last year prior to the predose examinations
12. Received ketotifen fumarate, cromolyn sodium, or nedocromil sodium by any route of administration within 30 days prior to the predose examinations
13. Exposure to an investigational drug within 30 days prior to the predose examinations
14. History of allergic reaction to ketotifen

15. Any prior exposure to norketotifen

## 4.3. Subject Withdrawal Criteria

The subject has the right to withdraw from the study at any time.

The following are reasons for removing a subject from the study:

- The subject withdraws consent.
- The subject does not adhere to study rules and procedures.
- The subject develops an AE necessitating withdrawal.
- The subject requires concomitant medication not allowed per protocol.
- The Investigator feels it is in the subject's best interest to terminate participation.
- The sponsor terminates the study.
- The subject is lost to follow-up.

The reason for subject's withdrawal must be documented in the electronic case report form (eCRF).

The Day 14/Early Termination visit procedures should be performed prior to discontinuation for all subjects and the Day 28 Follow-up Phone Call should be performed as scheduled for discontinued subjects. If a subject is lost to follow-up, i.e. fails to return for study visits, all reasonable efforts should be made to contact the subject and complete all safety follow-up procedures and these efforts should be documented in the medical records.

If a subject withdraws from the study drug due to an AE, the subject will be asked to return to the clinic for, at a minimum, the evaluations scheduled for Day 14/Early Termination visit. The Day 28 Follow-up Phone Call should also be performed as scheduled for these subjects. If the AE has still not resolved, additional follow-up will be performed, as appropriate, and documented in the subject's medical records. As a minimum requirement, ongoing AEs are to be followed for 30 days after the subject's last dose of study medication.

If, following a subject's randomization, the subject's Day 1 (predose) central laboratory SARS-CoV2 diagnostic test or HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV) serology assessments return a positive result, the subject's study drug must be discontinued and the subject referred to their primary healthcare provider for further evaluation. The subject will be asked to return to the clinic for, at a minimum, the evaluations scheduled for the Day 14/Early Termination visit and the Day 28 Follow-up Phone Call should also be performed as scheduled for these subjects. Note: Clinically significant Day 1 predose laboratory values that are reported after a subject has been randomized into the study should be recorded as medical history and should not be recorded as AEs (see Section 6.4.1.4).

If the results of a subject's predose laboratory assessments show a laboratory abnormality that, in the investigator's judgement, poses a risk to the subject's safety, the investigator, in consultation with the Medical Monitor, will determine whether the subject's study drug should be discontinued on a case-by-case basis.

# 5. TREATMENT OF SUBJECTS

## 5.1. Description of Study Drug

A description of the study drug is provided in Table 1.

**Table 1: Description of Investigational Product**

| | NKT Capsules | Placebo Capsules |
|---|---|---|
| **Dosage Form/ Route** | Oral capsule containing NKT hydrogen fumarate powder | Oral capsule containing 50 mg microcrystalline cellulose (Avicel®) powder |
| **Strength** | 33.3 mg NKT (equivalent to 46.4 mg NKT hydrogen fumarate) | N/A |

## 5.2. Treatments to be Administered

Subjects will be randomly assigned to one of the two treatment groups (NKT 200 mg/day or placebo) in a 1:1 ratio. Each of the two treatments will consist of three capsules in order to maintain the blind:

- **NKT 200 mg/day:** three NKT 33.3 mg capsules taken twice daily for 7 days
- **Placebo:** three placebo capsules taken twice daily for 7 days

A dose reduction to 100 mg taken once daily (three capsules either in the morning or evening) is permitted for subjects experiencing significant tolerability issues, if deemed appropriate based on the Investigator's clinical judgment. Dose reductions must be documented in the eCRF.

## 5.3. Study Drug Materials and Management

### 5.3.1. Packaging and Labeling

Study drug will be supplied in high density polyethylene (HDPE) bottles containing 45 capsules of NKT 33.3 mg or matching placebo. The bottles will be labeled with a 2-panel label. The primary panel of the label adhered to the bottles will contain the following information, at a minimum: a unique randomization number, the protocol number, blinded contents, directions for use, storage condition, and the statement "*Caution: New Drug – Limited by Federal law to investigational use.*" The second panel of the label will be a tear-off panel containing the identical information provided on the primary label as well as a blinded scratch-off portion that conceals the unblinded treatment information. The second panel will be torn off at the time of dispensing of each bottle to a subject, and the label will be maintained in the site's study files. In the event of an emergency and only in cases where unblinding is deemed necessary by the investigator (as outlined in Section 5.5), the site personnel can scratch off the blinded area on the label to reveal the subject's treatment.

All packaged and labelled supplies will be formally released in accordance with International Council on Harmonisation (ICH) Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

### 5.3.2. Storage

Study drug should be stored at room temperature (20° to 25°C; excursions permitted to 15° to 30°C) in a location that is locked with access restricted to authorized study personnel.

### 5.3.3. Administration

Subjects will take 3 capsules of their assigned study drug twice daily (morning and evening) for 7 days. The first dose will be administered at the clinic on Day 1 after all predose assessments have been completed. If the first dose is administered before 4:00 PM on Day 1, the subject will be instructed to take a second dose of study drug on the evening of Day 1. If the first dose is administered at 4:00 PM or later on Day 1, the subject will be instructed not to take a second dose of study drug on Day 1 and to continue with twice daily (morning and evening) dosing starting on the morning of Day 2.

Subjects should be instructed to take their study drug dose at approximately the same times each day. Subjects should also be informed that the study drug bottle provided to them contains 3 extra capsules (total of 45 capsules) to allow coverage for accidental loss, but the excess capsules should not be taken once the 7-day regimen has been completed.

If the subject misses a study drug dose, they should be instructed to take it as soon as they remember **unless** their next scheduled dose is within the next 4 hours. If their next dose is scheduled to be taken within the next 4 hours, they should skip the missed dose and resume dosing with their next regularly scheduled dose.

Study drug should be taken on an empty stomach (1 hour before or 2 hours after a meal) with approximately 240 mL of room temperature water. For in-clinic dosing on Day 1, site staff should ensure that at least 2 hours have passed since the subject's last meal prior to dosing, and subjects will be instructed not to eat until at least 1 hour after their study drug dose. Subjects should be instructed to follow the same guidelines with regard to timing of dosing relative to meals for study drug dosing at home.

