# A Phase 1, First-In-Human, Randomized, Double-Blind, Placebo-Controlled, Single Dose-Escalation Study to Evaluate the Safety and Pharmacokinetics of Single Oral Doses of VT-1598 in Healthy Adult Subjects

**DMID Protocol Number:** 17-0087

**DMID Funding Mechanism:** HHSN272201500007I

**Pharmaceutical Support:** NQP 1598, Ltd.

**IND Sponsor:** DMID

**Lead Principal Investigator:** Cassandra Key, MD

**DMID Clinical Project Manager:** Maureen Mehigan

**Draft or Version Number:** 5.0

**Day Month Year**
18 Jun 2021

# STATEMENT OF ASSURANCE

Each Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protections (OHRP) for federally-funded human subjects research. Each FWA will designate at least one Institutional Review Board (IRB)/Independent Ethics Committee (IEC) registered with OHRP, for which the research will be reviewed and approved by the IRB/IEC and will be subject to continuing review [45 CFR 46.103(b)]. The IRB/IEC designated under an FWA may include an institution's IRB/IEC, an independent IRB/IEC, or an IRB/IEC of another institution after establishing a written agreement with that other institution.

# STATEMENT OF COMPLIANCE

The study trial will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects;
- Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application);
- International Conference on Harmonization: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions;
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research;
- National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable;
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable;
- Applicable Federal, State, and Local Regulations and Guidance.

# SIGNATURE PAGE

**Protocol Title**: A Phase 1, First-In-Human, Randomized, Double-Blind, Placebo-Controlled, Single Dose-Escalation Study to Evaluate the Safety and Pharmacokinetics of Single Oral Doses of VT-1598 in Healthy Adult Subjects

**Protocol Number:** 17-0087

**Protocol Version (Issue Date):**

The signature below provides the necessary assurance that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH E6 Good Clinical Practice (GCP) guidelines.

I agree to conduct the study in compliance with GCP and applicable regulatory requirements.

I agree to conduct the study in accordance with the current protocol and will not make changes to the protocol without obtaining the sponsor's approval and IRB/IEC approval, except when necessary to protect the safety, rights, or welfare of subjects.

Site Investigator Signature:

Signed: _____ Date: _____

*Cassandra Key, MD*

*Site Principal Investigator*

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event/Adverse Experience |
| ACTH | Adrenocorticotropic Hormone |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| BMI | Body Mass Index |
| CAR | Clinical Agents Repository |
| CDC | Centers for Disease Control and Prevention |
| CFR | Code of Federal Regulations |
| CMS | Clinical Material Services |
| CPKt | Creatinine Phosphokinase |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CROMS | Clinical Research Operations and Management Support |
| CRU | Clinical Research Unit |
| CYP | Cytochrome P |
| DHHS | Department of Health and Human Services |
| DMID | Division of Microbiology and Infectious Diseases |
| DSMB | Data and Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EDTA | Ethylenediaminetetraacetic Acid |
| FDA | Food and Drug Administration |

| | |
|---|---|
| FSH | Follicle Stimulating Hormone |
| GGT | Gamma-Glutamyl Transferase |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| HBsAg | Hepatitis B Surface Antigen |
| HCV | Hepatitis C Virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| HLGT | High-Level Group Term |
| ICF | Informed Consent Form |
| ICH | The International Council for Harmonization |
| ICON BAL | ICON Bioanalytical Laboratory |
| ICON GPHS | ICON Government and Public Health Solutions |
| IEC | Independent or Institutional Ethics Committee |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| IUD | Intrauterine Device |
| LARC | Long Acting Reversible Contraceptive |
| LC-MS/MS | Liquid Chromatography with Tandem Mass Spectrometry |
| LLN | Lower Limit of Normal |
| MedDRA® | Medical Dictionary for Regulatory Activities |
| MOP | Manual of Procedures |
| N | Number (typically refers to subjects) |

| | |
|---|---|
| NEJM | New England Journal of Medicine |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| NOAEL | No-Observed-Adverse-Effect-Level |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| QA | Quality Assurance |
| QC | Quality Control |
| SAD | Single Ascending Dose |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SAP | Statistical Analysis Plan |
| SDCC | Statistical and Data Coordinating Center |
| SMC | Safety Monitoring Committee |
| SOCS | Safety Oversight Committee Support |
| SOP | Standard Operating Procedure |
| ULN | Upper Limit of Normal |
| US | United States |
| VCT | Verified Clinical Trials |
| WHO | World Health Organization |

# PROTOCOL SUMMARY

| | |
|---|---|
| **Title:** | A Phase 1, First-In-Human, Randomized, Double-Blind, Placebo-Controlled, Single Dose-Escalation Study to Evaluate the Safety and Pharmacokinetics of Single Oral Doses of VT-1598 in Healthy Adult Subjects |
| **Design of the Study:** | This is a Phase 1, first-in-human, randomized, double-blind, placebo-controlled, single ascending dose (SAD) study, in six (6) cohorts (five fasted cohorts, one fed cohort). Each cohort contains 8 subjects (N = 8), 6 subjects will be given an oral dose of VT-1598 and 2 subjects will receive placebo. |
| **Study Phase:** | 1 |
| **Study Population:** | Up to forty-eight (48) healthy male and female subjects, ages 18-45 (inclusive). |
| **Number of Sites:** | 1 |
| **Description of Study Product or Intervention:** | VT-1598 will be supplied as 40 mg and 80 mg tablets.<br><br>Placebo will be supplied as the same size, weight, and color as the VT-1598 tablets. |
| **Study Objectives:** | Primary:<br>• To determine the safety of single-ascending oral doses of VT-1598 in healthy adult subjects in a fasted state.<br>• To determine the safety of single oral dose of VT-1598 in healthy adult subjects in a fed state. |

| | |
|---|---|
| | Secondary:<br>• To determine the pharmacokinetic (PK) profile in plasma and urine of VT-1598 and its primary metabolite, VT-11134, in healthy adult subjects<br>• To determine the effect of a high-fat, high-calorie meal on the PK profile of VT-1598 and VT-11134 when a single oral dose of VT-1598 is given. |
| **Study Outcome Measures:** | Primary:<br>• Safety will be evaluated for single-ascending fasting oral doses of VT-1598. Safety will be assessed by adverse events from start of dosing to Day 21, clinical laboratory tests at baseline and from Day 4 to Day 21, ECGs at baseline and on Day 4 and Day 21, and vital signs at baseline and from Day 1 to Day 21;<br>• Safety will be evaluated for single oral dose of VT-1598 administered after being fed a high-fat, high calorie meal. Safety will be assessed by adverse effects from start of dosing to Day 21, clinical laboratory tests at baseline and from Day 4 to Day 21, ECGs at baseline and on Day 4 and Day 21, and vital signs at baseline and from Day 1 to Day 21.<br>Secondary:<br>• PK profiles of VT-1598 and its primary metabolite, VT-11134, will be assessed by measurement of VT-1598 and VT-11134 levels in both plasma and urine after VT-1598 administration in each cohort, when fasting. Plasma for PK analysis will be collected at planned time points up to 480 hours post-dose and urine for PK analysis will be collected in planned intervals up to 72 hours post-dose; |

| | |
|---|---|
| | • PK profiles of VT-1598 and its primary metabolite, VT-11134, will be assessed by measurement of VT-1598 and VT-11134 levels in both plasma and urine after administration of VT-1598 following consumption of a high-fat, high calorie meal. Plasma for PK analysis will be collected at planned time points up to 480 hours post-dose and urine for PK analysis will be collected in planned intervals up to 72 hours post-dose. |
| **Duration of Individual Subject Participation:** | Individual subject participation will be approximately 50 days to include up to 28 days pre-enrollment (screening period) and 21 days of follow-up post-dosing. Note: Subjects who participate in both cohorts 3 and 6, their participation will exceed 50 days. |
| **Estimated Time to Last Subject/Last Study Day:** | Approximately 6 months. |

## Table 1: Single Dose* Escalation

| | | | |
|---|---|---|---|
| ***Cohort 1 - fasting*** ***Dose: 40 mg*** | 6 subjects** | Single 40 mg VT-1598 tablet | Safety data for Cohort 1 subjects through Day 7 will be confirmed by reviewing objective pre-defined criteria before continuing to Cohort 2. |
| | 2 subjects** | Single 40 mg matching Placebo | |
| ***Cohort 2 - fasting*** ***Dose: 80 mg*** | 6 subjects** | Two 40 mg VT-1598 tablets | Safety data for Cohort 2 subjects through Day 7 will be confirmed by reviewing objective pre-defined criteria before continuing to Cohort 3. |
| | 2 subjects** | Two 40 mg matching Placebo tablets | |
| ***Cohort 3 - fasting*** ***Dose: 160 mg*** | 6 subjects** | Four 40 mg VT-1598 tablets | Safety data for Cohort 3 subjects through Day 7 will be confirmed by reviewing objective pre-defined criteria before continuing to Cohort 4 and 6. Interim analysis of PK data (Cohorts 1-3)*** |
| | 2 subjects** | Four 40 mg matching Placebo tablets | |
| ***Cohort 4 – fasting*** ***Dose: 320 mg*** | 6 subjects** | Four 80 mg VT-1598 tablets | Cumulative safety data for all subjects in Cohorts 1-4 through Day 21 will be reviewed by the SMC for recommendation/confirmation of dosing before continuing to Cohort 5 |
| | 2 subjects** | Four 80 mg matching Placebo tablets | |
| ***Cohort 5 – fasting*** ***Dose: 640 mg*** | 6 subjects** | Eight 80 mg VT-1598 tablets | |
| | 2 subjects** | Eight 80 mg matching Placebo tablets | |
| ***Cohort 6 – fed (high-fat, high-calorie meal)*** ***Dose: 160 mg*** | 6 subjects | Four 40 mg VT-1598 tablets | Cohort 6 is comprised of the same subjects as Cohort 3****. These subjects will receive the same treatment in Cohort 6 as Cohort 3. Cohort 6 may start enrolling prior to convening the SMC meeting and prior to the start of Cohort 5. |
| | 2 subjects | Four 40 mg matching Placebo tablets | |

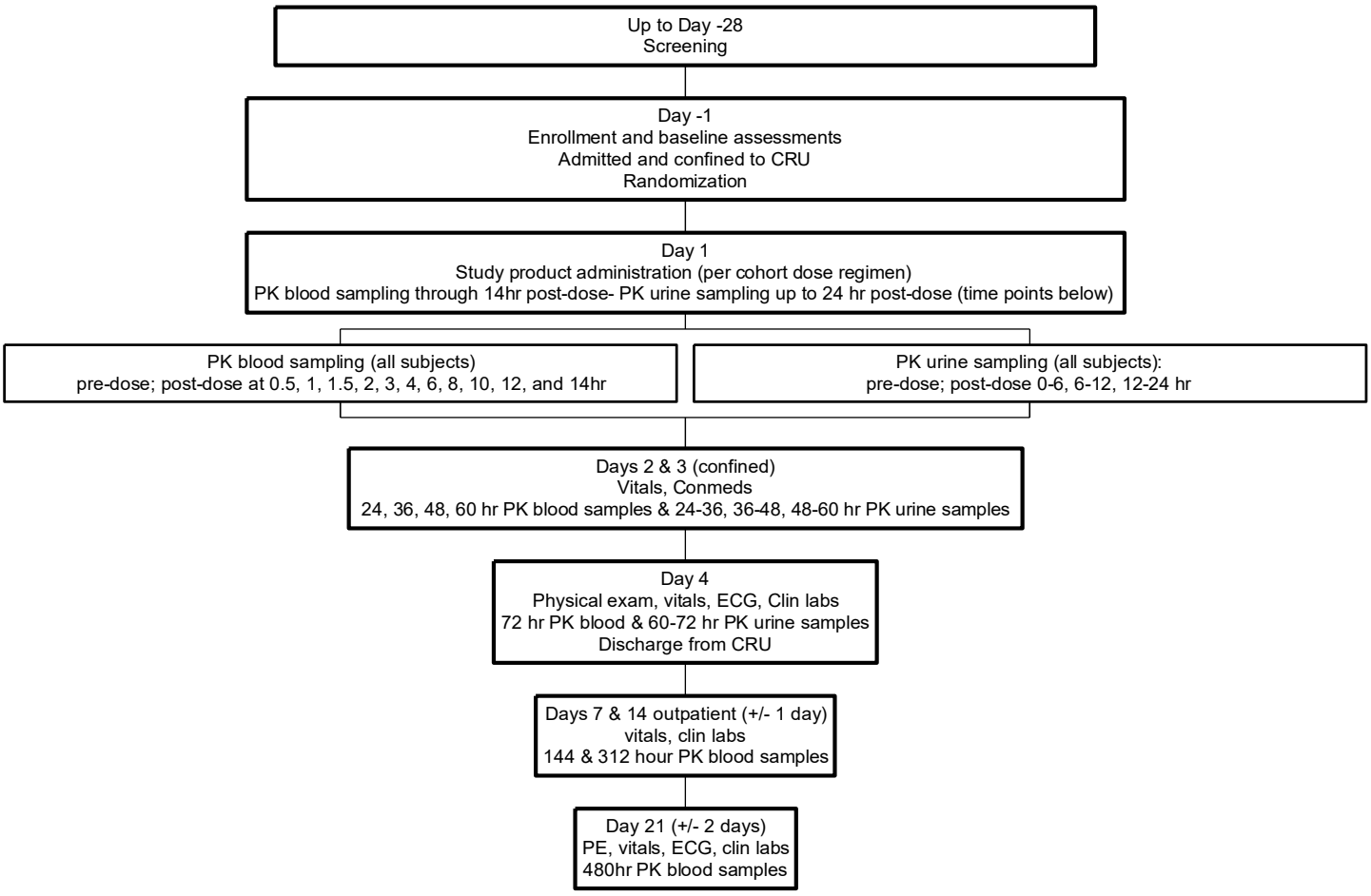
*Dose refers to the free base equivalent of the drug.

**Within each fasted cohort two sentinel subjects will be admitted initially, and the randomization scheme will be designed to ensure that one subject will receive VT-1598 and the other will receive placebo. All sentinel subject safety data through Day 3 is reviewed by PI prior to dosing remainder of cohort.

***PK data only; enrollment for Cohort 4 will not stop for the PK interim analysis.

**** The Cohort 6 replacement subjects will receive the same treatment as assigned to the Cohort 3 subject they are replacing.

**Figure 1: Schematic of Study Design**



# 1 KEY ROLES

| | |
|---|---|
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| **Statistical and Data Coordinating Center:** | Emmes Company, LLC<br>401 North Washington Street, Suite 700<br>Rockville, MD 20850<br>Phone: 301-251-1161<br>Email: phase1@emmes.com |

***Contact information for additional key personnel is located in the Manual of Procedures (MOP) for this study.***

# 2 BACKGROUND AND SCIENTIFIC RATIONALE

## 2.1 Background

CYP51 (lanosterol demethylase) is a metalloenzyme essential for fungal growth and catalyzes an early step in the biosynthetic pathway of ergosterol, a sterol required for fungal cell membrane formation and integrity.[1] Inhibition of CYP51 not only blocks the pathway leading to ergosterol but also results in the accumulation of 14-methylated sterols, some of which are toxic to the fungus. Fungal CYP51 is the molecular target of the class of drugs referred to as 'azole antifungals'. All currently approved azole drugs contain either an imidazole or triazole ring system[2] that binds tightly to the catalytic heme-iron of fungal CYP51 as well as to the heme-iron of many off-target mammalian cytochrome P450 (CYP) enzymes. This inherent lack of selectivity is responsible for many of the side effects associated with the azole antifungals. For example, the potent inhibition of one or more human CYP enzymes found in the liver (e.g., CYP3A4, CYP2C9, CYP2C19) or in the adrenal and sex organs (e.g., CYP11B, CYP19, CYP17) is the basis for azole drug-drug interactions (DDI)[3] and endocrine toxicities, including reproductive warnings,[4] respectively.

Additional azole class toxicities that are less well understood but may be related to other off-target human CYP interactions include hepatic toxicity, skin photosensitivity, and vision impairment. In the acute care setting, the dose-limiting side effects not only are limitations in and of themselves but also prevent attainment of plasma drug levels that might reduce the long-standing high mortality rates attributed to invasive fungal infections. For example, the mortality rate (40%) due to coccidioidal meningitis in a 2008 study has not changed since 1980.[5]

VT-1598 is a novel, potent antifungal compound designed to selectively bind to fungal CYP51 rather than human CYP enzymes so as to minimize the off-target effects associated with currently approved azole antifungals agents. In both in vitro and in vivo studies, VT-1598 has demonstrated highly-potent antifungal activity against *Coccidioides* species.

Approximately 50,000 cases of coccidioidomycosis are estimated to occur annually that are sufficiently severe to require medical attention. Among these cases, several thousand patients suffer serious pulmonary sequelae, and disseminated infection will result in death in approximately 160 individuals.[6,7,8,9] The disease can be highly-debilitating and places considerable demands on healthcare resources. In a survey of nearly 500 recently diagnosed cases of coccidioidomycosis in Arizona, 85% of cases had disease limited to the lungs, the median duration of illness was 4 months, and the median time lost from work was 2 weeks. Forty-one percent of patients required hospitalization, incurring an average cost of $30,000 per patient just for inpatient care.[10] From 2000-2011, 25,217 coccidioidomycosis-associated

hospitalizations occurred in California, involving 15,747 patients. Among these patients, there were 1,220 deaths: 626 due to primary pulmonary coccidioidomycosis, 309 due to other forms of progressive disease, and 196 due to coccidioidal meningitis.[11] Coccidioidal meningitis is the most severe form of disseminated disease, and is associated with a high degree of morbidity and mortality. Khan and Brady identified 1251 hospitalizations in 623 patients with coccidioidal meningitis in non-federal facilities in Arizona from 2008-2014.[12] Readmission was common (41%) and 61% of hospitalizations included time in the intensive care unit.

Treatment regimens (choice of agent and doses) for coccidioidomycosis vary considerably depending on the clinical presentation of the disease, and all current regimens have significant limitations. Currently, ketoconazole and amphotericin B are the only antifungal agents approved for this disease, despite significant toxicity concerns. The Infectious Diseases Society of America guidelines recommend that coccidioidomycosis be managed with various antifungal agents including off-label use of fluconazole and itraconazole, as well as amphotericin B, depending on disease presentation.[13] However, with currently available antifungal agents, coccidioidomycosis continues to be associated with substantial, preventable morbidity and mortality, and relapse is a common occurrence. Treatment outcomes are particularly poor for disseminated disease (~40% mortality) and a comparison of matched cohorts from 1980 and 2008 suggests that outcomes did not improve over that time span.[5] In addition, existing oral agents are generally administered at high doses for extended durations and are associated with significant toxicity, including a risk of serious hepatotoxicity that increases with dose and duration of treatment. High-dose and prolonged use of the commonly-prescribed fluconazole is also associated with congenital anomalies in infants exposed in utero. Finally, all prescribed azole antifungals have significant DDIs due to poor selectivity for fungal versus human CYP enzymes, complicating both treatment decisions and drug monitoring. Therefore, there is an urgent need for new therapeutic options that can address gaps in efficacy and provide a better safety profile.

**Nonclinical Studies**

**Nonclinical Pharmacology**

**Binding and Inhibition**

In vitro pharmacology studies have demonstrated that VT-1598 is a potent inhibitor of fungal CYP51 and that the activity of VT-1598 is highly selective for fungal CYP51 versus human CYPs.

## Microbiology

VT-1598 was tested under Clinical Laboratory Standards Institute guidelines against a broad panel of fungal samples (N = 10-50/species) including clinical yeast, mold and endemic fungal isolates, and showed potent intrinsic antifungal activity (geometric mean minimum inhibitory concentrations ranging from 0.004 to 3.5 µg/mL for the 15-different species tested).

## Activity in Animal Models of Infection

In murine models of invasive infections *with Coccidioides posadasii, Cryptococcus neoformans, Candida albicans, and Aspergillus fumigatus*, and of a mucosal infection with C. *albicans,* VT-1598 free base or tosylate salt at oral once daily doses ranging from 3 to 50 mg/kg (doses expressed as the free base equivalent) were highly effective in reducing fungal burden and demonstrated a survival benefit of up to 100% protection across multiple studies. In two models, VT-1598 reduced fungal burden to below pre-treatment levels. In murine central nervous system models of coccidioidomycosis and cryptococcosis, VT-1598 not only achieved highly significant survival benefit, it also reduced brain fungal burden up to 5-6.5 orders of magnitude, with undetectable viable fungus in several of the tissue samples assessed.

## Nonclinical Drug Metabolism and Pharmacokinetics

## Pharmacokinetics

Single-dose PK studies were conducted in Swiss albino mice, Sprague-Dawley rats, Beagle dogs, and cynomolgus monkeys, with the primary goal to identify the version/form and formulation that would give optimized exposures for preclinical safety assessment. Repeat-dose PK and toxicokinetics studies showed that orally administered VT-1598 was well absorbed and reached a maximum measured plasma concentration ($C_{max}$) of 30-40 µg/mL in rats and 50-60 µg/mL in monkeys after repeated doses up to 28 days in duration. VT-1598 exposures increased as doses increased in all animal species, but exposure increases were less than dose-proportional. Terminal elimination half-lives were relatively long (25-33 hours in rats and 64-72 hours in monkeys), leading to accumulation in repeat-dose studies (2- to 4-fold increases in rats and 10- to 15-fold increases in monkeys). In the large majority of studies, no differences were observed between males and females (although there were higher exposures in females at the end of the 28-day Good Laboratory Practice [GLP] rat toxicity study). VT-1598 has very high plasma protein binding (≥99.9%).

## Metabolism

VT-1598 was metabolized to varying extents when incubated with mouse, rat, dog, monkey, or human liver microsomes and with rat, dog, and human hepatocytes. A single metabolite was

observed following incubations with human hepatocytes; its structure is consistent with O-dealkylation at the internal ether linkage of VT-1598.

**CYP Interactions**

When tested in biochemical assays using 1 mg/mL microsomal protein, VT-1598 weakly inhibited human CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP11B1/2, CYP17, and CYP19). The range of half maximal inhibitory concentration ($IC_{50}$) values was 6.8 to >200 µM. When tested in assays using 0.01-0.1 µg/mL, $IC_{50}$ values were lower: CYP1A2 ($IC_{50}$ = >4.5 µM), CYP2D6 ($IC_{50}$ = >4.5 µM), CYP2C9 ($IC_{50}$ =>4.5 µM), CYP2B6 ($IC_{50}$ = 3.8 µM), CYP3A4/5 ($IC_{50}$ = 2.8 µM with testosterone as substrate), CYP2C8 ($IC_{50}$ = 0.96 µM), CYP2C19 ($IC_{50}$ = 0.91 µM), and CYP3A4/5 ($IC_{50}$ = 0.59 µM) with midazolam as substrate.

**Nonclinical Safety Assessments**

**Safety Pharmacology**

The effects of orally-administered VT-1598 on the neurological and pulmonary systems were evaluated in Sprague-Dawley rats. No observable adverse effects were found at the top dose of 150 mg/kg VT-1598 in either study. Evaluation of cardiovascular function in telemetered monkeys revealed no adverse changes in heart rate, blood pressure, cardiac rhythm or morphology, including the QT/QTc interval, at oral doses up to 300 mg/kg administered twice-daily for 7 days. VT-1598 did not inhibit the human ether-à-go-go related gene (commonly known as hERG) potassium current up to the highest soluble concentration tested (with the estimated $IC_{50}$ of >2.9 µM).

**Toxicology**

Oral VT-1598 has been evaluated in general toxicity studies in rats and monkeys of up to 28 days in duration. Based on the pivotal 28-day GLP toxicology studies, rats were more sensitive to the toxicological effects of oral administration of VT-1598 than monkeys.

In the 28-day GLP rat toxicity study, once daily oral doses of VT-1598 resulted in test article-related mortality at 300 mg/kg/day. VT-1598-related changes in body weight, food consumption, clinical pathology parameters, organ weights and/or histopathology were observed ≥10 mg/kg/day but were considered to be non-adverse. Exposure to VT-1598 and its primary metabolite (VT-11134) increased less than proportionally to the increase in dose and accumulated with repeated dosing as predicted by the long half-life of the molecule (terminal elimination half-life was calculated to be 25-33 hours). The no-observed-adverse-effect-level (NOAEL) for VT-1598 established in this study was 100 mg/kg/day; Day 28 $C_{max}$ and an area under the plasma concentration versus time curve from time zero to 24 hours post-dose ($AUC_{0-}$

$_{24}$) in males were 12.6 µg/mL and 201 µghr/mL, respectively, and $C_{max}$ and $AUC_{24}$ values in females were 32.0 µg/mL and 475 µg·hr/mL, respectively.

In the 28-day GLP oral toxicity study in cynomolgus monkeys following twice daily dosing with VT-1598, findings were generally limited to the highest dose tested (100 mg/kg/dose) and included clinical observations, mild increase in QTc interval, and increased organ weights with correlative histopathological changes. Increased adrenal gland and liver weights were associated with cortical hypertrophy and hepatocellular hypertrophy, respectively, which were observed across dose-groups, although not necessarily dose-dependent. No test article-related changes were present in recovery animals. Exposure to VT-1598 and VT-11134 generally increased in a dose- related manner; however, the increase in exposure was less than proportional to the increase in dose. VT-1598 and VT-11134 accumulated with repeated dosing as predicted by the long half- life of the molecule (terminal elimination half-life was calculated to be 64-72 hours). The NOAEL for VT-1598 for this study was the high dose level of 100 mg/kg/dose (200 mg/kg/day), associated with a Day 28 $C_{max}$ of 65.2 µg/mL, and $AUC_{24}$ of 1,330 µgh·r/mL.

**Genotoxicity**

VT-1598 was found to be negative for genotoxicity in the in vitro bacterial reverse mutation assay, the in vitro chromosome aberrations assay in human peripheral lymphocytes, and the in vivo bone marrow micronucleus assay in rats.

**Clinical Studies**

To date, no clinical studies have been conducted with VT-1598**.**

## 2.2 Scientific Rationale

### 2.2.1 Purpose of Study

Coccidioidomycosis, also called Valley Fever, is an infectious disease caused by dimorphic fungi of the genus *Coccidioides*. *Coccidioides* species (*C. immitis* and *C. posadasii*) are endemic to the lower Sonoran life zone of the western hemisphere, including southern Arizona, the southern and central valleys of California, southwestern New Mexico, and west Texas in the US.[6] Recent reports have documented the presence of *C. immitis* as far north as south-central Washington state.[14]

In endemic states in which coccidioidomycosis is reportable to the US Centers for Disease Control and Prevention (CDC); (Arizona, California, Nevada, New Mexico, and Utah), the incidence of coccidioidomycosis increased from 5.3 cases per 100,000 population in 1998 to 42.6 cases per 100,000 population in 2011.[15] During that time period, 111,717 cases of coccidioidomycosis were reported to the CDC.[15] Arizona and California account for 66 and 31

percent, respectively, of all nationally reported infections.[15] Reportable-disease data rely on positive diagnostic test results and given the low rate of testing even in highly endemic areas, it is clear that the actual number of coccidioidomycosis cases far exceeds the reported numbers.[16] With population and industrial expansion into the southwestern deserts, the numbers of infections are expected to continue to climb. Additionally, the National Institute of Allergy and Infectious Diseases (NIAID) has designated *Coccidioides* species as a Category C pathogen due to its potential to be engineered as a bioterrorism weapon.[17]

VT-1598 has been shown in preclinical studies to be a potent and selective, orally-available inhibitor of fungal CYP51. Fungal CYP51 is the target of the azole class of antifungal drugs. Azoles rely heavily on the potent interaction between either an imidazole or triazole moiety and the active site heme iron of this CYP, which also leads to potent inhibition of human CYPs. VT-1598 blocks the production of ergosterol, an essential component of the fungal cell membrane. Due to VT-1598's high fungal CYP selectivity, low cross reactivity with human CYP, and highly-potent antifungal activity, VT-1598 should have a greater clinical safety margin than currently available azole antifungal treatments. As a result of VT-1598's substantial potency against *Coccidioides* species, VT-1598 was selected for further preclinical development targeting the treatment of coccidioidomycosis.

### 2.2.2 Study Population

Up to 48 subjects aged 18-45 (inclusive) who are in good health and meet all eligibility criteria will be enrolled in the study. The demographics in the local population should ensure that male, female and minorities (African American and Hispanics) will be represented in the enrolled population. Subjects will be recruited using IRB-approved advertising/web site listing of the essential inclusion and exclusion criteria. Subjects will self-schedule online for a screening appointment based on their desire to participate and their evaluation of their suitability based on inclusion/exclusion criteria. Children, pregnant or breast-feeding women, prisoners, and other vulnerable populations will not be enrolled. See Section 9.4 Exclusion of Women, Minorities and Children (Special Populations).

Neither women nor minorities will be excluded from participation in this study. Women of child bearing potential may be included as per the inclusion criteria (Section 5.1 Eligibility Criteria). Subjects will be recruited without regard to gender or race. It is expected that race will reflect that within the community.

## 2.3 Potential Risks and Benefits

### 2.3.1 Potential Risks

As VT-1598 has not yet been studied in humans, no information is currently available regarding AEs associated with its use.

When oral VT-1598 was evaluated in general toxicity studies in rats and monkeys, the following side effects were noted:

- slight decreases in body temperature and heart rate
- minimal to mild increases in serum cholesterol
- decreases in mean body weight and food consumption
- decreases in lymphocyte and eosinophil counts and/or increases in monocyte counts
- moderate to marked prolongations of APTT and prothrombin times
- minimal to mild decreases in alkaline phosphatase
- mild to moderate decreases in serum albumin
- mild decrease in serum creatinine
- mild to moderate, dose-dependent increases in gamma-glutamyl transferase (GGT)
- mild to moderate decreases in urine pH and specific gravity
- mild increase in urine volume.

Among the currently-available azole antifungal agents, numerous clinically-significant drug interactions have been identified.[18] Most of these interactions are a result of competitive inhibition of liver oxidative metabolism via reversible binding to CYP enzymes. Azoles interfere mainly with CYP3A4, CYP2C9, and CYP2C19 characterized by individual affinity and they therefore exhibit slightly different drug interaction profiles. In addition, itraconazole, posaconazole and isavuconazole are inhibitors of gastric P-glycoprotein, which limits systemic exposure to many drugs by inhibiting gastrointestinal absorption.

Adverse effects of the currently-available azole antifungals vary across the individual agents and are described in the following paragraphs:

Fluconazole: Fluconazole is generally well tolerated and serious adverse events (SAEs), mainly hepatotoxicity, are rare. Gastrointestinal disturbances are the most common complaints. High doses (400-800 mg/day) of fluconazole may be associated with a rare and distinct set of birth defects in infants whose mothers were treated with the drug during the first trimester of pregnancy. The US Food and Drug Administration (FDA) is evaluating the results of a Danish study that concluded there is a possible increased risk of miscarriage with the use of oral fluconazole for yeast infections.

Ketoconazole: Nausea and vomiting may occur when using ketoconazole. Serious and sometimes fatal liver problems, including the need for liver transplant, have occurred with the use of ketoconazole. Ketoconazole can cause elevated plasma concentrations of certain drugs and may prolong QT intervals, sometimes resulting in life-threatening ventricular dysrhythmias such as torsades de pointes. Ketoconazole, when used in high doses, may cause adrenal insufficiency.

Itraconazole: Itraconazole causes frequent gastrointestinal symptoms, mainly nausea and vomiting; other common adverse effects include elevated hepatic transaminases, hypokalemia (sometimes severe), and rashes. Serious hepatotoxicity leading to liver failure has been reported with itraconazole but is rare. Heart failure due to itraconazole is caused by a direct negative inotropic effect and has resulted in a “black box” warning in the label.

Voriconazole: The most common AEs after treatment with voriconazole include visual disturbances in up to 20-40% of recipients. Most reports are of blurring, photopsia, photophobia, and color changes soon after dosing; these are reversible and tend to dissipate with continued dosing. Like the other triazoles, voriconazole has been associated with hepatotoxicity which can rarely be serious or fatal and is dose-related. Other side effects include visual and auditory hallucinations, confusion, skin rashes (mostly photosensitivity), QTc prolongation, and peripheral neuropathy.

Posaconazole: The safety profile of posaconazole is improved compared to voriconazole. Common AEs include headaches and gastrointestinal disturbances. Hepatotoxicity is uncommon and reported in 2-3% of recipients. Hypokalemia and rashes occur but less commonly than with itraconazole and voriconazole.

Isavuconazole: The most frequent adverse effects of isavuconazole are nausea, vomiting, diarrhea, headache, elevated liver chemistry tests, hypokalemia, constipation, dyspnea, cough, peripheral edema and back pain. Isavuconazole is contraindicated for use in patients with familial short QT syndrome and rare but serious hepatic reactions have also been reported with its use.

As noted above, the differentiating properties of VT-1598 should translate to greater efficacy with an improved safety and tolerability profile compared to the existing azole agents. In addition, the animal toxicology studies completed to date do not suggest any unusual or unexpected toxicities related to VT-1598 exposure. The present study provides for careful monitoring for the AEs that have been observed with existing azole agents. In addition, all subjects that have pre-existing abnormalities in body systems associated with the more severe AEs reported for existing azoles (e.g., visual disturbances, hepatic disease, and cardiac conduction abnormalities) will be excluded from participation.

As with taking any product/drug, there is a risk of allergic reaction. There may be risk of death if there is a very serious allergic reaction. Other risks include temporary physical discomfort and potential emotional stress due to the nature of the exams and specimen collection procedures. The risks associated with insertion of the indwelling intravenous catheter and frequent blood draws are fainting, pain, bruising, and scarring. The catheter may be at risk for clotting and infection. These risks are discussed with the subject during the consent process.