### 5.3.4. Accountability

The site will maintain an accurate record of the receipt of study drug and a drug disposition record, specifying the study drug bottle's unique randomization number dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request and recorded in the Trial Master File.

### 5.3.5. Study Drug Handling and Disposal

At the completion of the study, all used subject study drug bottles containing remaining study drug and all unused study drug supplies will be returned to the Sponsor or designee, per the Sponsor's instructions. Empty study drug containers, if any, will be discarded upon satisfactory completion of the compliance and accountability procedures. Final reconciliation must be

completed by the monitor prior to discarding any empty study drug containers or returning any study drug.

## 5.4. Randomization

Subjects will be randomly assigned to one of the two treatment groups (NKT 200 mg/day or placebo) in a 1:1 ratio.

Sites will be supplied with study drug bottles clearly labeled with a unique randomization number. When a subject is deemed eligible to be randomized, the site staff will retrieve the next sequentially numbered bottle and assign it to the subject. The site will record the study drug bottle's unique randomization number assigned to the subject in the eCRF.

## 5.5. Blinding

The study will be conducted in a double-blind fashion by using placebo matching NKT in appearance, labeling, and packaging. All subjects, investigators, study personnel and data analysts will be blinded to the treatment assigned at randomization until study completion. The randomization schedule will be kept confidential and will not be accessible to anyone until unblinding, except for drug supply vendor staff, the unblinded statistician, and Sponsor personnel for expedited safety reporting, as required by local regulations. The scratch-off label panel of each study drug bottle dispensed must be maintained in the site's study files (as outlined in Section 5.3.1) and must be available for inspection by the sponsor at any time to allow confirmation that the blind has been maintained.

Unblinding by request of an investigator should occur only in the event of an emergency or occurrence of an AE for which it is necessary to know the study treatment to determine an appropriate course of therapy for the subject. Prior to unblinding, the investigator should contact the sponsor to discuss the case and the reasons for unblinding. If this is impractical and the investigator decides that the treatment assignment of an individual subject needs to be disclosed, the investigator or qualified designee can perform emergency unblinding via the scratch-off label panel that is to be maintained in the site's study files (see Section 5.3.1). The investigator must notify the sponsor as soon as possible, without revealing the treatment assignment of the unblinded subject. The investigator must document the patient identification, the date and time for breaking the blind and must clearly explain the reasons for breaking the code. This information must be documented and submitted to the sponsor.

## 5.6. Treatment Compliance

The date and time of each study drug administration at home and the number of capsules taken will be recorded by the subject in the eDiary.

Subjects should bring their study drug bottles when returning to the clinic for the Day 7 visit, whether or not the bottle is empty. The site staff will perform compliance checks of the bottles to verify that the correct number of doses were taken. A record of the study drug dispensed and returned will be documented.

## 5.7. Prior and Concomitant Medications/Therapies

### 5.7.1. Prior Therapy

Prior therapies are defined as therapies that were taken prior to the initiation of study treatment. All prior therapy (prescription drugs, OTC drugs, procedures without any medication) used by a subject within 14 days prior to the initiation of study treatment will be recorded in the eCRF and the information will include a name of used drug or used procedures, duration of treatment, and reason for use.

### 5.7.2. Concomitant Therapy

Concomitant therapies are defined as therapies taken at or after the initiation of study treatment. The following information will be recorded for all therapies (prescription drugs, OTC drugs, procedures without any medication) used during the study (from Day 1 to Day 28 or early termination) in the eCRF.

- Name of used drug or used procedures
- Route of administration
- Dosage and units
- Duration of treatment
- Reason for use

#### 5.7.2.1. Prohibited Concomitant Therapy

The use of the medications listed in Table 2 is prohibited from Day 1 to Day 14/Early Termination.

**Table 2: Prohibited Medications**

| |
|---|
| Systemic antiviral drugs (except therapy for clinical progression/recurrence of infection, as described in Section 6.6) |
| Antimicrobial [a] and antifungal drugs [b] |
| Antipyretics/analgesics (except acetaminophen for rescue therapy, as described in Section 5.7.2.2) |
| Antitussives/expectorants |
| Combination cold remedies |
| Antihistamines [b] |
| Corticosteroids [b] |
| Immunosuppressants |
| Herbal medicines or complementary therapies indicated for respiratory viral infection |
| Other investigational drugs |

a. Except for the treatment of complications of ILI suspected to be a bacterial infection after Day 1.
b. Dermal preparations will be permitted, but application to the eyes, nose or ears, or by inhalation is prohibited.

#### 5.7.2.2. Rescue Therapy

If ILI symptoms are so severe that the subject needs rescue therapy between Day 1 and Day 14, the use of acetaminophen at a dose of 3000 mg/day or less will be permitted only for the relief of fever or pain. If acetaminophen is used, the subject will record the date, time, and dose of each administration in the eDiary. The measurement of body temperature and assessments of ILI symptoms, and ability to perform activities of daily life by the subject must occur immediately before the use of acetaminophen or more than 4 hours after acetaminophen administration.

### 5.7.3. Contraception

All female subjects must have a negative urine pregnancy test at the predose assessments.

Female subjects who are of nonchildbearing potential will not be required to use contraception. Females of nonchildbearing potential are defined as permanently sterile (i.e., due to hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or postmenopausal (defined as more than 1 year since last menstrual period).

Female subjects of childbearing potential must be willing to use a highly effective method of birth control (i.e., contraceptive measure with a failure rate of <1% per year) in conjunction with male barrier contraception (i.e., male condom) from the time of signing the consent form until 30 days after the last dose of study drug. Highly effective methods of contraception allowed in this study include:

- Oral hormonal contraceptives used for at least 3 months prior to study drug administration and throughout the study.
- Intrauterine device (IUD, non-hormonal) in place for at least 3 months prior to study drug administration and throughout the study.
- Male partner sterilization (performed at least 6 months prior to study drug administration), with verbal confirmation of surgical success (for female subjects on the study, the vasectomized male partner should be the sole partner for that subject).