In addition to the above risks, the risk of volunteering for this study includes a potential failure to protect the subject's private health and other information through an accidental breach of confidentiality. This risk of breach of confidentiality and the associated safeguards to protect confidentiality will be defined in each informed consent document.

### 2.3.2 Potential Benefits

There are no known benefits to subjects participating in this study. The knowledge gained in this trial may help society, especially those exposed to *Coccidioides* species.

# 3 STUDY DESIGN, OBJECTIVES AND ENDPOINTS OR OUTCOME MEASURES

## 3.1 Study Design Description

### 3.1.1 Overall Study Design

This is a Phase 1, randomized, double-blind, placebo-controlled, SAD study in healthy adult subjects. It is designed to evaluate the safety and PK of single oral doses of VT-1598. Subjects who provide informed consent and meet all study eligibility criteria will be enrolled in the study and randomized to receive either VT-1598 or placebo in 6 dosage cohorts (five fasted cohorts and one fed cohort). For all cohorts, Screening, Enrollment, Treatment Period, and Follow-Up procedures/activities (Day -28 to Day 21) will follow the same process, with the exception of the fed Cohort (Cohort 6) who receives the study product after a high-calorie, high-fat meal vs. when fasted (Cohorts 1-5). Cohort 6 may be started prior to the SMC meeting or prior to the start of Cohort 5 (but no less than 60 days following their first dose after completion of Cohort 3).

### 3.1.2 Dosing Scheme and Duration of Study

For each dosage cohort, 6 subjects will receive VT-1598 and 2 subjects will receive placebo.

Within each of the fasted cohorts (Cohorts 1-5), two sentinel subjects will be admitted initially, and the randomization scheme will be designed to ensure that one subject will receive VT-1598 and the other will receive placebo. The dosing of the next 6 subjects for each subsequent fasting dose escalation group (Cohorts 2-5) will not be initiated until at least 3 days have passed and none of the predefined objective halting criteria for sentinels have been met. The remaining 6 subjects in the cohort will then be admitted and dosed.

Pending subject availability, the fed group (Cohort 6) will be comprised of the same subjects as Cohort 3, however they will not be randomized; the same 6 subjects who received VT-1598 and the 2 subjects who received placebo in Cohort 3 will receive the same treatment in Cohort 6. Cohort 6 subjects are dosed at the same level as Cohort 3 (160 mg) following a high-fat, high-calorie meal. Cohort 6 will not include sentinel subjects. Providing no halting criteria is met, Cohort 3 subjects may proceed to Cohort 6 and be dosed prior to the Safety Monitoring Committee meeting but no less than 60 days following their first dose (wash-out period). Subjects who complete Cohort 3 but are not eligible or withdraw prior to dosing for Cohort 6 will be replaced. The Cohort 6 replacement subjects will receive the same treatment as assigned to the Cohort 3 subject they are replacing.

Safety data through Day 7 for every subject in the current cohort will be available prior to making dose escalation decisions. Dose escalation may occur if none of the predefined objective halting criteria for dose escalation have been met. The duration of individual subject participation, from start of screening until final follow-up, will be up to 50 days (Note: Subjects who participate in cohort 3/6, their participation will exceed 50 days). Screening for eligibility will occur from Day -28 to Day -2. Subjects will be admitted to the CRU on the day before dosing (Day -1). Subjects will be administered VT-1598 or placebo on Day 1 and will remain in the CRU for at least 72 hours post-dose (Day 4) for safety monitoring and PK assessments. Subjects will return to the CRU on Days 7, 14, and 21 for safety monitoring and PK assessments.

The study duration from the start of screening until last follow-up of the last dose cohort will be approximately 6 months.

### 3.1.3 Number of Subjects

A sufficient number of subjects will be screened to enroll up to 48 subjects into the study in 6 cohorts, and each cohort contains 8 subjects (6 for active drug VT-1598 and 2 for placebo). Cohort 6 (fed Cohort).Subjects will be enrolled from 1 site in the US.

### 3.1.4 Rationale for Starting Dose

The proposed clinical start dose is based on the FDA guidance document “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Healthy Volunteers”, July 2005. The rat was determined to be the most sensitive species in 28-day toxicity studies. The NOAEL for this study was 100 mg/kg/day (dose expressed as the free base equivalent throughout the document). Using 100 mg/kg/day as the NOAEL in rat, the human equivalent dose calculation of 40 mg for a starting dose incorporates a 28-fold safety margin.

### 3.1.5 Dose Escalations

The initial cohort of 8 subjects will be administered 40 mg of VT-1598 (6 subjects) or placebo (2 subjects) as a single oral dose. Two sentinel subjects will be included in cohorts 1-5 as described in Section 3.1.2 Dosing Scheme and Duration of Study.

Dose escalation to each successive cohort will occur if none of the predefined dose escalation halting criterion is met (for all subjects through Day 7). This will be communicated through the following process:

1. A halting criteria report will be provided by the SDCC to the study
2. If based on the data entered in EDC, none of the halting criteria are met, then the email from the SDCC will be provided and the Sponsor will notify the study team that the next cohort can be opened for enrollment.

3. If any of the halting criteria are met, the SDCC will provide the dose escalation report and an ad-hoc SMC meeting will be convened to seek recommendation from the SMC.

There will be a scheduled SMC data review meeting prior to start of Cohort 5.

The nominal dose-escalation scheme will be 40, 80, 160, 320 and 640 mg or matching placebo administered in a fasting state. The effect of a high-fat, high-calorie meal on the PK of VT-1598 is planned in an additional cohort that will be dosed at 160 mg. The fed cohort will be dosed at 160 mg, after the 320 mg fasted cohort has been dosed. This provides additional safety data to cover the possibility that the bioavailability of VT-1598 is increased in the presence of food. The highest proposed dose in this study is 640 mg, which is 53% of the body surface area equivalent of the NOAEL in the most sensitive species.

In order to efficiently identify the optimal therapeutic doses for use in future clinical trials, a flexible scheme of dose escalation, (based on ongoing study data) will be used that allows intermediate doses higher or lower than the planned doses (40, 80, 160, 320 and 640 mg), upon protocol amendment and with IRB approval. However, no cohort will be dosed higher than the 640 mg free base equivalent.

See Figure 1 Schematic of Study Design.

## 3.2 Study Objectives

### 3.2.1 Primary

- To determine the safety of single-ascending oral doses of VT-1598 in healthy adult subjects in a fasted state;
- To determine the safety of single oral dose of VT-1598 in healthy adult subjects in a fed state.

### 3.2.2 Secondary

- To determine the pharmacokinetic (PK) profile in plasma and urine of VT-1598 and its primary metabolite, VT-11134, in healthy adult subjects;
- To determine the effect of a high-fat, high-calorie meal on the PK profile of VT-1598 and VT-11134 when a single oral dose of VT-1598 is given.

### 3.2.3 Study Endpoints or Outcome Measures

### 3.2.4 Primary Outcome Measures

- Safety will be evaluated for single-ascending fasting oral doses of VT-1598. Safety will be assessed by adverse events from start of dosing to Day 21, clinical laboratory tests at baseline and from Day 4 to Day 21, ECGs at baseline and on Day 4 and Day 21, and vital signs at baseline and from Day 1 to Day 21;

- Safety will be evaluated for single oral dose of VT-1598 administered after being fed a high-fat, high calorie meal. Safety will be assessed by adverse effects from start of dosing to Day 21, clinical laboratory tests at baseline and from Day 4 to Day 21, ECGs at baseline and vital signs at baseline and from Day 1 to Day 21.

### 3.2.5 Secondary Outcome Measures

- PK profiles of VT-1598 and its primary metabolite, VT-11134, will be assessed by measurement of VT-1598 and VT-11134 levels in both plasma and urine after VT-1598 administration in each cohort, when fasting. Plasma for PK analysis will be collected at planned time points up to 480 hours post-dose and urine for PK analysis will be collected in planned intervals up to 72 hours post-dose;

- PK profiles of VT-1598 and its primary metabolite, VT-11134, will be assessed by measurement of VT-1598 and VT-11134 levels in both plasma and urine after administration of VT-1598 following consumption of a high-fat, high calorie meal. Plasma for PK analysis will be collected at planned time points up to 480 hours post-dose and urine for PK analysis will be collected in planned intervals up to 72 hours post-dose.

# 4 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

## 4.1 Study Product Description

VT-1598 is a novel oral agent for the treatment of fungal infections. VT-1598 in its physical form is a lightly colored solid with a molecular formula of $C_{31}H_{20}F_4N_6O_2$ and a molecular weight of 584.5 g/mol.

### 4.1.1 Formulation, Packaging, and Labeling

VT-1598 will be supplied as 40 mg and 80 mg tablets. Each tablet is formulated as a spray-dried dispersion with standard excipients including Eudragit® L100, microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and FD&C Yellow #5 aluminum lake (United States Pharmacopeia).

Placebo will be supplied as matching tablets (to 40 mg and 80 mg VT-1598 tablets) containing the inactive components of VT-1598. In order to maintain the blind, the placebo tablets, are the same size, weight, and color as the VT-1598 tablets.

VT-1598 and placebo tablets will be packaged in identical white opaque, high density polyethylene (HDPE) bottles containing 30 tablets. Each container will also be labeled in compliance with applicable regulatory requirement, including the FDA-required cautionary statement “Caution: New Drug-Limited by Federal (or United States) Law to Investigational Use”.

### 4.1.2 Product Storage and Stability

VT-1598 must be stored in a secure location at a controlled room temperature of 15°C to 25°C (59°F to 77°F) and protected from light and moisture.

Matching placebo tablets must be stored in a secure location at a controlled room temperature of 15°C to 25°C (59°F to 77°F) and protected from light and moisture.

## 4.2 Acquisition/Distribution

VT-1598 will be provided by NQP 1598, Ltd. or its designee.

Matching placebo will be provided by NQP 1598, Ltd, or its designee.

Study products (VT-1598 and placebo) will be distributed through the DMID Clinical Material Services (CMS, Fisher BioServices) and shipped from the DMID CMS to the ICON CRU site upon request and approval by DMID.

## 4.3 Dosage/Regimen, Preparation, Dispensing and Administration of Study Intervention/Investigational Product

Only subjects enrolled in the study may receive study products, and only authorized site staff may supply or administer study products. The unblinded pharmacist or designee will prepare the study product.

Subjects will take the study product on Day 1 as follows:

Designated tablets of VT-1598 or placebo are taken in the morning by mouth after an overnight fast of at least 8 hours. The dose given will be the dose designated for that dosage cohort (see Table 1). In the nominal dose escalation, subjects will be administered the study product and remain in a fasting state for 4 hours post-dose. In the planned additional cohort to evaluate the impact of a meal on PK at a previously evaluated dose level, the subjects will fast overnight for at least 8 hours prior to the start of a high-fat, high-calorie meal which will be entirely consumed in less than 30 minutes. The dose of study product will be administered 30 minutes after the start of the meal. The dates and times of study product administration and meal start, and end times will be recorded in the subjects' electronic Case Report Form (eCRF). Any subject who does not finish the meal within 30 minutes will not be dosed and will be replaced.

Water consumption for all cohorts will be restricted from one hour prior to dosing to one hour after dosing. Subjects will consume approximately 240 mL of ambient temperature water with the dose of study product. An additional 120 mL of water, if needed by the subject to swallow multiple tablets, will be documented in the eCRF. Each subject dose is to occur with 5 minutes. Any deviations from the dosage schedule will be recorded.

The planned final doses of VT-1598 or placebo for subjects in each cohort are described in Table 1. Details regarding planned dosing are included in Section 3.1.2 Dosing Scheme and Duration of Study and in the MOP.

## 4.4 Accountability Procedures for the Study Intervention/Investigational Product(s)

The United States Food and Drug Administration (FDA) requires accounting for the disposition of all investigational products. The Site Principal Investigator (PI) is responsible for ensuring that a current record of product disposition is maintained, and product is dispensed only at an official study site by authorized personnel as required by applicable regulations and guidelines. The Site PI will delegate to the Research Pharmacist responsibility for study product accountability.

The Research Pharmacist (or designee) will keep a record of the dates and amounts of study product received (including packing slips), the amount dispensed to study subjects, any amount destroyed, the amount unused, and temperature and storage conditions. Product accountability will be recorded by the Research Pharmacist on a Product Disposition Record or equivalent document with a separate accountability record for study product and placebo. The pharmacy records must be available for inspection by the DMID monitoring contractors and is subject to inspection by a regulatory agency (e.g., FDA) at any time. An assigned Study Monitor will review the pharmacy records.

Unused investigational product will be stored in the Investigational Pharmacy until clinical trial accountability is completed. At study termination, all unused investigational product will be handled in accordance with the MOP following complete drug accountability and monitoring. Unused placebo will be handled in accordance with the MOP.

# 5 SELECTION OF SUBJECTS AND STUDY ENROLLMENT AND WITHDRAWAL

Upon arrival to the clinic, subjects are checked for eligibility through the Verified Clinical Trials (VCT) process (after signing the IRB - approved VCT consent) and are then given the IRB approved consent and HIPPA forms. After a presentation of the consent and when subjects indicate their desire to proceed, the subject is brought to a private room and given an opportunity to ask questions of the licensed nurse or MD delegated to perform consenting. After signing consent, protocol procedures are executed.

Study retention strategies will include education and explanation of the study schedule and procedures during Screening and Enrollment visits. In addition, reimbursements will be disbursed at specific time points during the study with the amount contingent on completing study procedures. Participating subjects will be reminded of visits ahead of time, and study staff will contact subjects who miss appointments to encourage them to return for completion of safety evaluations.

## 5.1 Eligibility Criteria

### 5.1.1 Subject Inclusion Criteria

Subjects may be entered in the study only if all the following criteria are met:

1. Willing and able to provide written informed consent and authorization for use of protected health information;
2. Willing and able to comply with protocol requirements, instructions, and protocol-stated restrictions (including confinement to the CRU) and is likely to complete the study as planned;
3. Male or female subjects, 18-45 years of age (inclusive);
4. Subject is in good health to be safely enrolled in this protocol as determined by medical history and physical exam.
5. BMI of 18-35 kg/m$^2$, inclusive, and minimum weight of 50 kg;
6. If a female participant is of childbearing potential*, she must use a highly effective contraceptive method† from 30 days before enrollment through the 3 months after dosing.

*A woman is considered of childbearing potential unless post-menopausal (subject is at least 50 years old and has history of ≥2 years without menses without other known or suspected cause and has a FSH level >40 IU/L), or permanently surgically sterilized.

†A highly effective contraceptive method includes surgical sterilization methods such as tubal ligation, bilateral oophorectomy, salpingectomy, hysterectomy, or successful tubal obliteration (e.g., Essure®) with documented radiological confirmation test at least 90 days after the procedure, or long-acting reversible contraception (progestin-releasing subdermal implants, copper intrauterine devices (IUDs), levonorgesterel-releasing IUDs.

7. Males* having sexual intercourse with women of childbearing potential must agree to consistent use of condoms from study product administration through 3 months after dosing**;
   * including vasectomized men
   ** and must also agree to not donate sperm during this same time period
8. Subject has adequate venous access for blood collection.

### 5.1.2 Subject Exclusion Criteria

1. has a chronic condition that may increase risk to subject or interfere with endpoint assessment (e.g., liver disease, kidney disease, immunodeficiency).
2. Chronic condition diagnosed within 90 days of the screening visit
3. Unstable chronic disease* within 6 months of the screening visit
   *as defined by need for medical intervention that lead to a change in medications and/or required hospitalization, surgery/procedure, or ED/urgent care visit
4. History of psychiatric condition that has required hospitalization in the last 5 years or patient is considered unstable by study investigator
5. Any condition that in the opinion of the Investigator could significantly impact drug absorption, distribution, or elimination;
6. Any out of normal range laboratory value* at screening or enrollment (Section 8.1 and Appendix B).

   *A laboratory value that is Grade 1 (with the exception of ALT, AST, Total bilirubin, hemoglobin or serum creatinine) will be allowed if not considered to be clinically significant by the investigator.
7. Abnormal ECGs. See Section 7.1 Clinical Evaluations for exceptions;
8. Electrocardiographic QTcF interval >430 msec for males and >450 msec for females at Screening;
9. Positive test for antibodies to HIV-1, HIV-2, HBsAg, or HCV;
10. Positive urine drug test. The drugs that will be screened for includes amphetamines, barbiturates , cocaine, opiates, cannabinoids, phencyclidine, and benzodiazepines.

11. Female subject of childbearing potential who is pregnant*, lactating, or planning to become pregnant during the study period or 3 months after the final dose of study product;

    *Having a positive serum pregnancy test at the Screening Visit or any other specified time point prior to the dose of study product.