Male subjects with partners of childbearing potential must use a male barrier method of contraception (i.e., male condom) in addition to a second method of acceptable contraception used by their female partners from Screening until 30 days after the last dose of study drug. In addition to the list of highly effective contraception methods above, other acceptable methods of contraception for the female partner include:

- Diaphragm or cap.
- Established use (3 months before study drug administration) of oral, implantable, transdermal, or injectable hormonal method of contraception associated with inhibition of ovulation.
- Hormonal IUDs (e.g., Mirena®) in place for at least 3 months prior to study drug administration and throughout the study.

Subjects who practice true abstinence, because of the subject's lifestyle choice (i.e., the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (e.g., calendar, ovulation, symptothermal,

post-ovulation methods) and withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the consent form becomes sexually active, they must agree to use contraception as described previously.

For subjects who are exclusively in same sex (homosexual) relationships, contraceptive requirements do not apply. If a subject who is in a same sex relationship at the time of signing the consent form becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

# 6. STUDY ASSESSMENTS AND PROCEDURES

Refer to Section 3.5 for considerations related to the impact of the COVID-19 pandemic on the ability to perform study visits and procedures.

## 6.1. Schedule of Assessments

The Schedule of Assessments is presented in Table 3.

**Table 3: Schedule of Assessments**

| **Phase** | | **Screening/ Baseline** | **Treatment** | | **Follow-up** | |
|---|---|---|---|---|---|---|
| **Visit** | | **Visit 1** | | **Visit 2** | **Visit 3** | **Phase Call** |
| **Day** | | **Day 1** | | **Day 7** | **Day 14/Early Termination** | **Day 28** |
| | | **Predose** | **Post-dose** | | | |
| **Visit Window (days)** | | **--** | **--** | **±1** | **±2** | **±3** |
| Informed Consent | | X | | | | |
| Eligibility Review | | X | | | | |
| Medical History | | X | | | | |
| Vital Signs [a] | | X | | X | X | |
| Physical Examination [b] | | X | | X | X | |
| 12-lead ECG | | X | | X | X | |
| Serology Screen [c] | | X | | | | |
| Urine Pregnancy Test | | X | | | X | |
| Labs: Hematology, Chemistry, Urinalysis | | X | | X | X | |
| Nasopharyngeal and/or Other Swab(s) for SARS-CoV2 RDT (if available) and Central Lab Virology Panel Testing [d, e] | | X [d,e] | | | | |
| Randomization | | X | | | | |
| Study Drug Administration [f] | | | Twice Daily [f] | | | |
| Subject eDiary | Body Temperature | Four Times Daily [g] | | Twice Daily | | |
| | Symptom Severity | Twice Daily | | | | |
| | Ability to Perform Normal Daily Activities | Once Daily | | | | |
| AEs | | | X | X | X | X |
| ILI-related Complications [h] | | X | X | X | X | X |
| Concomitant Medications | | X | X | X | X | X |

AE=adverse event; ECG=electrocardiogram; ILI=influenza-like illness; RDT=rapid diagnostic test; SARS-CoV2=Severe Acute Respiratory Syndrome-Coronavirus 2

NOTE: In the event that subject in-clinic visits cannot be performed, a number of alternative methods for performing safety assessments may be considered as alternatives when necessary (e.g., phone contact, virtual visit, drive-through limited contact visit, home health visit). The following safety parameters are considered critical to ensure subject safety in the study and all efforts should be made to ensure they are performed/collected as scheduled: vital signs (systolic and diastolic blood pressure,

pulse rate, respiratory rate, oxygen saturation [by pulse oximetry], and body temperature), blood samples for chemistry and hematology assessments , nasopharyngeal swab samples for respiratory virus testing, AEs, ILI-related complications, concomitant medications (see Section 3.5).

a. Height and weight will be measured at Day 1 only. All other vital sign measurements will be performed after subjects have been seated for at least 5 minutes and will include blood pressure, pulse rate, respiratory rate, oxygen saturation (by pulse oximetry), and body temperature.
b. A complete physical examination (general appearance, skin, head [eye, ear, nose], neck, mouth/throat, lymph nodes, cardiovascular, respiratory, gastrointestinal, neurological, and musculoskeletal) will be performed at the Day 1 and Day 14/Early Termination Visits. A symptom-directed physical examination will be performed at Day 7, if warranted, and will include evaluation of the appropriate body systems as determined by the Investigator based on the subject's symptoms.
c. Serology screening includes tests for hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus 1 and 2 antigens/antibodies.
d. If an FDA authorized point-of-care RDT for SARS CoV2 is available to the site, the Sponsor may allow the test to be performed in the clinic by the site to exclude subjects with a positive result for SARS CoV2. An appropriate predose swab sample for the SARS CoV2 RDT (nasopharyngeal, pharyngeal, nasal, saliva, or other) will be collected, as specified by the manufacturer of the RDT being used; details of the RDT test and the result will be recorded in the eCRF. If an RDT is performed and the result is positive, the subject will be excluded from the study and no further swab samples will be required. All subjects who are eligible to be randomized into the study, including those with a negative RDT result or those with no RDT performed due to lack of availability, will also have a predose nasopharyngeal swab collected and sent to the central lab for confirmatory SARS CoV2 and virology panel testing.
e. Subjects who return a positive result on the central lab confirmatory SARS-CoV2 test after randomization will be discontinued from study drug and referred to their primary care provider for further evaluation and care. Discontinued subjects should complete all Day 14/Early Termination visit safety assessments and the Day 28 Phone Call.
f. Study drug will be administered twice daily (morning and evening) for 7 days. The first dose will be administered at the clinic on Day 1 after all predose assessments have been completed. If the first dose is administered before 4:00 PM on Day 1, the subject will be instructed to take a second dose of study drug on the evening of Day 1. If the first dose is administered at 4:00 PM or later on Day 1, the subject will be instructed not to take a second dose of study drug on Day 1 and to continue with twice daily (morning and evening) dosing starting on the morning of Day 2.
g. Body temperature will be measured by the subject and recorded in the eDiary four times daily from Day 1 to Day 5 and twice daily from Day 6 to Day 14.
h. ILI-related complications include hospitalization, death, sinusitis, otitis media, bronchitis, or pneumonia.