12. Received any study product in a clinical trial within 30 days prior to Screening;
13. Admitted or documented illicit drug use or alcohol abuse within 6 months prior to Screening or during their participation in the trial;
14. Consumed alcohol within 72 hours of Day -1, until after the visit to the CRU on Day 14 or have a positive alcohol test at Screening or on admission to the CRU;
15. Tobacco* use within 90 days prior to the Screening Visit or while a subject is enrolled in the study OR A positive urine drug test for cotinine;

    *Tobacco use includes vaping, smoking tobacco, the use of snuff and chewing tobacco, and other nicotine or nicotine- containing products.

16. Use of prescription drugs within 14 days prior to the dose of study product with the exception of hormonal contraceptives, which are permitted throughout the study;
17. Received any non-prescription medications, vitamins, or dietary supplements* within 7 days of dosing, unless prior approval is granted by both the Investigator and the Sponsor;

    *Excluded from this list is intermittent use of acetaminophen at doses of ≤2 g/day or ibuprofen ≤1200 mg/day. Herbal supplements must be discontinued 7 days prior to the dose of the study product.

18. History of intolerance or hypersensitivity to azole antifungals;
19. Blood donation or other significant blood loss within 60 days of screening and for the duration of the study;
20. Inability or difficulty swallowing whole capsules/tablets and/or multiple capsules/tablets;
21. Consumption of beverages and foods containing caffeine for 24 hours prior to Day -1 until discharge from the CRU on Day 4;
22. Consumption of grapefruit, or juices containing grapefruit or Seville oranges within 7 days prior to the scheduled dose of the study product until after the visit to the CRU on Day 14;
23. Subject has plans to enroll or is already enrolled in another clinical trial that could interfere with safety assessment of the investigational product at any time during the study period*;

    *Includes trials that have a study intervention such as a drug, biologic, or device

24. Having dietary restrictions that would preclude the subject from participating in either fed or fasting cohorts;
25. Having sensitivity or allergy to aspirin.

## 5.2 Withdrawal from the Study, Discontinuation of Study Product, or Study Termination

### 5.2.1 Withdrawal from the Study or Discontinuation of the Study Product

Subjects may voluntarily withdraw their consent for study participation at any time without penalty or loss of benefits to which they are otherwise entitled.

An investigator may also withdraw a subject from receiving the study product for any reason. Follow-up safety evaluations will be conducted, if the subject agrees. If a subject withdraws or is withdrawn prior to completion of the study, the reason for this decision must be recorded in the case report forms (CRFs). If a subject withdraws from the study, he/she may request destruction of any samples taken, and the Investigator must document this in the site study records and communicate this request to the Sponsor. However, the investigator will inform the subject that already collected data will be retained and analyzed even if the subject withdraws from this study.

The reasons for withdrawal might include, but are not limited to the following:

- Subject withdraws consent;
- subject becomes noncompliant;
- medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator might compromise the safety of the subject, interfere with the subject's successful completion of this study, or interfere with the evaluation of responses;
- subject lost to follow-up;
- request of primary care provider;
- at the request of the IRB/IEC, FDA, or NIAID;
- the subject’s well-being, based on the opinion of the investigator.

The investigator will inform the subject that already collected data will be retained and analyzed even if the subject withdraws from this study. Subjects will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care. If the subject has received the study drug, data collected for withdrawn subjects will be evaluated for safety and PK.

In all cases of withdrawal, the reason for withdrawal will be recorded. Subjects who receive any amount of study product and who are discontinued from the study will be asked to complete all Day 21 safety assessments including follow-up of any AEs prior to termination from the study.

**Lost to Follow Up**

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible;
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study;
- In cases where the subject is deemed 'lost to follow-up', the Investigator or designee must make every effort to regain contact with the subject (e.g., multiple telephone calls on various dates/time, a certified letter to the subject's last known mailing address, or equivalent methods). These contact attempts should be documented in the subject's medical record.
- should the subject continue to be unreachable, only then will they be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

**Early Withdrawal**

In the event that a subject is prematurely discontinued from the study after receiving any amount of the study product but prior to discharge from the CRU, the Unscheduled Visit (Section 6.7 Unscheduled Study Visits) procedures should be performed prior to discharging the subject from the CRU. If a subject receives any amount of study product and is prematurely discontinued from the study after discharge from the CRU, but prior to the Day 21/End-of-Study visit, an attempt should be made to have the subject return to the CRU to perform the Unscheduled Visit (Section 6.7 Unscheduled Study Visits)

### 5.2.2 Subject Replacement

Subjects who have not received any amount of study product and discontinue from participation may be replaced, as well as subjects who experience emesis within the first 12 hours following dosing.

Subjects who complete Cohort 3 but are not eligible or withdraw prior to dosing for Cohort 6 will be replaced. The Cohort 6 replacement subjects will receive the same treatment as assigned to the Cohort 3 subject they are replacing.

Additionally, the first subject in each cohort to discontinue from participation due to loss to follow up, after receiving any amount of study product, is not replaced; if more than one subject in any cohort discontinues participation, these subjects will be replaced. Replacement of any subject is at the discretion of the Investigator in consultation with the Sponsor. Replacement subjects should be allocated to the same treatment as the subject they replaced.

### 5.2.3 Study Termination

As DMID, FDA and NQP 1598, Ltd. may terminate the study in the interest of subject safety and welfare. In addition, DMID reserves the right to terminate the study at any time for any other reason. If DMID terminates the study, the PI, IRB, SMC, ISM, designated contractors of DMID, ,NQP 1598, Ltd., and the FDA will be informed, activities will be closed, and a study report will be prepared.

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study subjects and assure appropriate follow-up for the subjects. The investigator will provide a detailed written explanation of the termination to the IRB.

# 6 STUDY PROCEDURES

## 6.1 Screening

### 6.1.1 Day -28 to Day -2 (Screening)

Subjects will be screened within 28 days prior to study product administration. A sufficient number of subjects will be screened to enroll 48 subjects in the study. After the subject has signed the IRB-approved ICF, the following evaluations will be performed as indicated in the Schedule of Study Procedures and Evaluations (Appendix A VT-1598 Schedule of Study Procedures and Evaluations) and as detailed in Section 7 Description of Clinical and Laboratory Evaluations:

- Demographics (date of birth, sex, and ethnic origin);
- complete medical/medication history to include all past illnesses, alcohol and tobacco/vaping, illicit drug use history (previous 6 months), and all other drugs/medications taken, including non- prescription and herbal products,(previous 30 days) prior to screening procedures; complete physical examination including vital signs (heart rate, blood pressure, oral temperature and respiration rate, taken after being at rest for at least 5 minutes), height, and weight (for BMI calculation). If abnormal, these measurements may be repeated once; within 15 minutes of the original assessment;
- obtain 12-lead ECGs after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period) to assess heart rate, rhythm, and interval information such as RR, PR, QRS, QT, QTc and QTcF;
- obtain blood samples for fasting (at least 8 hours) clinical chemistry, hematology, coagulation tests, serum pregnancy test [if female of childbearing potential], FSH [if female and post-menopausal], and immunology screen (serum HIV, HBsAg, and HCV antibodies);
- obtain urine sample for urinalysis, drugs of abuse and cotinine;
- obtain urine test for alcohol;
- review of Inclusion/Exclusion criteria to determine eligibility for entry into the study;
- consult about birth control methods, permitted/non-permitted medications, non-medications, dietary and activity restrictions.

## 6.2 Enrollment

### 6.2.1 Day -1 (Admission to Clinic; approximately 24 hours prior to dosing)

Eligible subjects will return to the CRU on Day -1, the day prior to dosing, will undergo baseline evaluations as indicated in the Schedule of Study Procedures and Evaluations (Appendix A VT-1598 Schedule of Study Procedures and Evaluations ) and as detailed in Section 7, Description of Clinical and Laboratory Evaluations, Study Procedures/Evaluations:

- Review inclusion/exclusion criteria;
- confirm that subject adhered to dietary restrictions (no food/beverages containing alcohol for previous 72 hours or caffeine for the previous 24 hours; no grapefruit, grapefruit juice, or juices containing grapefruit, or Seville oranges for previous 7 days); see Section 5.2.1);
- review and record prior concomitant medications and non-pharmacologic treatments/procedures history since Screening;
- review any change in medical history since Screening;
- complete a targeted physical examination (general appearance, heart, lungs, skin, and abdomen);
- obtain resting vital signs (heart rate, blood pressure, oral temperature and respiration rate, taken after being at rest for at least 5 minutes), and weight, BMI. If abnormal, these measurements may be repeated once, within 15 minutes of the original assessment;
- obtain blood samples for baseline fasting (at least 8 hours) clinical chemistry, hematology, coagulation tests, serum pregnancy test [if female of childbearing potential]);
- obtain urine sample for urinalysis, drugs of abuse (amphetamines, barbiturates, cocaine, opiates, cannabinoids, phencyclidine, and benzodiazepines) and cotinine;
- obtain urine test for alcohol;
- if screening criteria are satisfied, admit subject to CRU. If screening criteria are not satisfied, the subject is then entered as a screening failure into the AdvantageEDC$^{SM}$ (Electronic Data Capture System, Emmes).

## 6.3 Treatment Period

### 6.3.1 Day 1 – Inpatient CRU

Study product will be administered on the morning of Day 1. Subjects are inpatients in the CRU and will undergo procedures as indicated in the Schedule of Study Procedures and Evaluations (Appendix A VT-1598 Schedule of Study Procedures and Evaluations) and as detailed in, Section 7 Description of Clinical and Laboratory Evaluations, listed below:

- Review and record any concomitant medications and non-pharmacologic treatments/procedures since admission to the CRU;
- confirm that subject adhered to fasting requirements of at least 8 hours before the dosing (for fasted cohorts; fed cohort will receive dose 30 minutes after starting a high-fat, high calorie meal);
- obtain baseline urine sample for PK analysis (t=0), to be taken any time within 6 hours prior to dose;
- obtain baseline blood sample for PK analysis (t=0), to be taken a time within 60 minutes prior to the dose (for fasted cohorts; within 30 minutes prior to the start of the pre-dose meal for the fed cohort);
- targeted physical examination (general appearance, heart, lungs, skin and abdomen) including pre-dose resting vital signs (heart rate, blood pressure, oral temperature and respiration rate, taken after being at rest for at least 5 minutes and anytime within 60 minutes prior to dosing) (for fasted cohorts; within 30 minutes prior to the start of the pre-dose meal for the fed cohort);. If abnormal, these measurements may be repeated once within 15 minutes of the original assessment;
- obtain 12-lead ECGs after at least 5 minutes in the supine position (taken pre-dose any time within 60 minutes prior to dosing for fasting cohorts and any time within 60 minutes prior to dosing for the fed cohort); triplicate readings, at least 1 minute apart within a 15-minute period);
- administer study product. For the nominal dose escalations (Cohorts 1-5), study drug will be administered in a fasting state and subjects will remain fasted for at least 4 hours post-dose. In Cohort 6, the planned additional cohort to evaluate the effect of a meal on PK, the subjects will be fed a high-fat, high-calorie meal which will be entirely consumed in less

than 30 minutes. The dose of the study product will be administered 30 minutes after the start of the meal.

Following the administration of study product, the following procedures will be performed. PK samples (blood and urine) will be obtained (after the ECGs and vital signs whenever possible if the times coincide with one another):

- Obtain blood samples for PK analysis at 0.5 h (±5 min), 1 h (±10 min), 1.5 h (±10 min), 2 h (±10 min), 3 h (±10 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 10 h (±10 min), 12 h (±10 min), and 14 h (±10 min) hours post-dose;
- collect urine samples for PK analysis in the following intervals following study product administration on Day 1: 0-6, 6-12, 12-24, hours post-dose;
- obtain post-dose (6 h [±10 min]) blood sample for possible use in future research studies, if applicable. See Section 9.3 Consent for Future Use of Stored Specimens and Data. Consent for Future Use of Stored Specimens and Data and Schedule of Procedures (Appendix A VT-1598 Schedule of Study Procedures and Evaluations);
- 12-lead ECGs obtained after at least 5 minutes in the supine position; taken post-dose [4 hours (+/-10 minutes)]; triplicate readings, at least 1 minute apart within a 15-minute period);
- obtain resting vital signs (heart rate, blood pressure, oral temperature and respiration rate, taken after being at rest for at least 5 minutes) at 1 h (±10 min), 2 h (±10 min), 4 h (±10 min), and 8 h (±10 min), post-dose. If abnormal, these measurements may be repeated once, within 15 minutes of the original assessment;
- collect and record adverse events (AEs) and concomitant medications.

### 6.3.1 Day 2 – Inpatient CRU

Subjects are inpatients in the CRU and will undergo procedures as indicated in the Schedule of Study Procedures and Evaluations (Appendix A VT-1598 Schedule of Study Procedures and Evaluations) and as detailed in Section 7 Description of Clinical and Laboratory Evaluations, Study Procedures/Evaluations: listed below:

- Review and record any concomitant medications and non-pharmacologic treatments/procedures since Day 1;
- obtain blood samples for PK analysis at 24 h (±30 min), and 36 h (±30 min) post-dose;

- collect urine samples for PK analysis in the following intervals following study product administration on Day 1: 24-36, 36-48 hours post-dose;
- obtain resting vital signs (heart rate, blood pressure, oral temperature and respiration rate, taken after being at rest for at least 5 minutes) at 24 h (±30 min), post-dose. If abnormal, these measurements may be repeated once, within 15 minutes of the original assessment;
- collect and record adverse events (AEs).

### 6.3.2 Day 3 – Inpatient CRU

Subjects are inpatients in the CRU and will undergo procedures as indicated in the Schedule of Study Procedures and Evaluations (Appendix A VT-1598 Schedule of Study Procedures and Evaluations) and as detailed in Section 7 Description of Clinical and Laboratory Evaluations. Study Procedures/Evaluations: listed below:

- Review and record any concomitant medications and non-pharmacologic treatments/procedures since Day 2;
- obtain blood sample for PK analysis at 48 h (±30 min) and 60 h (± 30 min) post-dose;
- collect urine sample for PK analysis in the following interval following study product administration on Day 1: 48-60 hours post-dose;
- obtain resting vital signs (heart rate, blood pressure, oral temperature and respiration rate, taken after being at rest for at least 5 minutes) at 48 h (±30 min), post-dose. If abnormal, these measurements may be repeated once, within 15 minutes of the original assessment;
- collect and record adverse events (AEs).

### 6.3.3 Day 4 – Discharge from CRU

Subjects are inpatients in the CRU and will undergo procedures as indicated in the Schedule of Study Procedures and Evaluations (Appendix A VT-1598 Schedule of Study Procedures and Evaluations) and as detailed in Section 7 Description of Clinical and Laboratory Evaluations. Study Procedures/Evaluations: listed below, prior to discharge from CRU:

- Review and record any concomitant medications and non-pharmacologic treatments/procedures since Day 3;
- obtain blood sample for PK analysis at 72 h (±30 min) post-dose;

- collect urine sample for PK analysis in the following interval following study product administration on Day 1: 60-72 hours post-dose;
- obtain blood samples for fasting (at least 8 hours and prior to 10 AM ) clinical chemistry, hematology, and coagulation tests;
- obtain urine sample for urinalysis;
- targeted physical examination (general appearance, heart, lungs, skin and abdomen) including resting vital signs (heart rate, blood pressure, oral temperature and respiration rate, taken at 72 hours (±30 min) post-dose and after being at rest for at least 5 minutes). If abnormal, these measurements may be repeated once, within 15 minutes of the original assessment;
- 12-lead ECGs obtained after at least 5 minutes in the supine position; taken at 72 hours (±30 min) post-dose; triplicate readings, at least 1 minute apart within a 15-minute period;
- collect and record adverse events (AEs);
- review post-discharge instructions (including birth control methods, permitted/non-permitted medications, non-medications, dietary and activity restrictions), and schedule follow-up visits;
- discharge from CRU.

## 6.4 Follow-up

Subjects will return to the CRU within the window indicated for each follow-up timepoint and will undergo procedures as indicated in the Schedule of Study Procedures and Evaluations (Appendix A VT-1598 Schedule of Study Procedures and Evaluations) and as detailed in Section 7 Description of Clinical and Laboratory Evaluations. Study Procedures/Evaluations: listed below:

### 6.4.1 Day 7 ± 1

- Review and record any concomitant medications and non-pharmacologic treatments/procedures since Day 4;
- review any change in medical history since Day 4;

- obtain resting vital signs (heart rate, blood pressure, oral temperature and respiration rate, taken after being at rest for at least 5 minutes). If abnormal, these measurements may be repeated once, within 15 minutes of the original assessment;
- obtain blood sample for PK analysis at 144 (±24) hours post-dose;
- obtain blood samples for fasting (at least 8 hours) clinical chemistry, hematology, and coagulation tests;
- obtain urine sample for urinalysis;
- collect and record adverse events (AEs);
- review post-discharge instructions (including birth control methods, permitted/non-permitted medications, non-medications, dietary and activity restrictions);
- subjects are released from the CRU after all assessments and procedures are completed and instructed to return for further follow-up evaluation on Day 14.

### 6.4.2 Day 14± 1

- Review and record any concomitant medications and non-pharmacologic treatments/procedures since Day 7;
- review any change in medical history since Day 7;
- obtain resting vital signs (heart rate, blood pressure, oral temperature and respiration rate, taken after being at rest for at least 5 minutes). If abnormal, these measurements may be repeated once, within 15 minutes of the original assessment;
- obtain blood sample for PK analysis at 312 (±24) hours post-dose;
- obtain blood samples for fasting (at least 8 hours) clinical chemistry, hematology, and coagulation tests;
- obtain urine sample for urinalysis;
- collect and record adverse events (AEs);

- review post-discharge instructions (including birth control methods, permitted/non-permitted medications, non-medications, dietary and activity restrictions);
- subjects are released from the CRU after all assessments and procedures are completed and instructed to return for final study visit on Day 21.

## 6.5 Final Study Visit

### 6.5.1 Day 21 ± 2

- Review and record any concomitant medications and non-pharmacologic treatments/procedures since Day 14;
- review any change in medical history since Day 14;
- obtain 12-lead ECGs after at least 5 minutes in the supine position (triplicate readings, at least 1 minute apart within a 15-minute period) to assess heart rate, rhythm, and interval information such as RR, PR, QRS, QT, QTc and QTcF;
- obtain blood sample for PK analysis at 480 (±48) hours post-dose;
- obtain blood samples for fasting (at least 8 hours) clinical chemistry, hematology, coagulation and serum pregnancy test [if female of childbearing potential] tests;
- obtain urine sample for urinalysis;
- targeted physical examination (general appearance, heart, lungs, skin and abdomen) including resting vital signs (heart rate, blood pressure, oral temperature and respiration rate, taken after being at rest for at least 5 minutes). If abnormal, these measurements may be repeated once, within 15 minutes of the original assessment;
- collect and record adverse events (AEs);
- review post-study period instructions (including use of contraceptives and instructions to report pregnancy, should it occur, up to 3 months following dose of study drug).

## 6.6 Early Termination Visit

The clinic will make every effort to perform all assessments outlined for the Final Study Visit (Day 21±2) if a subject is terminated prematurely from the study. All information collected will be documented in the study records including eCRF.

## 6.7 Unscheduled Study Visits

Subjects will return to the CRU at the direction of the site investigator for follow-up and data from unscheduled visits or procedures (if any) will be captured in the EDC system. Safety assessments including the following onsite evaluations: AE, PE, and any other study procedures deemed necessary by the PI will be obtained.

Subjects returning to the CRU for Unscheduled visit(s) may undergo procedures as indicated in the Schedule of Study Procedures and Evaluations (Appendix A VT-1598 Schedule of Study Procedures and Evaluations) and as detailed in Section 7 Description of Clinical and Laboratory Evaluations Study, Procedures/Evaluations: listed below:

- Review and record any concomitant medications and non-pharmacologic treatments/procedures since last visit;
- standard 12-lead ECG (recording in triplicates) to assess heart rate, rhythm, and interval information such as PR, QRS, QT, QTc and QTcF, obtained after at least 5 minutes in the supine position;
- obtain blood samples for clinical chemistry, hematology, and coagulation tests;
- obtain blood sample for PK analysis;
- obtain urine sample for urinalysis.
- targeted physical examination (general appearance, heart, lungs, skin and abdomen; additional evaluation will be targeted to the suspected organ system described in any AE.) including resting vital signs (heart rate, blood pressure, oral temperature and respiration rate, taken after being at rest for at least 5 minutes. If abnormal, these measurements may be repeated once, within 15 minutes of the original assessment;
- collect and record adverse events (AEs).

## 6.8 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific MOP requirements. The noncompliance may be either on the part of the subject, the site principal investigator, or the site personnel. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the site principal investigator and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the SDCC protocol deviation reporting procedures.

All protocol deviations, as defined above, must be addressed in study subject data collection forms. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart. Protocol deviations must be sent to the local IRB per their guidelines. The site principal investigator and personnel are responsible for knowing and adhering to their IRB requirements.

# 7 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

## 7.1 Clinical Evaluations

### 7.1.1 Safety Tests and Assessments

Safety assessments will include attention to relevant changes in the following parameters, which are identified as occurring after the start of study product, regardless of whether the change is in an examination finding, test result, or symptom(s) reported by a subject, and regardless of presumed relationship to VT-1598.

**Height, Weight, BMI**

Height and/or body weight will be collected at times specified in the Schedule of Assessments and Procedures Appendix A VT-1598 Schedule of Study Procedures and Evaluations. BMI is calculated from height at Screening and weight at time of assessment.

**Vital Signs**

Vital signs (resting) to include body temperature, heart rate (pulse), breathing rate, and blood pressure will be obtained at times specified in the Schedule of Assessments and Procedures Appendix A VT-1598 Schedule of Study Procedures and Evaluations. Vital signs should be taken after at least 5 minutes at rest. If abnormal, these measurements may be repeated once, within 15 minutes of the original assessment.

The pre-dose Day 1 vital signs measurements should be taken any time within 60 minutes prior to dosing (within 30 minutes prior to the start of the pre-dose meal for the fed cohort). Day 1 post-dose vital signs measurements should be taken within ± 10 minutes of the nominal timepoint. All other vital signs measurements during the inpatient stay should be taken within ± 30 minutes of the nominal time point. For outpatient visits, vital signs measurements should be taken within the visit window.

**Physical Exam**

A complete physical examination will include review of resting vital signs (taken after being at rest for at least 5 minutes); general appearance; head, eyes, ears, nose, and throat; neck; chest and lungs; cardiovascular system, abdomen, musculoskeletal system, lymph nodes, extremities/skin, and neurological system will be performed at Screening.

A targeted physical examination (general appearance, heart, lungs, skin and abdomen) will include review of the resting vital signs which will be taken at 72 hours (±30 min) post-dose and

after being at rest for at least 5 minutes. Additional evaluation will be targeted to the suspected organ system described in any AE. Targeted physical examinations will be performed at times specified in the Schedule Assessments and Procedures Appendix A VT-1598 Schedule of Study Procedures and Evaluations .

**Electrocardiograms**

Standard 12-lead ECGs to assess heart rate, rhythm, and interval information such as PR, QRS, QT, and QTc will be obtained at times specified in the Schedule of Assessments and Procedures Appendix A VT-1598 Schedule of Study Procedures and Evaluations. The QT interval will be corrected using the Fridericia formula (QTcF).

Electrocardiograms should be taken after at least 5 minutes in the supine position. The pre-dose Day 1 ECGs should be taken within 60 minutes prior to dosing (within 60 minutes prior to dosing for the fed cohort); the post-dose ECG on Day 1 should be taken at 4 hours post-dose ( ± 30 minutes). The Day 4 ECG should be taken at 72 hours (± 30 minutes) post-dose. For the Day 21 outpatient visit, the ECG should be taken within the visit window.

Subjects will be placed in a supine position for at least 5 minutes prior to recording an ECG. Triplicate 12- lead ECG readings will be collected at scheduled times as shown in Appendix A VT-1598 Schedule of Study Procedures and Evaluations . The screening ECG will be used by the PI to determine subject's eligibility for enrollment. The Day 1 pre-dose ECG will be reviewed to determine if subjects are safe and appropriate to dose and will be used to determine baseline for waveform and QTc.

All ECGs will be reviewed by the PI or designee. ECGs with the following readings will be considered acceptable for study and will not be considered abnormal for study purposes unless the PI or physician designee believes they represent a new medical condition when compared to baseline ECGs. In such cases an AE will be documented, and the subject will be followed for safety evaluations as appropriate. The following pre-existing conditions identified at enrollment will not be considered adverse events and will be documented on the Medical History eCRF:

- Sinus bradycardia;
- Sinus arrhythmia.

Subjects without a history of prolonged QTc and an abnormal baseline QTcF interval (not meeting exclusion criteria) should undergo repeat ECG assessment within screening period prior to randomization to confirm prolongation. If the repeat ECG QTcF is within normal limits the subject may be considered for enrollment

The Sponsor may review all or individual screening or Day 1 ECGs or may delegate to PI determine if meets intention of entry criteria goal of enrolling healthy normal study subjects.

The mean of triplicate QTcF measurements post-dose will be used to assess QTcF prolongation (including assessment of halting rules described in Section 8.6), and will be compared to the mean of the baseline measurements to calculate change from baseline.

In the event of a prolongation of QTc post dosing, the site will start telemetry monitoring of the subject and capture triplicate 12 lead ECG (3 tracings within a 5-minute period) every 30 minutes (±10 minutes) until the average for the triplicates has returned within 60ms of the baseline value at which time telemetry maybe discontinued. Persistent (1 hour or more) elevation in QTcF (>500ms) should prompt immediate consideration of transfer to appropriate emergency department for further evaluation, monitoring, and/or treatment.

In the event of a change in ECG wave forms consistent with a change in cardiac function or conduction when compared to baseline tracings, or in the event of a subject with possible cardiac related symptoms, repeat ECG should be obtained every 30 minutes (±10 minutes) until wave form change reverts to baseline appearance, or symptoms resolve, or are determined not to be cardiac in origin. Subjects with cardiac related symptoms associated with ECG changes will be transferred to appropriate emergency department for further evaluation and treatment.

### 7.1.2 Assessment of Concomitant Medications/Treatments other than Study Product

**Prohibited Medications/Non-Medications**

Subjects are required to abide by the following rules regarding intake of medications and other substances before and during the study:

- Refrain from the use of all prescription medications (with the exception of hormonal contraceptives), including any type of prescription antibiotic drug (topical or systemic) for at least 14 days prior to administration of the dose of study product on Day 1 until after the final study visit to the CRU;

- refrain from the use of all non-prescription medications, vitamins, or dietary supplements, within 7 days prior to administration of the dose of study product on Day 1 until after the visit to the CRU on Day 14;

- herbal supplements must be discontinued 7 days prior to the dose of study product on Day 1 until after the visit to the CRU on Day 14;

- the consumption of beverages and foods containing alcohol is prohibited for 72 hours prior to Day -1 until after the visit to the CRU on Day 14. A urine alcohol test will be performed at Screening and upon admission to the CRU;

- the consumption of beverages and foods containing caffeine is prohibited for 24 hours prior to Day -1 until discharge from the CRU on Day 4;

- consumption of grapefruit, grapefruit juice, or juices containing grapefruit, or Seville oranges is prohibited within 7 days prior to the dose of study product until after the visit to the CRU on Day 14;

- the use of tobacco product, including smoking and the use of snuff and chewing tobacco, and other nicotine or nicotine-containing products, is not permitted by a subject within 90 days of Screening for the study or while a subject is enrolled in the study. A urine test for cotinine will be performed at Screening and upon admission to the CRU;

- the use of illegal drugs is not permitted while a subject is enrolled in this study. A urine drug test, including amphetamines, barbiturates, cocaine, opiates, phencyclidine, cannabinoids and benzodiazepines, will be performed at Screening and upon admission to the CRU.

If a subject is unable to comply with the restrictions described above, the subject's continued participation in the study will be re-evaluated by the Investigator, in consultation with the Medical Monitor.

**Permitted Medications/Non-Medications**

Medications to treat any AEs the subject experiences during the study are permitted at the Investigator's discretion and/or in consultation with the Medical Monitor. Intermittent use of acetaminophen at doses of ≤ 2 g/day or ibuprofen ≤1200 mg/day is allowed throughout the study. Hormonal contraceptives are permitted throughout the study.

**Meals and Dietary Restrictions/Dosing Under Fasting Conditions**

Subjects will fast overnight for at least 8 hours prior to dosing on Day 1. Subjects will remain fasted until at minimum 4 hours after dosing, at which time lunch may be consumed. Other meals will be supplied at appropriate times thereafter while subjects are resident in the unit.

**Food Impact Evaluation Under Fed Conditions**

Subjects will fast overnight for at least 8 hours prior to the start of a high-fat, high-calorie meal which will be entirely consumed in less than 30 minutes. The dose of VT-1598 will be administered 30 minutes after the start of the meal (defined as the time when the first bite of the

meal is taken) with 8 ounces (240 mL) of water. The high-fat, high-calorie test meal will be comprised of a breakfast of approximately 900-1000 calories, with approximately 150 calories from protein, 250 calories from carbohydrates, and 500-600 calories from fat (an example of a high-fat, high-calorie breakfast is: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes fried with butter and 8 ounces or 240 mL of whole milk). No other food will be ingested until after a minimum of 4 hours after dosing, at which time lunch may be consumed. Water can be allowed as desired except for one hour before and after drug administration. Other meals will be supplied at appropriate times thereafter while subjects are resident in the unit.

**Exercise**

Subjects will be prohibited from engaging in strenuous activity within 48 hours prior to dosing and should be discouraged from engaging in strenuous activity within 48 hours prior to returning to the CRU on Days 7, 14, and 21 Subjects will not engage in strenuous activity at any time during the confinement period. Walking at a normal pace will be permitted.

### 7.1.3 Assessment of Subject Compliance with Study Intervention/Investigational Product/Investigational Device

Subjects will be directly observed at the time of dosing by a member of the clinical research team who is licensed to administer the study product. Study personnel will examine the oral cavity of each subject following each dose to assure that all study product was swallowed. Administration will be documented and entered into the eCRF.

## 7.2 Laboratory Evaluations

### 7.2.1 Clinical Laboratory Evaluations

All laboratory assessments will be done by the clinical site's certified laboratory. Laboratory toxicity grading will be determined by use of the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 2007 and the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table November 2007, as modified for this study and appropriate for the administration of VT-1598 (Appendix B VT-1598 Toxicity Grading Criteria for Normal Human Subjects).

At Screening and at baseline, laboratory test values that fall outside the reference range on the laboratory reports and deemed not clinically significant by the Investigator may be repeated at the discretion of the Investigator (to assess for transitional conditions). A laboratory value that is Grade 1 (with the exception of ALT, AST, Total bilirubin, hemoglobin or serum creatinine) will be allowed if not considered to be clinically significant by the investigator

If a single repeat Screening evaluation or baseline is within the reference range, the subject may be further considered for study eligibility **Note:** Hematuria during active menses causing urinalysis results outside the reference range will not be considered clinically significant (not an AE). Post-dose serum cortisol levels Grade 2 or greater must be repeated and if confirmed, then an ACTH stimulation test should be performed.

*See Appendix B VT-1598 Toxicity Grading Criteria for Normal Human Subjects.

**Pregnancy Testing**

All women of childbearing potential must undergo serum pregnancy testing at Screening and Baseline to assess protocol eligibility. Serum pregnancy tests will be performed thereafter as specified in the Schedule of Assessments and Procedures. Appendix A VT-1598 Schedule of Study Procedures and Evaluations

Female subjects reporting as post-menopausal must undergo testing for serum FSH levels to assess childbearing potential at Screening.

**Immunology**

All subjects must undergo testing for the detection of antibodies to HIV-1 and HIV-2, HBsAg, and antibodies to HCV at Screening to assess protocol eligibility.

**Clinical Chemistry Panel**

All subjects must undergo clinical chemistry testing (albumin, glucose, blood urea nitrogen or urea, potassium, calcium, sodium, chloride, total protein, creatinine, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total carbon dioxide, creatine phosphokinase, phosphorus, magnesium, gamma-glutamyl transferase (GGT), alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin and serum cortisol) at Screening and Baseline to assess protocol eligibility. Clinical chemistry tests will be performed thereafter as specified in the Appendix A Schedule of Assessments and Procedures. Subjects must fast a minimum of 8 hours before blood collection for a clinical chemistry panel. Serum cortisol levels must be drawn prior to 10 a.m.

**Hematology and Coagulation**

All subjects must undergo hematology (red blood cell count, total and differential white blood cell counts, hemoglobin, hematocrit, and platelet count) and coagulation (activated partial thromboplastin time, prothrombin time, and international normalized ratio) testing at Screening and Baseline to assess protocol eligibility. Hematology and coagulation tests will be performed thereafter as specified in the Appendix A Schedule of Assessments and Procedures.

**Urinalysis**

All subjects must undergo urinalysis testing (leukocyte esterase, blood, pH, and specific gravity [microscopic tests to be completed if dipstick urinalysis is abnormal]) at Screening and Baseline to assess protocol eligibility. Urinalysis testing will be performed thereafter as specified in the Appendix A Schedule of Assessments and Procedures.

### 7.2.2 Research Assays

Plasma and urine samples will be analyzed to determine concentrations of VT-1598 and VT-11134 using validated liquid chromatography/tandem mass spectrometry methods by the bioanalytical contractor, ICON BAL.