## 6.2. Demographics, Baseline Characteristics, and Medical History

The following information will be recorded for each subject:

- Date of birth
- Sex
- Ethnicity
- Race
- Current smoking status
- Prior and concomitant therapies (as outlined in Section 5.7)
- Influenza vaccination within the last 6 months
- Onset and severity of ILI symptoms
- Medical history, which includes any previous significant medical conditions, all concurrent medical conditions, and surgical history within 12 months

## 6.3. Efficacy Assessments

### 6.3.1. Subject eDiary

The subject will self-measure/assess the outcome measures described in the sections that follow and record the results electronically directly in the subject eDiary. The subject eDiary consists of an electronic application used on the subject's own mobile smartphone device (provided it meets certain requirements) or a Sponsor-provided device (if needed).

Once the subject is deemed eligible for randomization, the device will be set up by the site staff and subjects will be instructed on how to use the device and how to assess the outcome measures. After the initiation of the study treatment on Day 1, only the measurements and assessments in the remaining available time periods of that day will be conducted (refer to Table 4, Table 5, and Table 6 for time periods and windows).

Subjects will also record rescue medication use in the eDiary as outlined in Section 5.7.2.2. If the subject takes rescue acetaminophen, body temperature, symptom severity, and activities of daily living should be assessed before taking acetaminophen or more than 4 hours after the last dose of acetaminophen.

#### 6.3.1.1. Body Temperature

Using a Sponsor-provided electronic thermometer, the subject will self-measure axillary temperature. Any perspiration at the measurement site should be wiped off prior to the measurement. The subject will measure and record body temperature 4 times daily (morning, noon, evening, and bedtime) from Day 1 to Day 5, and twice daily (morning and evening) from Day 6 to Day 14. The subject should measure body temperature during the time periods described in Table 4 or at the closest possible time point.

**Table 4: Time Windows of Body Temperature Measurements**

| Study Days | Time Period of Day | Time Window |
|---|---|---|
| Day 1 to Day 5 | Morning | Before 10:00 am |
| | Noon | 10:00 am – 2:59 pm |
| | Evening | 3:00 pm – 7:59 pm |
| | Bedtime | 8:00 pm or later |
| Day 6 to Day 14 | Morning | Before 12:00 pm |
| | Evening | 6:00 pm or later |

#### 6.3.1.2. ILI Symptom Severity

The subject will self-assess 7 symptoms associated with ILI (headache, feverishness or chills, muscle or joint pain, fatigue, cough, sore throat, and nasal congestion) on a 4-point rating scale (0=None; 1=Mild; 2=Moderate; 3=Severe; Appendix 3).

The subject will assess ILI symptoms twice daily (morning and evening) from Day 1 through Day 14. The subject should assess symptoms during the time periods described in Table 5 or at the closest possible time point.

**Table 5: Time Windows of ILI Symptom Severity Assessments**

| Study Days | Time Period of Day | Time Window |
|---|---|---|
| Day 1 to Day 14 | Morning | Before 12:00 pm |
| | Evening | 6:00 pm or later |

#### 6.3.1.3. Ability to Perform Normal Daily Activities

The subject will self-assess his or her ability to perform normal daily activities on a scale of 0 to 3 (0=No difficulty performing normal daily activities; 1=Some difficulty performing normal daily activities; 2=Moderate difficulty performing normal daily activities; 3=Great difficulty performing normal daily activities) (Appendix 4).

The subject will assess ability to perform normal daily activities once daily (evening) from Day 1 to Day 14. The subject will perform this assessment during the time periods described in Table 6 or at the closest possible time point.

**Table 6: Time Windows of Assessments of Ability to Perform Activities of Daily Life**

| Study Days | Time Period of Day | Time Window |
|---|---|---|
| Day 1 to Day 14 | Evening | 6:00 pm or later |

## 6.4. Safety Assessments

Safety and tolerability assessments include:

- AEs
- Vital signs, including blood pressure, heart rate, respiratory rate, oxygen saturation (by pulse oximetry), and body temperature
- Physical examination
- 12-lead ECG
- Laboratory tests, including hematology/coagulation, blood chemistry, and urinalysis
- ILI-related complications (hospitalization, death, sinusitis, otitis media, bronchitis, or pneumonia)

### 6.4.1. Adverse and Serious Adverse Events

If an AE or SAE occurs, the investigator will institute support and/or treatment as deemed appropriate. If a serious or treatment-related AE is unresolved at the time of the last day of the study, an effort will be made to follow-up until the AE is resolved or stable, the subject is lost to follow-up, or there is some other resolution of the event. The investigator should make every attempt to follow SAEs to resolution.

#### 6.4.1.1. Definitions

##### 6.4.1.1.1. Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All AEs that occur after any subject has been enrolled, before, during, or after treatment and until study exit, whether or not they are related to the study, must be recorded.

##### 6.4.1.1.2. Definition of a Serious Adverse Event

An SAE is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or within 30 days following study drug administration, whether or not they are related to the study, must be recorded on forms provided by the Sponsor or designee.

#### 6.4.1.2. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

If the relationship between the AE/SAE and the investigational product is determined to be “possible” or “probable” the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

#### 6.4.1.3. Severity of Adverse Events

AE intensity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, which uses the following general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

  *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

  **Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 6.4.1.1.2. An AE of severe intensity may not be considered serious.

#### 6.4.1.4. Recording Adverse Events

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation during the study will be recorded. Clinically significant changes (per the Investigator's judgement) in laboratory values, vital signs (including body temperature), or ECGs should be recorded as AEs. (Note: Clinically significant Day 1 predose [Screening] laboratory values that are reported after a subject has been randomized into the study should be recorded as medical history and should not be recorded as AEs.) The symptoms of ILI being captured as efficacy assessments in this study (headache, feverishness or chills, muscle or joint pain, fatigue, cough, sore throat, and nasal congestion) should not be recorded as AEs.

Information about AEs will be collected from the signing of the consent form until the end of the subject's participation in the study. SAE information will be collected from the signing of consent form until 30 days following study drug administration. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study drug.

If a subject withdraws from the study drug due to an AE or SAE, the subject will be asked to return to the clinic for, at a minimum, the evaluations scheduled for the Follow-up Phase. If the AE/SAE has still not resolved, additional follow-up will be performed, as appropriate, and

documented in the subject's medical records. As a minimum requirement, ongoing AEs/SAEs are to be followed for 30 days after the subject's last dose of study medication.