**Analytical Sample Collection and Handling**

Blood samples for the determination of VT-1598 and VT-11134 plasma concentrations will be collected as shown in Table 2:

**Table 2: Blood PK Sampling Timepoints**

| **Blood Sampling Timepoints for VT-1598 and VT-11134 Pharmacokinetic Analyses** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Day 1 (pre-dose) | Cohorts 1-5 (fasting): Taken within 60 minutes prior to dosing<br>Cohort 6 (fed): Taken within 30 minutes prior to start of pre-dose meal. | | | | | | | | | | |
| Day 1 (hours post dose*) | 0.5 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | 10 | 12 | 14 |
| Day 2 (hours post dose**) | 24 | 36 | | | | | | | | | |
| Day 3 (hours post dose**) | 48 | 60 | | | | | | | | | |
| Day 4 (hours post dose**) | 72 | | | | | | | | | | |
| Day 7 (hours post dose)*** | 144 | | | | | | | | | | |
| Day 14 (hours post dose)*** | 312 | | | | | | | | | | |
| Day 21 (hours post dose)*** | 480 | | | | | | | | | | |

*The 0.5-hour post dose blood sample should be taken within ± 5 minutes of the nominal timepoint. The remaining post dose blood samples on Day 1 should be taken within ± 10 minutes of the nominal time points.

**The post dose blood samples during the inpatient stay should be taken within ± 30 minutes of the nominal time point on Days 2, 3 and 4.

***For outpatient visits, blood samples should be taken within the visit window.

The exact dates and times of blood collection must be recorded in the eCRF and source documents. The blood samples will be obtained via direct venipuncture or via indwelling intravenous catheter using saline flushes to maintain catheter patency. Specific details for blood sample collection, process blood to plasma, and sample handling are included in the MOP for this study.

Urine samples for the determination of VT-1598 and VT-11134 amounts will be collected in the intervals shown in Table 3:

**Table 3: Urine PK Sampling Timepoints**

| **Urine Sampling Timepoints for VT-1598 and VT-11134 Pharmacokinetic Analyses** | | | | |
|---|---|---|---|---|
| Day 1 (pre-dose) | Collected from -6 hours until 0 hours pre-dose (For fasted cohorts) | | | |
| Day 1 (hours post dose) | 0-6 | | >6-12 | >12-24 |
| Day 2 (hours post dose) | 24-36 | 36-48 | | |
| Day 3 (hours post dose) | 48-60 | 60-72 | | |

The exact dates, start and stop time for each intervals and volumes of urine collection must be recorded in the eCRF and source documents. For each interval, volume will be measured, and an aliquot will be retained and analyzed for the determination of VT-1598 urine concentrations. Specific details for urine specimen collection and handling are included in the MOP for this study.

**Laboratory Specimen Preparation, Handling, and Storage**

Detailed instructions for plasma and urine specimen preparation, handling and storage are outlined in the MOP for this study.

**Total Blood Volume Drawn**

The total volume of blood that will be drawn from each subject is described in Table 4.

**Table 4: Total Volume of Blood Drawn From Each Subject**

| **Type** | **Laboratory Test** | **Sample Volume (mL)** | **Number of Samples** | **Total Volume (mL)** |
|---|---|---|---|---|

| | | | |
|---|---|---|---|
| Safety: | | | |
| Clinical chemistry | 3.5 | 7 | 24.5 |
| Cortisol | 3.5 | 7 | 24.5 |
| Hematology | 2 | 7 | 14 |
| Coagulation | 2.7 | 7 | 18.9 |
| Serology | 4 | 1 | 4 |
| future assays[a] | 6 | 1 | 6 |
| Pharmacokinetic: | 3 | 20 | 60 |
| When using an indwelling catheter 1.0 mL of blood will be removed prior to sample collection | | | |
| **Total** | 24.7 | 50 | 151.9 |
| [a] EDTA Blood sample will be collected 6 hours post-dose; plasma will be processed and stored to allow for the option to test for additional parameters. See Section 9.3 Consent for Future Use and Storage of Specimens. | | | |

**Laboratory Specimen Shipping**

All PK and future use specimens will be shipped to the Fisher Biorepository for storage and/or transfer to the ICON BAL. Detailed instructions for shipping plasma and urine samples are outlined in the MOP for this study.

# 8 ASSESSMENT OF SAFETY

## 8.1 Assessing and Recording Safety Parameters

Safety will be assessed by collection of AEs, physical examinations, clinical laboratory results, vital signs, and ECG from time of dosing until final visit.

### 8.1.1 Adverse Events (AEs)

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All adverse events should be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator) date of resolution/stabilization of the event, outcome and severity. All AEs occurring while in study must be documented appropriately regardless of relationship. All AEs will be followed to resolution/stabilization.

Any medical or laboratory condition that is present at the time that the subject is screened up through ingestion of the dose should be considered as baseline/pre-existing condition and not reported as an AE. However, if it deteriorates at any time during the study after ingestion of the dose, it should be recorded as an AE.

**Adverse Events Grading**

AEs will be assessed by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or appropriate sub-investigator using a protocol-defined grading system. For events not included in the protocol-defined grading system (Section 8 Assessment of Safety/Appendix B VT-1598 Toxicity Grading Criteria for Normal Human Subjects), the following guidelines will be used to quantify severity:

- • Mild (Grade 1): Events require minimal or no treatment and do not interfere with the subject's daily activities;

- • Moderate (Grade 2): Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning and daily activities and use of over the counter medication;
- • Severe (Grade 3): Events interrupt the subject's usual daily activities and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

**Relationship to Study Products:** The assessment of the relationship of an AE to the administration of study product is made only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator based on all available information at the time of the completion of the eCRF. Whether the AE is related or not, is not a factor in determining what is or is not reported in this trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event;
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

## 8.2 Serious Adverse Events (SAEs)

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

- Death;
- a life-threatening adverse event[1];
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or;
- a congenital anomaly/birth defect;
- important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to

prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

[1] Life-threatening adverse event. An adverse event is considered "life-threatening" if, in the view of either the site principal investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event, had it occurred in a more severe form, might have caused death.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study drug);
- recorded on the appropriate SAE data collection form and eCRF;
- followed through resolution;
- reviewed and evaluated by an Independent Safety Monitor (ISM) (as deemed necessary), the SMC (periodic review unless related), DMID, and the IRB;

SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE/SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

## 8.3 Specification of Safety Parameters

### 8.3.1 Dose Escalation Criteria

The initial cohort of 8 subjects will be administered 40 mg of VT-1598 (6 subjects) or placebo (2 subjects) as a single oral dose. Two sentinel subjects will be included in Cohorts 1-5 as described in Section 4.2 Acquisition/Distribution.

Dose escalation to each successive cohort of subjects will occur if none of the predefined dose escalation halting criteria are met (for all subjects through Day 7). Emmes will provide notification to the PI upon analysis of data for the cohort (for all subjects through Day 7) for halting criteria as described in Section 3 Study Design, Objectives and Endpoints or Outcome Measures, Dose Escalation. If any of the criteria for dose escalation are met, or, at the discretion of the PI or DMID Medical Monitor, the study enrollment and dosing will be stopped until the

SMC reviews the data and provides its recommendations. There will be a scheduled SMC data review meeting prior to start of Cohort 5.

The nominal dose- escalation scheme will be 40, 80, 160, 320 and 640 mg) or matching placebo administered in a fasting state. The effect of a high-fat, high-calorie meal on the PK of VT-1598 is planned in an additional cohort that will be dosed at 160 mg. The fed cohort will be dosed at 160 mg, after the 320 mg fasted cohort has been dosed. This provides additional safety data to cover the possibility that the bioavailability of VT-1598 is increased in the presence of food under the fed state. The highest proposed dose in this study is 640 mg, which is 53% of the body surface area equivalent of the NOAEL in the most sensitive species.

### 8.3.2 Reporting Serious Adverse Events

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group, at the following address:

**DMID Pharmacovigilance Group**

**Clinical Research Operations and Management Support (CROMS)**

**6500 Rock Spring Dr. Suite 650**

**Bethesda, MD 20817, USA**

**SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)**

**SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)**

**SAE Email Address: PVG@dmidcroms.com**

In addition to the SAE form, select SAE data fields must also be entered into Advantage EDC. Please see the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.

The site will send a copy of the SAE report(s) to the ISM (as deemed necessary) when they are provided to the DMID Pharmacovigilance Group. The DMID Medical Monitor and DMID Clinical Project Manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the site principal investigator or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the site

principal investigator or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

### 8.3.3 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the investigator, DMID, the Investigational New Drug (IND) sponsor, will report any suspected adverse reaction that is both serious and unexpected. DMID will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. DMID will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its IND(s) or under any principal investigator's IND(s) and NQP 1598, Ltd. in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. DMID will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All serious events designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

### 8.3.4 Reporting of Pregnancy

A Notification of Pregnancy form will be completed for any female study subject or for any female partner of a male study subject who becomes pregnant following their exposure to study product (Day 1) through 3 months after the dose of study product. The site will discuss pregnancy reporting with subjects at the Final Study visit with instructions and provide contact information in case pregnancy occurs. The pregnant subject will be followed by monthly telephone calls until 2 months after the birth of the baby or until the end of the pregnancy (in case pregnancy is terminated) at which time the Pregnancy Outcome form will be completed. Infants born to these study subjects will also be monitored for SAEs for up to 2 months after birth (information regarding SAEs will be captured on the Pregnancy Outcome form and the SAE form). If an SAE occurs during the pregnancy, the SAE will be reported on the appropriate SAE form and provided to DMID pharmacovigilance. Pregnancy Outcome forms will be used to collect, but not be limited to, data on the following information, should it be identified during the monthly telephone calls, at the end of the pregnancy, or at the follow-up telephone call at 2 months after birth of the baby:

1. Prior maternal history including congenital abnormalities or pregnancy complications;
2. estimated date of conception;
3. estimated and actual date of delivery or pregnancy termination;
4. mode of delivery;
5. maternal complications;
6. neonatal complications (i.e. lethal or nonlethal congenital abnormality).

## 8.4 Type and Duration of Follow-up of Subjects after Adverse Events

All AEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE/SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

## 8.5 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

Abnormal laboratory values, performed as part of hematology, chemistry panel, or urinalysis but not listed in Appendix B, VT-1598 Toxicity Grading Criteria for Normal Human Subjects, will be evaluated by the study clinicians, recorded in the source document and, if clinically significant, considered AEs and graded according to the criteria details described in Section 8.1 Assessing and Recording Safety Parameters.

The site principal investigator or appropriate sub-investigator is responsible for recording all AE and SAEs that are observed or reported during this study, regardless of the relationship to study product. AE and SAEs or abnormal clinical findings will be collected, assessed, documented, reported, and followed appropriately.

## 8.6 Halting Rules

### 8.6.1 Study Halting Criteria

If any of the criterion below are met, the study will be suspended (enrollment and dosing), and the SMC ad hoc meeting will convene:

- Any SAE, regardless of the relationship to the study drug, throughout duration of study, unless confirmed to be of reasonable alternative etiology.

- 5 or more subjects in study (cumulative among all cohorts) experience a same grade 2 (or higher) related AE (laboratory or systemic) which is coded in the same high-level group term (HLGT) per MedDRA coding, throughout duration of study.

### 8.6.2 Dose Escalation Halting Criteria

**Sentinel Subject Halting Rules**

If any of the criterion below are met, the cohort will be suspended (enrollment and dosing), and the SMC ad hoc meeting will convene:

- Any SAE (regardless of the relationship to the study drug) through Day 3 of the study;
- any Grade 2 (or higher) adverse event (laboratory or systemic) if not resolved within 1 day, through Day 3 of the study.

**Cohort Dose Escalation Halting Rules**

If any of the criterion below are met, the escalation to the next cohort will be suspended (enrollment and dosing), and the SMC ad hoc meeting will convene.

- 2 or more subjects in a cohort experience the same grade 2 (or higher) related AE (laboratory or systemic) which is coded in the same HLGT per MedDRA coding, through Day 7 of the study;
- 2 or more subjects within a cohort with post-dose QTcF > 500 ms or change from baseline >60 ms through Day 7 of the study.

## 8.7 Safety Oversight

### 8.7.1 Independent Safety Monitor (ISM)

An ISM is a physician with relevant expertise whose primary responsibility is to provide to DMID an independent safety assessment in a timely fashion. This ISM is identified by the investigator site and approved by DMID. Participation is for the duration of the DMID study and is a voluntary position that does not receive payment. The ISM must meet the requirements of the NIAID conflict of interest policy.

The ISM:

- Is in close proximity to the study site and has the authority and ability to readily access study participant records in real time;

- may be a member of the participating institution's staff but preferably be from a different organizational group within the institution;
- should not be in a direct supervisory relationship with the investigator;
- should have no direct involvement in the conduct of the study.

The ISM will:

- Sign a Conflict of Interest (COI) certification at the time they are asked to participate and provide updates to this information as needed;
- receive reports of Serious Adverse Events (SAEs) from the site investigator;
- evaluate the SAE and report their clinical assessment to DMID, through DMID-CROMS SOCS in a timely manner using the AE form and email the report to DMID-CROMS SOCS;
- communicate with the investigator at the participating site as needed;
- review additional safety related events at the request of DMID;
- provide additional information to DMID and/or the DSMB by teleconference as requested.

### 8.7.2 Safety Monitoring Committee (SMC)

The SMC is an independent group of experts (at least 3 members) that monitors subject safety and advises DMID. SMC members will be separate and independent of study personnel participating in this study and should not have scientific, financial, or other conflicts of interest related to the study. The SMC will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial. A quorum will consist of a simple majority.

The SMC will review the safety data at the following timepoints:

- Organizational meeting (prior to start of the study);
- data review meeting;
- between Cohorts 4 and 5;
- scheduled meeting upon completion of dosing and final visit for all cohorts;
- ad hoc meeting(s)

- When a halting criterion is met for sentinels, dose escalation or the overall study;
- at the request of DMID to review a potential safety concern identified by the either the PI, DMID medical monitor, participating investigator, or the ISM.

Procedures for SMC reviews/meetings will be defined in the SMC charter. The SMC will review applicable data to include, but not limited to, enrollment, demographic, dosing, laboratory, and safety data at scheduled time points during the study as defined in the charter. The SMC will receive data in aggregate. The SMC may request to receive data by study product vs placebo in a closed session. The SMC may also request that the blind be broken for individual subjects, as needed, to assess safety issues. As an outcome of each review/meeting, the SMC will make a recommendation in writing to continue, modify, or terminate the study.

# 9 HUMAN SUBJECTS PROTECTION

## 9.1 Institutional Review Board/Independent Ethics Committee

The site principal investigator will obtain IRB approval for this protocol to be conducted at his research site and send supporting documentation to the DMID before initiating recruitment of subjects. The investigator will submit applicable information to the IRB on which it relies for the review, to conduct the review in accordance with 45 CFR 46, ICH E6 GCP, and as applicable, 21 CFR 56 (Institutional Review Boards) and 21 CFR 50 (Protection of Human Subjects), other federal, state, and local regulations. DMID must receive the documentation that verifies IRB-approval for this protocol, associated informed consent documents, and upon request any recruitment material and handouts or surveys intended for the subjects, prior to the recruitment and enrollment of subjects.

Any amendments to the protocol or consent materials will be approved by the IRB before they are implemented. IRB review and approval will occur at least annually throughout the enrollment and follow-up of subjects and may cease if annual review is no longer required by applicable regulations. The investigator will notify the IRB of deviations from the protocol and reportable SAEs, as applicable to the IRB policy.

## 9.2 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained and documented. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

The site principal investigator or designee will describe the protocol to potential subjects face-to-face. The key information about the purpose of the study, risks and discomforts, and any potential benefits to society will be presented first to the subject.

Subjects will also receive an explanation that the trial involves research, and a detailed summary of the proposed study procedures and study interventions/products. This will include the probability for random assignment to treatment groups, all possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, that are currently unforeseeable), and the expected duration of the subject's participation in the trial.

Subjects will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. Subjects will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Subjects will be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They will be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the research project.

Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. The subjects will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

The extent of the confidentiality of the subjects' records will be defined, and subjects will be informed that applicable data protection legislation will be followed. Subjects will be informed that the monitor(s), auditors(s), IRB, NIAID, and regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the subject is authorizing such access.

Subjects will be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject's identity will remain confidential. Subjects will be informed whether private information collected from this research and/or specimens may be used for additional research, even if identifiers are removed.

Subjects will be allowed sufficient time to consider participation in this research trial and have the opportunity to discuss this trial with their family, friends or legally authorized representative, or think about it prior to agreeing to participate.

Informed consent forms will be IRB approved and subjects will be asked to read and review the consent form. Subjects must sign the informed consent form prior to starting any study procedures being done specifically for this trial.

Once signed, a copy of the informed consent form will be given to the subject(s) for their records. The subject(s) may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subject(s) will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

New information will be communicated by the site principal investigator to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and subjects will be re-consented per IRB requirements, if necessary. Subjects will be given a copy of all informed consent forms that they sign.

## 9.3 Consent for Future Use of Stored Specimens and Data

At enrollment, subjects will be asked for consent to collect a venous blood sample (6 mL) for plasma at the presumed $C_{max}$ (6 hours post dose) in addition to PK blood samples to be retained for possible use in future research studies. Permission to collect and store these samples will be completely voluntary; subjects who are otherwise eligible to participate in the study but do not consent to collection of future use specimens will not be excluded from the study. These clinical samples will be shipped to and stored up to two (2) years from the end of the study at the Fisher Biorepository (DMID CMS) and may be shared with investigators at the participating site and with other investigators at other institutions.

Residual clinical samples with consent for future use will be available upon the completion of the study; however, future use clinical samples may be requested from DMID and shipped from the DMID CMS at any time. Residual clinical samples without consent for future use should be destroyed upon the completion of the study.

The samples will not be sold or used directly for production of any commercial product. No human genetic tests will be performed on the samples. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect subject confidentiality. The recipients of specimens will be informed that these specimens have a NIH certificate of confidentiality.

There are no benefits to subjects in the collection, storage and subsequent use of their specimens for future research. Reports about future research done with subjects' samples will NOT be kept in their health records.

Subjects may be given the option to decide if they want their samples to be used for future research or have their samples destroyed at the end of this trial. The subject's decision can be changed at any time by notifying the study doctors or nurses in writing. However, if the subject originally consents to future use and subsequently changes his/her decision, any data from a previously collected sample may still be used for this research.

Subjects may be given the option to decide if they want their **residual** specimens to be used for future research or have these specimens destroyed at the end of this trial. The subject's decision can be changed at any time by notifying the study doctors or nurses in writing. However, if the

subject originally consents to the future use of **residual** specimens and subsequently changes his/her decision, any data from a previously collected specimen may still be used for future research.

## 9.4 Exclusion of Women, Minorities, and Children (Special Populations)

Children under age 18 years will be excluded from participation because insufficient data are available in adults to judge potential risk in children, and as a Phase 1 trial in healthy individuals, there is no known benefit. For these same reasons, this trial will not include other special classes of subjects, such as fetuses, neonates, prisoners, institutionalized individuals, or others who may be considered vulnerable populations.

Neither women nor minorities will be excluded from participation in this study. Women of child bearing potential may be included as per the inclusion criteria (Section 5.1). Subjects will be recruited without regard to gender or race. It is expected that race will reflect that within the community.

## 9.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in the study. No information concerning the study, or the data generated from the study will be released to any unauthorized third party without prior written approval of the DMID and the subject. Subject confidentiality will be maintained when study results are published or discussed in conferences. The study monitors or other authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

All records will be kept locked and all computer entry and networking programs will be carried out with coded numbers only and with password protected systems. All non-clinical specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number.

To protect privacy, we have received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or

other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below.

## 9.6 Certificate of Confidentiality

To protect privacy, we have received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the FDA).

A Certificate of Confidentiality does not prevent the subject from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from reporting without the subject's consent, information that would identify the subject as a participant in the research project regarding matters that must be legally reported including: child and elder abuse, sexual abuse, or wanting to harm themselves or others.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains, or for the purposes of other research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

## 9.7 Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for the research tests, procedures, and study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the subject, subject's insurance or third party.

Subjects are compensated for their participation in this trial. Compensation will be in accordance with the local IRB's policies and procedures, and subject to IRB approval.

If it is determined by the site principal investigator that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care

facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating site. No financial compensation will be provided to the subject by the NIAID, NIH or by the participating site to the subject for any injury suffered due to participation in this trial.

# 10 STATISTICAL CONSIDERATIONS

A formal Statistical Analysis Plan (SAP) will be created prior to final data lock. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures. Any deviation from the analyses outlined in the protocol will be described in the SAP.

For continuous variables, data will be summarized using descriptive statistics (such as sample size,mean, median, standard deviation, minimum, and maximum). For discrete variables, data will be summarized using frequencies and percentages.

## 10.1 Study Hypotheses

The objectives of the study are to obtain safety and pharmacokinetic data for VT-1598. There are no formal hypotheses being tested in this Phase 1 trial study.

## 10.2 Sample Size Considerations

As this study is the first assessment of VT-1598 in humans and is primarily aimed at safety and PK evaluation, power calculations have not been performed. The sample size of 8 subjects (6 subjects receiving VT-1598 and 2 subjects receiving placebo) per cohort is based on clinical experience and judgment and should provide adequate clinical information to meet the objectives of the study. The comparisons of fed to fasted PK are exploratory rather than formal analyses of fed bioequivalence and fed and fasted profiles from 6 subjects are sufficient for the intended purpose.

## 10.3 Treatment Assignment Procedures

### 10.3.1 Randomization Procedures

Each subject who completes the study Screening assessments, meets all eligibility criteria, and is accepted for the study will be assigned a unique sequential identification number and, with the exception of replacement subjects, will receive the corresponding treatment according to the randomization schedule. Replacement subjects will receive the same treatment assignment as the subject being replaced. Subjects who are not randomized within 28 days of their Screening visit will be considered out-of-window and not eligible for randomization. These subjects will be eligible to re-screen provided they previously met all other eligibility criteria.

The randomization schedule will be generated centrally through the AdvantageEDC$^{SM}$ (Electronic Data Capture System, Emmes) by the unblinded study biostatistician, and a list will

be transferred to the unblinded study pharmacist prior to start of the study for the purpose of an emergency back-up. For Cohort 1 through Cohort 5, within each cohort 8 subjects will be randomized in a 3:1 ratio to active treatment and placebo. Cohort 6 will not use randomization. For Cohort 1 through Cohort 5, the first two subjects will be randomized in a 1:1 fashion to active drug and placebo to ensure that one of the first two subjects receives active treatment and the other receives placebo for sentinel dosing placebo. The product assignment of the remaining six subjects in each cohort will be randomly assigned 5:1 active drug to placebo to ensure the 3:1 ratio for the entire dosing cohort. Enrollment will occur at one site. An appropriate amount of back-up subjects will be brought in per cohort in the event of subject withdrawal prior to dosing.

After completing the final study visit (Day 21) and at least 60 days after dosing, Cohort 3 subjects will have enrollment "rollover" to Cohort 6. Cohort 3 subjects continuing as Cohort 6 subjects will not be randomized but will receive placebo if he or she received placebo as part of Cohort 3 and will otherwise receive drug. Cohort 3 subjects that do not continue to Cohort 6 will be replaced, and the replacement subjects will receive the same type of treatment (placebo vs. drug) that the subject being replaced received as part of Cohort 3. Cohort 3 subjects that are no longer eligible for the trial after the washout period will not be continued to Cohort 6 but will be replaced. Cohort 6 "rollover" or replacement enrollment may occur before or after planned SMC meeting to be held once Cohort 4 has completed follow-up.

Following review of all eligibility criteria, subjects will be registered and randomized using AdvantageEDC$^{SM}$. Randomization will occur following admittance to the unit and confirmation of eligibility is confirmed.

Per ICH guideline E6: Good Clinical Practice (GCP), screening records will be kept at the participating site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed screening will be recorded in the SDCC AdvantageEDC$^{SM}$.

Enrollment of subjects will be done online using the enrollment module of AdvantageEDC$^{SM}$. The randomization code will be prepared by statisticians at the SDCC and included in the enrollment module for this trial. AdvantageEDC$^{SM}$ will assign each subject to a treatment arm after the demographic and eligibility data have been entered into the system. A designated individual at the participating site will be provided with a code list for emergency unblinding purposes by the unblinded study biostatistician, which will be kept in a secure place.

Instructions for use of the enrollment module are included in the AdvantageEDC$^{SM}$ User's Guide. Manual back-up procedures and instructions are provided for use in the event that a participating site temporarily loses access to the Internet or the online enrollment system is unavailable.

### 10.3.2 Masking Procedures

**Blinding**

The Study Pharmacist at the site will be unblinded as to treatment assignment. Study subjects, the PI and study site personnel other than the Study Pharmacist and verifier, the bioanalytical laboratory staff, and Fisher repository personnel will remain blinded to all randomization assignments throughout the study. The DMID medical monitor and NIAID personnel, NQP 1598 Ltd., and ICON GPHS (CRO) personnel will remain blinded to all subject randomization assignments.

All laboratory personnel performing experimental assays as part of this study will be masked to treatment group, subject ID, and study visit for all study specimens. The SDCC will generate sample picklists for each laboratory to determine which specimens will be tested. At the discretion of DMID, unmasking of laboratories may occur after all data have been locked, analyzed and interpreted and the final CSR has been completed.

The randomization schedule will be provided to the unblinded study personnel (the Study Pharmacist and a verifier) at the site. The Pharmacist will perform dose preparation; the unblinded verifier is a member of the pharmacy team who will not participate in dose preparation. Unblinded personnel at the site will not be involved in study-related assessments or have subject contact for data collection following study drug administration.

Selected individuals not involved in the conduct of the study, including members of the SMC, may have access to unblinded data as needed for safety review or other data review. The site pharmacist will remain unblinded during the course of the study.

**Emergency Unblinding**

Emergency unblinding of treatment assignment for a subject may be necessary due to a medical emergency, or any other significant medical event, should knowledge of the subject's treatment assignment impact the subject's care. Should an SAE or other circumstance require the blind to be broken to ensure a subject's safety, the PI should immediately notify the DMID Medical Monitor if possible (within 24 hours) to discuss the case and reason for unblinding (a written narrative must follow within 48 hours of the event).

Procedures for emergency unblinding are detailed in the MOP for this study.

## 10.4 Planned Interim Analyses

Safety data will be reviewed by the SMC by treatment received in a closed session in the planned safety data review meeting between Cohort 4 and Cohort 5 and may also be reviewed by SMC in the closed session of ad hoc meetings.

There will be an interim analysis of PK data after completion of Cohort 3 which will be made available to all investigators, SDCC staff, NQP 1598 Ltd., and DMID staff involved in the study. The interim PK report will show PK data in aggregate only and will not include any information that could be potentially unblinding. Enrollment will not stop for the PK interim analysis. If PK is substantially different than expected, the protocol may be amended to change the timing of PK samples.

## 10.5 Final Analysis Plan

The safety analysis population will include all subjects that received any amount of study product and will be analyzed by treatment received. Placebo subjects may be pooled across multiple cohorts for analysis. The PK analysis population will include all subjects with at least one measurable PK concentration.

### 10.5.1 Adverse and Serious Adverse Events

AEs will be coded with MedDRA® (Version 22.1 or later) and summarized descriptively for each regimen by system organ class, HLGT, and preferred term. The AE profile will be characterized by severity and relationship to the study drug. SAEs will be identified.

### 10.5.2 Clinical Safety Labs, Vital Signs, and Electrocardiograms

Baseline for clinical safety labs, vital signs, and ECGs will be defined as the last result obtained before the dose of study product. Clinical safety labs, vital signs, and ECGs results and changes from baseline will be summarized by treatment arm and visit. Clinical safety labs and vital signs will be graded (Appendix B) and summarized by severity, treatment arm, and visit. If triplicate ECG measurements were performed at the same visit, then baseline is the mean value of the measurements for the visit closest to, but before, administration of study drug. Similarly, for analyses of change from baseline, mean values will be used in the case of replicate measurements at a single visit post-baseline.

Treatment-emergent abnormal laboratory test results will be identified. Treatment-emergent abnormal laboratory tests are tests for which the result was not graded as mild or worse at baseline but graded as mild or worse after dosing. Laboratory tests graded as mild at baseline,

but moderate or worse any time after dosing will also be regarded as treatment-emergent abnormal laboratory test results.

ECG measurements will include heart rate, RR interval, QT interval, QTcF interval, PR interval, and QRS duration. Baseline for ECG measurements is defined per protocol as the value pre-dosing on Day 1. Change from baseline will be summarized descriptively by regimen at each scheduled evaluation. QTc results will be summarized categorically according to the ICH Guideline E14 "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (October 2005).

- QTcF >450 ms;
- QTcF >450 ms, males only;
- QTcF >470 ms, females only;
- QTcF >480 ms;
- QTcF >500 ms;
- QTcF increases from baseline by at least 30 ms but less than 60 ms;
- QTcF increases from baseline by at least 60 ms.

## 10.6 Pharmacokinetic Analysis Plan

Plasma and urine samples from all subjects who received at least one dose of VT-1598 will be analyzed for the concentration of VT-1598 and VT-11134 by validated LC-MS/MS methods. Plasma concentration-time profiles and plots of amount excreted ($Ae_{(t_1-t_2)}$) per urine collection period will be constructed for each subject and each dosing cohort.

The following PK parameters will be estimated, by noncompartmental analysis methods using version 7.0 or higher of Phoenix WinNonlin®, for VT-1598 and VT-11134 plasma and urine concentration, as appropriate.

| | |
|---|---|
| $C_{max}$ | maximum measured plasma concentration |
| $T_{max}$ | time to reach maximum measured plasma concentration |
| $AUC_{last}$ | area under the plasma concentration versus time curve from time 0 to the time of the last quantifiable concentration |

| | |
|---|---|
| $AUC_{inf}$ | area under the plasma concentration versus time curve from time 0 and extrapolated to infinity |
| $\%AUC_{ex}$ | percentage of $AUC_{inf}$ obtained by extrapolation |
| $t_{1/2}$ | terminal phase half-life |
| $\lambda z$ | apparent first-order terminal elimination rate constant |
| $V_d/F$ | apparent volume of distribution |
| CL/F | apparent oral clearance |
| $Ae_{last}$ | cumulative amount excreted into the urine from time 0 to the time of the last quantifiable concentration |
| $Ae_{\%Dose}$ | cumulative amount excreted into the urine |
| $CL_R$ | renal clearance of drug |

Additional PK parameters may be estimated as appropriate. Dose proportionality for each PK exposure parameter ($C_{max}$, $AUC_{last}$, $AUC_{inf}$) will be assessed statistically and graphically.

The more detailed PK analysis will be available in the SAP for this study.

# 11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. The site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data and source documents, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

## 11.1 Compliance with Standards of Medical Research/ Deviations

This protocol will be conducted in accordance with the applicable ICH guidelines and GCP. Any instance of noncompliance with the protocol will result in a documented deviation. If a change is deemed necessary in order to protect the safety, rights or welfare of a subject, the Sponsor and IRB should be notified as soon as possible and preferably prior to introducing the deviation.

# 12 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted Program Quality Management Plan (cQMP), the participating site and its subcontractors are responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site principal investigator will provide direct access to all study-related sites, source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The site principal investigator will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The SDCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the participating site(s) for clarification and resolution.

DMID-designated clinical monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, ICH/GCP guidelines, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to DMID.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after the completion of the study. In the event of an assessment, audit or inspection, the Investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues, and to implement any corrective and/or preventative actions to address any findings/issues identified.

# 13 DATA HANDLING AND RECORD KEEPING

## 13.1 Data Management Responsibilities

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue permanent ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Data reported in the eCRF derived from source data collection forms should be consistent or the discrepancies should be explained.

The sponsor and/or its designee will provide guidance to the site principal investigators and other study personnel on making corrections to the data collection forms and eCRF.

Training will be provided for the Electronic Data Capture (EDC) system. All personnel using the EDC system must have the appropriate education, training, and experience, or any combination thereof. The Investigator will be provided with standard operating procedures (SOPs) (contained in the MOP or a vendor-specific SOP) on the use of the EDC system. Documentation for employee education, training, and previous experience that pertains to the EDC system must be present in the Investigator files.

If electronic data systems other than those provided and maintained by the Sponsor are used for documentation and data capture, the Investigator must ensure that the systems are validated and ensure regular data back-up.

The eCRF will be signed by the Investigator or a Sub-Investigator listed on the FDA 1572 form. It is the responsibility of the Investigator to ensure the eCRFs are completed and submitted to the Sponsor (or designee) in an accurate and timely manner. The processing of eCRFs will include an audit trail (to include changes made, reason for change, date of change, and person making change). At the completion of the study, the Sponsor will be provided with a final copy of each eCRF.

Management of clinical data will be performed in accordance with applicable Sponsor standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). Adverse events and concomitant medications will be coded using the MedDRA® and World Health Organization Drug Dictionaries (WHO DD) respectively. Medical eCRFs will be retained by the Sponsor and copies will be sent to the Investigator to maintain as the Investigator copy.

## 13.2 Data Coordinating Center/Biostatistician Responsibilities

Any source documents and laboratory reports must be reviewed by the clinical team and data management staff, who will ensure their accuracy and completeness. AEs must be recorded on the appropriate data collection form, assessed for severity and relationship, and reviewed by the site principal investigator or appropriate sub-investigator. AEs must be graded based on the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* September 2007, as modified for this study and as appropriate for the administration of VT-1598 Appendix B VT-1598 Toxicity Grading Criteria for Normal Human Subjects.

Electronic data capture is the responsibility of the clinical trial staff at the site under the supervision of the site PI. During the study, the PI must maintain complete and accurate documentation for the study.

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site principal investigator. During the study, the site principal investigator must maintain complete and accurate documentation for the study.

The data coordinating center for this study, Emmes, will be responsible for data management, quality review, analysis, and reporting of the study data.