Should a pregnancy occur, it must be reported and recorded on the Sponsor or designee's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

#### 6.4.1.5. Reporting Serious Adverse Events

All SAEs must be reported to the Sponsor or designee within 1 business day of the first awareness of the event. The Investigator must complete, sign, and date the SAE form, verify the accuracy of the information recorded on the SAE form against the corresponding source documents (if applicable), and send a copy by email to the Sponsor using the contact information below:

| **24-HOUR SAE REPORTING** | |
|---|---|
| **Email:** | safety@emergotherapeutics.com |
| **Phone:** | Primary: 919-879-0946<br>Back-up: 919-201-8133 |

Additional follow-up information, if required or available, should all be emailed to the Sponsor or designee within 1 business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the study file.

The Sponsor is responsible for notifying the relevant regulatory authorities of certain events. It is the PI's responsibility to notify the IRB or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7- or 15-day Expedited Safety Reports) from any other source that occur during the clinical trial. The Sponsor will notify the central IRB of these additional SAEs. Each site is responsible for notifying its local IRB or IEC of these additional SAEs, if applicable.

### 6.4.2. Vital Signs

Seated blood pressure (systolic and diastolic blood pressure), pulse rate, respiratory rate, oxygen saturation (by pulse oximetry), and body temperature will be assessed at the times indicated in the Schedule of Assessments (Table 3). Height and weight will be measured at the Screening Visit only. Vital signs may be repeated once if outside the relevant clinical reference ranges or based on the Investigator's (or designee) judgment. Vital signs may also be performed at other

times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Subjects must be seated for at least 5 minutes before blood pressure, respiratory rate, pulse rate, and oxygen saturation (by pulse oximetry) measurements.

### 6.4.3. Physical Examination

A complete or symptom-directed physical examination will be performed at the visits indicated in the Schedule of Assessments (Table 3). A complete physical examination will include evaluation of the following body systems at a minimum: general appearance, skin, head (eye, ear, nose), neck, mouth/throat, lymph nodes, cardiovascular, respiratory, gastrointestinal, neurological, and musculoskeletal. A symptom-directed physical examination, if warranted, will include evaluation of the appropriate body systems as determined by the Investigator based on the subject's symptoms.

### 6.4.4. 12-Lead ECG

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments (Table 3). Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

The PR, RR, QT, QTc intervals, QRS duration, and heart rate will be reported at each timepoint.

### 6.4.5. Laboratory Assessments

#### 6.4.5.1. Hematology, Clinical Chemistry, and Urinalysis

Blood and urine samples will be collected for clinical laboratory evaluations (clinical chemistry, hematology/coagulation, urinalysis, and serology) at the times indicated in the Schedule of Assessments (Table 3). Clinical laboratory parameters are listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

The Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

#### 6.4.5.2. Pregnancy Test

For all female subjects, a urine pregnancy test will be performed at the times indicated in the Schedule of Assessments (Table 3). Subjects with a positive result can be reconfirmed by a repeat assessment and will be excluded from participation if confirmed to be positive.

#### 6.4.5.3. Serology Screening

Viral serology screening includes tests for HBV surface antigen, HCV antibody, and HIV 1 and 2 antigens/antibodies at the times indicated in the Schedule of Assessments (Table 3). Subjects with a positive result can be reconfirmed by a repeat assessment and will be discontinued from study drug if confirmed to be positive (see Section 4.3).

### 6.4.6. ILI-Related Complications

The occurrence of any ILI-related complications including hospitalization, death, sinusitis, bronchitis, otitis media, and pneumonia, will be assessed at all visits as indicated in the Schedule of Assessments (Table 3).

## 6.5. Virologic Assessments

### 6.5.1. Nasopharyngeal and/or Other Swab(s) for SARS-CoV2 and Virology Panel Testing

Once a subject has been determined to be eligible for the study based on all other criteria, up to two swab samples may be collected predose at Visit 1 (Day 1) for SARS-CoV2 and respiratory virology panel testing.

If an FDA-authorized point-of-care RDT for SARS-CoV2 is available to the site, the Sponsor may allow the test to be performed in the clinic by the site to exclude subjects with a positive result for SARS-CoV2. An appropriate predose swab sample for the SARS-CoV2 RDT (nasopharyngeal, pharyngeal, nasal, saliva, or other) will be collected, as specified by the manufacturer of the RDT being used; details of the RDT test and the result will be recorded in the eCRF. If an RDT is performed and the result is positive, the subject will be excluded from the study and no further swab samples will be required.

All subjects who are eligible to be randomized into the study, including those with a negative RDT result or those with no RDT performed due to lack of availability, will also have a predose nasopharyngeal swab collected and sent to the central lab for confirmatory SARS-CoV2 and virology panel testing.

Note: A nasal or pharyngeal swab is not acceptable in place of a nasopharyngeal swab for the confirmatory central lab SARS-CoV2 and respiratory virology panel test. Detailed sample collection, processing, and shipping details will be described in a separate document.

In addition to SARS-CoV2, the central lab virology panel testing will include qualitative identification of the presence of common respiratory viral pathogens, including, but not limited to:

- Influenza A and B virus
- Respiratory syncytial virus
- Human metapneumovirus
- Adenovirus

Subjects who return a positive result on the central lab confirmatory SARS-CoV2 test after randomization will be discontinued from study drug and referred to their primary care provider for further evaluation and care (see Section 4.3). Discontinued subjects should complete the Day 14/Early Termination visit assessments and the Day 28 Phone Call.

## 6.6. Clinical Progression or Recurrence of Infection

If a subject appears to be deteriorating clinically or develops new symptoms of ILI consistent with recurrent ILI infection after initial ILI symptoms completely resolved, the Investigator should consider the possibility of secondary infections, decompensation of underlying conditions, or progression of viral infection. Subjects should be evaluated, and appropriate investigations should be performed, as clinically indicated.

Subjects showing signs of clinical progression or recurrence of infection on Day 7 or later may be given local standard of care for respiratory tract infections, including anti-viral agents, at the discretion of the Investigator. Such cases should be discussed in advance with the Medical Monitor.

Since unblinding of the study drug would not alter the management of the subject, unblinding in this situation is discouraged, and the subject should remain in the study and complete all required follow-up.

# 7. STATISTICS

A separate Statistical Analysis Plan (SAP) will be generated and finalized prior to database lock. The SAP will specify the details of all statistical analyses, including efficacy and safety analyses to be performed.

## 7.1. Determination of Sample Size

A total sample size of 320 subjects randomized in a 1:1 distribution was selected for this study.

The primary endpoint for the study is time to alleviation of symptoms (TTAS), defined as the time when all of the 7 symptoms of ILI (headache, feverishness or chills, muscle or joint pain, fatigue, cough, sore throat, and nasal congestion) have been assessed by the subject as 0 (None) or 1 (Mild) in the subject diary for a duration of at least 21.5 hours. Response must occur within 13 days, to be confirmed on the 14$^{th}$ day of follow-up. The null hypothesis is that the distribution of TTAS is the same in both groups.

In the previously completed Phase 2 study of NKT 100 mg in subjects with uncomplicated ILI (NKT-202), the median time to alleviation of symptoms (TTAS) in subjects with symptom onset within ≤48 hrs was 122 hours in the NKT group and 141 hrs in the placebo group (Section 1.2.3). The median TTAS was slightly longer in both treatment groups in influenza-infected subjects (NKT 122 hours vs placebo 141 hours) compared with non-influenza infected subjects (NKT 118 hours vs placebo 132 hours). The observed TTAS in the placebo group in this study was unusually high compared to that typically observed in previous Phase 2/3 clinical trials of anti-influenza agents. A meta-analysis of nine randomized controlled clinical trials of oseltamivir in adults with influenza showed an estimated median TTAS of 112.0 hours for placebo-treated subjects when excluding subjects in high risk categories (≥65 years of age, chronic illness, or chronic obstructive airways disease at baseline) (Dobson et al, 2015); more specifically, in the Phase 3 registration study of oseltamivir conducted in the US in adults with uncomplicated influenza, the median TTAS for placebo-treated subjects was 103.3 hours. Similarly, in two randomized controlled clinical trials of baloxavir in adults, the median TTAS in placebo-treated subjects were 77.7 hours and 80.2 hours; the TTAS was longer in

placebo-treated subjects enrolled in the Phase 3 trial in the US (117.9 hours) (Hayden et al, 2018).

Based on the data from NKT-202 and historical data for approved influenza antivirals, we assumed a median TTAS of 120 hours for placebo and 85 hours for NKT for the current trial. The study sample size of 320 was calculated with the assumption of nominal drop-outs, provides 80% power, and for a two-sided 0.05 log-rank test.

Subjects who return a positive result on the central lab confirmatory SARS-CoV2 test after randomization and are discontinued will not count towards the total sample size of 320 and will be replaced.

## 7.2. Analysis Populations

The following analysis populations will be used to summarize the study data.

Intent-to-Treat (ITT) Population: The ITT population will include all non-COVID subjects who are randomized to study drug. The ITT population will be used for primary efficacy, all secondary, and exploratory endpoints.

Safety Population: The safety population will include all non-COVID subjects who receive at least 1 dose of study drug (NKT or placebo). The safety population will be used to summarize all background and safety data.

COVID Population: The COVID population consists of randomized subjects who take at least 1 dose of study drug (NKT or placebo) but are subsequently confirmed to have COVID-19. These subjects will be included in listings, and AEs for these subjects will be reported separately from the Safety Population.

## 7.3. Handling of Missing Data

Missing data will not be imputed. Data from subjects whose influenza symptoms have not resolved by the last observation time point will be censored at that time point.

## 7.4. Subject Disposition

Among the subjects randomized to each treatment group, the number of randomized subjects found to have COVID-19, the number and percentage who complete the study and the number and percentage who prematurely discontinue the study drug will be summarized by treatment group. In addition, reasons leading to discontinuation of study drug will be summarized for each treatment group.

The number and percentage of subjects included in the ITT and safety populations will also be presented.

## 7.5. Demographics, Baseline Characteristics, and Medical History

Numerical demographics and baseline values will be listed and summarized by treatment group and overall using descriptive statistics (mean, standard deviation [SD], minimum, median, and maximum). Categorical values will be listed and summarized using frequency and percentage.

Medical history will be listed by subject.

## 7.6. Extent of Exposure and Treatment Compliance

The duration of treatment with study drug and the percent compliance will be summarized by treatment group using descriptive statistics.

## 7.7. Prior and Concomitant Therapies

Prior and concomitant therapies will be listed by subject.

## 7.8. Efficacy Analyses

The ITT population will be the primary population for efficacy analyses. The analysis of each efficacy endpoint will consist of comparison between NKT and placebo. For all inferential testing, a p-value of less than or equal to 0.05 on a two-sided test will be considered statistically significant. Inferential testing will be performed for secondary endpoints as outlined in Section 7.8.3 without adjustment for multiplicity of testing.

### 7.8.1. Efficacy Endpoints

The primary efficacy endpoint is:

- Time to alleviation of symptoms, defined as the time when all of the 7 symptoms of ILI (headache, feverishness or chills, muscle or joint pain, fatigue, cough, sore throat, and nasal congestion) have been assessed by the patient as 0 (None) or 1 (Mild) in the patient diary for a duration of at least 21.5 hours (24 hours – 10%).

Secondary efficacy endpoints include:

- Time to resolution of fever, defined as the time when the subject's self-measured axillary temperature becomes equal to or less than 37ºC (98.6ºF) and is maintained at equal to or less than 37ºC (98.6ºF) for a duration of at least 12 hours
- Proportion of subjects whose symptoms have been alleviated at each time point
- Change from baseline in composite symptom score at each time point
- Body temperature at each time point
- Time to alleviation of individual symptoms
- Time to resumption of normal activity, defined as the time when the subject assesses his/her activities as 0 (No difficulty performing normal daily activities) or 1 (Some difficulty performing daily activities)
- Use of rescue medication
- Time to alleviation of symptoms by confirmed viral pathogen (influenza vs non-influenza)

### 7.8.2. Primary Efficacy Analysis

The TTAS will be compared between the NKT group and the placebo group with the use of a generalized Wilcoxon test (log-rank test). The generalized Wilcoxon test is a nonparametric test for comparing survival curves which does not assume proportional hazards. Data from subjects whose symptoms have not resolved by the last observation time point will be censored at that time point.

The following hypothesis will be tested for the comparison of the primary efficacy endpoint:

Ho: $S_{NKT}(t) = S_{Placebo}(t)$ versus Ha: $S_{NKT}(t) \neq S_{Placebo}(t)$, where S(t) is the distribution of proportion of subjects with alleviation of symptoms at time t.

Kaplan-Meier curves will be plotted for each treatment group, and the median TTAS and its 95% CI will be calculated. In addition, the group difference in median TTAS and its 95% CI will also be calculated.

### 7.8.3. Secondary Efficacy Analyses

The secondary endpoints will be summarized using appropriate methods. Inferential tests will be used to evaluate the null hypotheses that the time-to-event, scores or measures, or change from baseline in scores are the same in the NKT group as the placebo group. Applicable methods will be used for testing: Log-Rank tests for time-to-event measures, Kruskal-Wallace for ordered or numeric measures, Fisher's Exact for binary outcomes, and a Likelihood Ratio test for other categorical variables.

**Time to Resolution of Fever:**

Time to resolution of fever, defined as the time when the subject's self-measured axillary temperature becomes less than 37ºC (98.6ºF) and is maintained at less than 37ºC (98.6ºF) for a duration of at least 12 hours, will be summarized in a similar fashion to the primary efficacy endpoint.

**Alleviation of Symptoms at Each Time Point:**

The number and percentage of subjects whose symptoms have been alleviated at each time point will be presented by treatment arm.

**Change from Baseline in Composite Symptom Scores:**

The change from baseline in composite symptom score at each time point will be summarized using descriptive statistics such as n, mean, median, SD, minimum and maximum.

**Subjects reporting normal temperature at each time point:**

The number and percentage of subjects reporting normal temperature at each time point will be presented by treatment group.

**Body temperature at each time point:**

Body temperature at each time point will be summarized using descriptive statistics such as n, mean, median, SD, minimum and maximum.

**Time to alleviation of individual symptoms:**

Time to alleviation of individual symptoms will be summarized in a similar fashion to the primary efficacy endpoint.

**Time to resumption of normal activity:**

Time to resumption of normal activity, defined as the time when the subject assesses his/her activities as 0 (No difficulty performing normal daily activities) or 1 (Some difficulty performing daily activities) will be summarized in a similar fashion to the primary efficacy endpoint.

**Ability to perform normal daily activities at each time point:**

The ability to perform normal daily activities will be summarized descriptively using counts and percentages. A trend-test will be used to evaluate the null hypothesis that there is no trend in the distribution of classifications (0-3) between groups.

**Use of rescue medication:**

The number and percentage of subjects who used rescue medication will be presented by treatment group.

**TTAS by confirmed viral pathogen (influenza vs non-influenza):**

Time to alleviation of symptoms will be summarized by confirmed viral pathogen (influenza vs non-influenza), in a similar fashion to the primary efficacy endpoint.

**Time to resolution of fever by confirmed viral pathogen (influenza vs non-influenza):**

Time to resolution of fever will be summarized by confirmed viral pathogen (influenza vs non-influenza), in a similar fashion to the primary efficacy endpoint.

## 7.9. Safety Analyses

### 7.9.1. Adverse Events

Any AEs reported prior to administration of the first dose of investigational product will be listed as pre-treatment AEs.

The verbatim AE terms will be coded using the Medical Dictionary Regulatory Activities (MedDRA) and will be classified by system organ class (SOC) and preferred term (PT).

A treatment-emergent AE (TEAE) is defined as an AE that begins after the start of study drug dosing. All TEAEs will be summarized by treatment.

Unless otherwise specified, summary counts of AEs will be the number of subjects reporting AEs and not the number of events reported. If the same AE (SOC or PT) is reported multiple times for the same subject, it will only appear once for that specified treatment and category in the summary tables.

AE intensity will be assessed as described in Section 6.4.1.3.

For the purposes of the summary tables, AEs will be classified as either being related to study drug or not related. AEs related to study drug will include AEs classified as ‘Probably Related’

or 'Possibly Related'. AEs not related to study drug will include AEs that are 'Unrelated'. For subjects with multiple AEs of the same PT and of different relationship, the AE with the strongest assessment of relationship will be used in the summaries presented by relationship.

The following AE summaries will be provided:

- Overall Summary of TEAEs. This table will summarize subjects with Any TEAEs, Related TEAEs, TEAEs by Maximum Intensity, SAEs, and TEAEs Leading to study Drug Discontinuation
- TEAEs by Treatment Group, SOC and PT
- TEAEs by Treatment Group, SOC, PT and Maximum Intensity
- Study Drug Related TEAEs by Treatment Group, SOC and PT
- Serious Adverse Events by Treatment Group, SOC and PT
- Study Drug Related Serious Adverse events by Treatment Group, SOC and PT
- Listing of SAEs
- List of TEAEs Leading to Study Drug Discontinuation

### 7.9.2. Clinical Laboratory Evaluations

Descriptive statistics (n, mean, SD, median, and range) of the laboratory parameters and changes from predose will be presented by Treatment Group. All laboratory data will be listed. Clinically significant laboratory values will be flagged in the listings. If laboratory values are repeated for any reason, they will be included in the listing but not included in the summaries.

The following laboratory summaries will be provided:

- Clinical Laboratory Hematology – Summary of Observed Values and Change from Baseline by Treatment Group and Time Point
- Clinical Laboratory Chemistry – Summary of Observed Values and Change from Baseline by Treatment Group and Time Point
- Clinical Laboratory Coagulation – Summary of Observed Values and Change from Baseline by Treatment Group and Time Point
- Clinical Laboratory Urinalysis – Summary of Observed Values and Change from Baseline by Treatment Group and Time Point

### 7.9.3. ECGs

Observed and change from baseline descriptive summaries will be provided for the following ECG parameters: PR, RR, QT, and QTc intervals, QRS duration, and heart rate. The frequency of normal or abnormal ECGs will be summarized by treatment and time point. Abnormal values will be flagged in the ECG listing.

### 7.9.4. Vital Signs

Descriptive summary statistics for observed values and change from baseline for each vital sign parameter (blood pressure [systolic and diastolic], pulse rate, respiratory rate, oxygen saturation [by pulse oximetry], and body temperature) will be provided by treatment and time point.

### 7.9.5. Incidence of ILI-related Complications

The incidence of ILI-related complications (hospitalization, death, sinusitis, otitis media, bronchitis, or pneumonia) will be enumerated by treatment.

# 8. ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

Refer to Section 3.5 for considerations related to the impact of the COVID-19 pandemic on the ability to perform study visits and procedures.

## 8.1. Ethics

### 8.1.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to the Sponsor or designee before he or she can enroll any subject into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB with information on any reportable serious adverse drug reactions from the current study or any other study being conducted by the Sponsor with the investigational product. The Sponsor or designee will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

### 8.1.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP guidelines, and applicable regulatory requirements.

### 8.1.3. Written Informed Consent

The PI will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that

they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated Informed Consent Form must be obtained before conducting any study procedures.

The PI must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

## 8.2. Subject Confidentiality

Procedures for protecting subject privacy must adhere to applicable data privacy laws and regulations. In order to maintain subject privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the subject by the subject number. The investigator will grant site monitors and auditors of the Sponsor or designee and regulatory authorities access to all subject data collected. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations. The investigator and the sponsor are responsible for ensuring that sensitive information is handled in accordance with local requirements (e.g., Health Information Portability and Accountability Act [HIPAA]).

Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained. Data on subjects collected during the study will be documented in an anonymous fashion and the subject will only be identified by the subject ID. In the emergent or rare event that for safety or regulatory reasons it is necessary to identify a subject, the sponsor, and the investigator are bound to keep this information confidential.

## 8.3. Electronic Source Data Capture

This study utilizes electronic source data capture. Site staff will enter source data electronically directly into the eCRF using a tablet device provided by the Sponsor. The eCRF is considered the source for subject data obtained and entered by the site staff in this study. Symptom assessments by the subject will also be entered electronically directly into the eDiary device and serve as the source data for subject self-assessments. If a paper transcription step is used for any source data, the paper documentation should be retained and made available for review and source data verification by the Sponsor and any/or regulatory authorities.

## 8.4. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor will evaluate the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRF, and that investigational product accountability checks are being performed.
- Perform source data verification, where applicable. If a paper transcription step is used for any of the source data, the data in the eCRF will be compared against the source documents to ensure that it was captured accurately. This may include a comparison of the data in the eCRF with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on the eCRF and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

To limit on-site visits by the Sponsor during the COVID-19 pandemic, remote monitoring will be performed regularly throughout the trial to maintain oversight of clinical site activities and adherence to protocol requirements (Section 3.5). Clinical sites will be asked to provide the appropriate materials to facilitate these monitoring activities.

## 8.5. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification (where applicable). The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator should notify the Sponsor immediately if contacted by a regulatory agency about an inspection.

## 8.6. Data Handling and Recordkeeping

### 8.6.1. Inspection of Records

The Sponsor or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source data, and other records relevant to study conduct.

### 8.6.2. Retention of Records

The Investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval of the investigational product under study, or if not approved, at least 2 years following the discontinuance of the investigation of the investigational product. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

## 8.7. Publication Policy

All information regarding this study will be kept strictly confidential. All data derived from the study will be the property of the Sponsor. The Sponsor retains the first right to disclose the data from this study in a publication. Any publications prepared by the investigator on the data generated at the site must meet the requirements set forth in the clinical trial agreement.

# 9. REFERENCES

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# 10. APPENDICES

# APPENDIX 1. Investigator's Agreement

I have received and read the Investigator's Brochure for Norketotifen. I have read the protocol for Study NKT-203 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

# APPENDIX 2. Clinical Laboratory Parameters

| Clinical Chemistry: | Hematology/Coagulation: | Urinalysis: |
|---|---|---|
| Alanine aminotransferase<br>Albumin<br>Alkaline phosphatase<br>Aspartate aminotransferase<br>Bilirubin (direct)<br>Calcium<br>Chloride<br>C-reactive protein (high sensitivity)<br>Creatinine<br>Creatine phosphokinase<br>Gamma-glutamyl transferase<br>Glucose<br>Inorganic phosphorus<br>Lactate dehydrogenase<br>Potassium<br>Sodium<br>Total bilirubin<br>Total $CO_2$ (measured as bicarbonate)<br>Total protein<br>Urea<br>Uric acid | Hematocrit<br>Hemoglobin<br>Mean cell hemoglobin<br>Mean cell hemoglobin concentration<br>Mean cell volume<br>Platelet count<br>Red blood cell (RBC) count<br>RBC distribution width<br>White blood cell (WBC) count<br>WBC differential:<br>Basophils<br>Eosinophils<br>Lymphocytes<br>Monocytes<br>Neutrophils<br>Prothrombin time<br>Partial thromboplastin time<br>International Normalized Ratio | Bilirubin<br>Blood<br>Color and appearance<br>Glucose<br>Ketones<br>Leukocyte esterase<br>Nitrite<br>pH<br>Protein<br>Specific gravity<br>Urobilinogen<br>Microscopic examination (to be performed if indicated) |
| **Serology:** | | |
| Hepatitis B surface antigen (HbsAg)<br>Hepatitis C virus (HCV) antibody (total)<br>Human immunodeficiency virus (HIV-1 and HIV-2) antigens/antibodies | | |

# APPENDIX 3. Assessment of ILI Symptom Severity

Please rate the severity of your symptoms on a scale of 0 to 3 based on how you feel right now:

0 = None

1 = Mild

2 = Moderate

3 = Severe

Symptoms to be evaluated:

Headache

Feverishness or Chills

Muscle or Joint Pain

Fatigue (Tiredness)

Cough

Sore Throat

Nasal Congestion

# APPENDIX 4. Assessment of Ability to Perform Normal Daily Activities

Please rate your ability to perform normal daily activities on a scale of 0 to 3 as shown below:

0 = No difficulty performing normal daily activities

1 = Some difficulty performing normal daily activities

2 = Moderate difficulty performing normal daily activities

3 = Great difficulty performing normal daily activities