## 13.3 Data Capture Methods

Clinical data (including but not limited to AEs, physical assessments, clinical laboratory values and concomitant medications) will be entered into Advantage EDC$^{SM}$, a 21 CFR Part 11-compliant electronic data capture (EDC) system managed by Emmes. The EDC system access is password protected. Access is granted to specific individuals based on the roles identified for the study. The clinical study site enters the data into EDC from the data collection forms completed by the study personnel. Data are validated through a query resolution process, comprising both automated and manual queries.

AE/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory values) and reactogenicity will be collected on data collection forms by study personnel then entered into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by the study data coordinating center.

## 13.4 Types of Data

Data for this study will include all data for safety and PK deemed necessary for the analysis per the protocol, demographic data, clinical laboratory values, concomitant medication, AE and medical history.

Externally collected data are received and processed to present a complete dataset reconciled with data collected in the EDC.

## 13.5 Study Records Retention

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

# 14 CLINICAL MONITORING

## 14.1 Site Monitoring Plan

Site monitoring is conducted to ensure that the human subjects' protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that this trial is conducted in accordance with the protocol, protocol-specific MOP and applicable sponsor standard operating procedures. DMID, the sponsoring agency, or its designee will conduct site-monitoring visits as detailed in the clinical monitoring plan.

Site visits will be made at standard intervals as defined by DMID and may be made more frequently as directed by DMID. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with site principal investigators to discuss any problems and actions to be taken and will document site visit findings and discussions.

# 15 PUBLICATION POLICY

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

- NIH Public Access Policy, http://publicaccess.nih.gov/;
- NIH Office of Extramural Research (OER) Grants and Funding, http://grants.nih.gov/grants/oer.htm.

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first subject. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. A delay of up to 2 years is available for trials that meet certain criteria and have applied for certification of delayed posting.

As part of the result posting a copy of this protocol (and its amendments) and a copy of the Statistical Analysis Plan will be posted on https://clinicaltrials.gov/.

For this trial the responsible party is DMID, which will register the trial and post results.

The responsible party does not plan to request certification of delayed posting.

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases
- 42CFR11
- NIH NOT-OD-16-149

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# 17 APPENDICES

# Appendix A. VT-1598 SCHEDULE OF STUDY PROCEDURES AND EVALUATIONS

**Schedule of Study Procedures and Evaluations – Cohort 1 through Cohort 6***

(X) – As indicated/appropriate

| Activity/ Day | Screening | Baseline | Inpatient (Treatment) Period | | | Follow-up Period | | | Unscheduled |
|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Visit 3 | | | Visit 4 | Visit 5 | Visit 6 | |
| | Day -28 to-2 | Day -1 | Day 1 | Days 2 & 3 | Day 4 | Day 7 (±1 day) | Day 14 (±1 day) | Day 21/ End-of-Study[s] (±2 days) | |
| Informed Consent | X | | | | | | | | |
| Demographics | X | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | | | |
| Height, Weight, BMI | X | X[a] | | | | | | | |
| Medical History[b] | X | X[c] | | | | X[c] | X[c] | X[c] | |
| Physical Examination | X[d] | X[e] | X[e] | | X[e] | | | X[e] | X[e] |
| Vital Signs[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] |
| ECG[g] | X[g] | | X[g] | | X[g] | | | X[g] | X[g] |
| Clinical Laboratory Tests[h] | X | X | | | X | X | X | X | X |

| Activity/ Day | Screening | Baseline | Inpatient (Treatment) Period | | | Follow-up Period | | | Unscheduled |
|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Visit 3 | | | Visit 4 | Visit 5 | Visit 6 | |
| | Day -28 to-2 | Day -1 | Day 1 | Days 2 & 3 | Day 4 | Day 7 (±1 day) | Day 14 (±1 day) | Day 21/ End-of-Study[s] (±2 days) | |
| Pregnancy Test[i] | X | X | | | | | | X | |
| FSH[j] | X | | | | | | | | |
| Drug Screen[k] | X | X | | | | | | | |
| Immunology Screen[l] | X | | | | | | | | |
| PK Blood Samples[m] | | | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] |
| PK Urine Samples[n] | | | X[n] | X[n] | X[n] | | | | |
| Future Use Specimen Collection | | | X | | | | | | |
| Prior/Concomitant Medications/Treatments | X | X | X[o] | X | X | X | X | X | X |
| Review/confirm adherence to dietary restrictions/birth control methods[p] | X | X | | | X | X | X | X | |
| Admit to CRU | | X | | | | | | | |
| Discharge from CRU | | | | | X | | | | |
| Receive study product[q,r] | | | X | | | | | | |
| Collect and Record AEs | | | X | X | X | X | X | X | X |

* Cohort 6 may enroll prior to the SMC meeting or prior to the start of Cohort 5 (but no less than 60 days after completion of Cohort 3).

Abbreviations: AE: adverse event; BMI: body mass index; CBC: complete blood count; CRU: clinical research unit; ECG: electrocardiogram; EW: early withdrawal; FSH: follicle-stimulating hormone; HIV-1: Human Immunodeficiency Virus-1; HIV-2: Human Immunodeficiency Virus-2; HBsAg: Hepatitis B surface antigen; Anti-HCV: anti-Hepatitis C virus; IMP: investigational medicinal product; PK: pharmacokinetics.

Footnotes to Schedule of Assessments and Procedures:

[a] Weight and BMI only.

[b] Including alcohol and tobacco use history.

[c] Update medical history as appropriate from previous visit.

[d] Complete physical examination (general appearance; head, eyes, ears, nose, and throat; neck; chest and lungs; cardiovascular system, abdomen, musculoskeletal system, lymph nodes, extremities/skin, and neurological system).

[e] Targeted physical examination (general appearance, heart, lungs, skin and abdomen). On Day 4, targeted PE will be performed at 72 hours (±30 min).

[f] Vital signs (heart rate, blood pressure, temperature, and respiratory rate) at Screening, Day -1, pre-dose on Day 1 and approximately 1, 2, 4, 8, 24 (Day 2), 48 (Day 3), 72 (Day 4), 144 (Day 7 outpatient visit), 312 (Day 14 outpatient visit) and 480 (Day 21 outpatient visit) hours after dosing. The pre-dose Day 1 vital signs measurements should be taken within 60 minutes of dosing. Day 1 post-dose vital signs measurements should be taken ±10 minutes of the nominal timepoint. All other vital signs measurements during the inpatient stay should be taken within ± 30 minutes of the nominal time point. For outpatient visits, vital signs measurements should be taken within the visit window. All vital signs are taken after subject is at rest for at least 5 minutes.

[g] ECGs will be performed at Screening; pre-dose taken within 60 minutes of dosing and post-dose, taken 4 hours) after dosing on Day 1; at 72 hour (± 30 minutes) prior to discharge from the CRU on Day 4 (±15 min), and on Day 21. All ECG readings are triplicate recordings, at least 1 minute apart within a 15-minute period and are taken after at least 5 minutes in the supine position. For the Day 21 outpatient visit, the ECG should be taken within the visit window.

[h] Clinical laboratory tests to include: clinical chemistry panel (albumin, glucose, blood urea nitrogen or urea, potassium, calcium, sodium, chloride, total protein, creatinine, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total carbon dioxide, creatine phosphokinase, phosphorus, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, magnesium, gamma-glutamyl transferase (GGT) and serum cortisol), CBC (red blood cell count, total and differential white blood cell count, hemoglobin, hematocrit, and platelet count), coagulation parameters (activated partial thromboplastin time, prothrombin time, and international normalized ratio), and urinalysis (leukocyte esterase, blood, pH, and specific gravity [microscopic tests to be completed if dipstick urinalysis is abnormal]). Subjects must fast at least 8 hours before blood collection for the clinical chemistry panel. Cortisol must be fasting and drawn before 10 a.m.

[i] Serum pregnancy test for women of childbearing potential at Screening, Day -1 and Day 21 (Final Study Visit).

[j] Follicle-stimulating hormone on all post-menopausal women at Screening.

[k] Urine drug test at Screening and on Day -1 to include cotinine, opiates, cocaine, cannabinoids, phencyclidine, benzodiazepines, barbiturates, amphetamines, and cotinine. Alcohol screen is performed by urine test.

[l] Immunology screen to include tests for the detection of antibodies to HIV-1 and HIV-2, HBsAg, and antibodies to HCV.

[m] PK blood samples will be collected on the following schedule following study product administration on Day 1: pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 36, 48, 60, 72, 144 (Day 7 outpatient visit), 312 (Day 14 outpatient visit) and 480 (Day 21 outpatient visit) hours post-dose. The pre-dose Day 1 PK blood sample should be taken within 60 minutes of before dosing for the fasted cohorts and within 30 minutes of the start of the pre-dose meal for the fed cohort; the Day 1 0.5-hour post dose blood sample should be taken within ± 5 minutes of the nominal timepoint. Remaining post-dose Day 1 PK blood samples should be taken within ± 10 minutes of the nominal time point. An additional 6 mL blood for future use is collected at 6 hours (±10 minutes) post dose. Day 2, 3 and 4 PK blood samples should be taken within ± 30 minutes of the nominal time point. For outpatient visits, PK blood samples should be taken within the visit window. PK blood samples take precedence; however, vital signs and ECGs should be completed before the blood draw, when possible.

[n] PK urine samples will be collected in the following intervals following study product administration on Day 1: --6to 0 hours before dose, and 0-6, 6-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours post-dose.

.[o] A review for concomitant medication will be performed before and after dosing on Day 1.

[p] Screening: review birth control methods, permitted/non-permitted medications, non-medications, dietary and activity restrictions; Day -1: confirm that subject adhered to dietary restrictions (no food/beverages containing alcohol for previous 72 hours or caffeine for the previous 24 hours; no grapefruit, grapefruit juice, or juices containing grapefruit, or Seville oranges for previous 7 days); Days 7 and 14 - confirm that subject adhered to post-discharge dietary restrictions (no consumption of grapefruit, or juices containing grapefruit or Seville oranges, no alcohol consumption) until after the visit to the CRU on Day 14; Review post-discharge instructions (including birth control methods, permitted/non-permitted medications, non-medications, dietary and activity restrictions)

[q]Cohorts 1-5 will receive study product when fasted and subjects will remain fasted for at least 4 hours post-dose; Cohort 6 is administered study product following a high-fat, high-calorie meal, which is consumed within 30 minutes and dosing is administered at 30 minutes after start of meal.

[r] For the nominal dose escalations, the study product will be administered in a fasting state and the subjects will remain fasted for 4 hours post- dose. Cohort 6 will be dosed with 160 mg of study product after ingestion of a high-fat, high-calorie meal

[s]For unscheduled visits, Safety assessments including updated history and the following onsite evaluations: AE, PE, and any other study procedures deemed necessary by the PI will be obtained. Early termination assessments will be the same as the Day 21 procedures

# Appendix B. VT-1598 TOXICITY GRADING CRITERIA FOR NORMAL HUMAN SUBJECTS

| Adverse Events* | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) |
|---|---|---|---|
| **Laboratory Adverse Events* (Blood, Serum or Plasma)** | | | |
| Sodium (hyponatremia) – mEq/L | 131-132 | 129-130 | <129 |
| Sodium (hypernatremia) – mEq/L | 144-145 | 146-147 | >147 |
| Potassium (hyperkalemia) – mEq/L | 5.2 – 5.4 | 5.5 – 5.6 | >5.6 |
| Potassium (hypokalemia) – mEq/L | 3.2-3.4 | 3.0 – 3.1 | <3.0 |
| Phosphorus – mg/dL (Hypo) | 2.3 – 2.4 | 2.1 – 2.2 | ≤2.0 |
| Phosphorus – mg/dL (Hyper) | N/A | N/A | N/A |
| Magnesium – mg/dL | 1.3-1.5 | 1.1-1.2 | <1.1 |
| Gamma- Glutamyl Transferase (GGT) – Male – U/L | N/A | N/A | N/A |
| Gamma- Glutamyl Transferase (GGT) – female – U/L | N/A | N/A | N/A |
| Glucose (hypoglycemia) – mg/dL | 65 – 69 | 55 – 64 | <55 |
| Glucose (hyperglycemia) – mg/dL Fasting | 106 – 125 | 126 – 200 | >200 |
| Blood Urea Nitrogen – mg/dL | 21-26 | 27 – 31 | > 31 |
| Creatinine (Male) – mg/dL | 1.3 – 2.0 | 2.1-2.3 | >2.3 |
| Creatinine (Female) – mg/dL | 1.0 – 1.7 | 1.8 – 2.0 | >2.0 |
| Calcium (hypocalcemia) – mg/dL | 8.0 – <LLN | 7.5 – 7.9 | <7.5 |

| Adverse Events* | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) |
|---|---|---|---|
| Calcium (hypercalcemia) – mg/dL | 10.4-10.8 | 10.9-11.4 | >11.4 |
| Chloride – mEq/L | N/A | N/A | N/A |
| CPKt-U/L (Male) | 1.1 - ≤ 1.5 x ULN | >1.5 - ≤ 3.0 x ULN | >3.0 ULN or higher |
| CPKt – U/L(Female) | 1.1 - ≤ 1.5 x ULN | >1.5 - ≤ 3.0 x ULN | >3.0 ULN or higher |
| A.M. Cortisol (serum, drawn prior to 10 a.m.) – ug/dL | 1-10% below LLN | 10-25 % below LLN | >25% below LLN with or without symptoms |
| Albumin (hypoalbuminemia) – g/dL | 2.8 – 3.4 | 2.5 – 2.7 | < 2.5 |
| AST – U/L | 1.1 - ≤ 2.5 x ULN | >2.5 - ≤ 5.0 x ULN | >5.0 x ULN or higher |
| ALT – U/L | 1.1 - ≤ 2.5 x ULN | >2.5 - ≤ 5.0 x ULN | >5.00 x ULN or higher |
| Total Bilirubin (serum) – mg/dL | 1.1 - ≤ 1.25 x ULN | >1.25 - ≤ 1.50 x ULN | >1.50 x ULN or higher |
| Direct Bilirubin – mg/dL | 1.1 - ≤ 1.25 x ULN | >1.25 - ≤ 1.50 x ULN | >1.50 x ULN or higher |
| Indirect Bilirubin – mg/dL | 1.1 - ≤ 1.25 x ULN | >1.25 - ≤ 1.50 x ULN | >1.50 x ULN or higher |
| Amylase – U/L | 1.1 - ≤ 1.5 x ULN | >1.5 - ≤ 2.0 x ULN | >2.0 x ULN or higher |
| Lipase – U/L | 1.1 - ≤ 1.5 x ULN | >1.5 - ≤ 2.0 x ULN | >2.0 x ULN or higher |
| Hemoglobin (Male) – g/dL | 11.2 - 12.2 | 10.0 – 11.1 | <10.0 |
| Hemoglobin (Female) – g/dL | 9.8 - 10.8 | 8.5 - 9.7 | <8.5 |
| WBC Increase – cell/$mm^3$ | 10,001– 15,000 | 15,001 – 20,000 | > 20,000 |
| WBC Increase – cell/$mm^3$ (African America Males) | 9,001 – 14, 000 | 14,001 – 19, 000 | >19,000 |
| WBC Increase – cell/$mm^3$ (African American Females) | 11,001 – 15,000 | 15,001 – 20,000 | >20,000 |

| Adverse Events* | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) |
|---|---|---|---|
| WBC Decrease – cell/mm$^3$ | 2,500– 3,999 | 1,500 – 2,499 | < 1,500 |
| WBC Decrease – cell/mm$^3$ (African American Males) | 2,200 – 2,499 | 1,200 – 2,199 | <1,200 |
| WBC Decrease – cell/mm$^3$ (African American Females) | 2,200 – 2,499 | 1,500 – 2,199 | <1,500 |
| Neutrophils Decrease – cell/mm$^3$ | 1,300 – <1,699 | 1,000 – 1,299 | < 1,000 |
| Neutrophils Decrease – cell/mm$^3$ (African American Males) | 1,000 – 1,299 | 800 - 999 | <800 |
| Neutrophils Decrease – cell/mm$^3$ (African American Females) | 1,100 – 1,299 | 1,000 – 1,099 | <1,000 |
| Platelets Decreased - cell/mm$^3$ | 120,000 – <150,000 | 100,000 – 119,999 | <100,000 |
| PT (prothrombin time) – seconds | 11.6 – 12.6 | 12.7 – 13.7 | >13.7 |
| PT INR (Prothrombin INR) | 1.2-1.4 | 1.5-1.9 | 2.0 or higher |
| PTT (partial thromboplastin time) –seconds | 30.1 – 36.8 | 36.9 – 43.6 | >43.6 |
| Total Protein – g/dL | 5.5 - 5.9 | 5.0 - 5.4 | <5.0 |
| Alkaline phosphatase – IU/L (Male) | 1.1 - ≤ 2.0 x ULN | >2.0 - ≤ 3.0 x ULN | >3.0 x ULN or higher |
| Alkaline phosphatase – IU/L (Female) | 1.1 - ≤ 2.0 x ULN | >2.0 - ≤ 3.0 x ULN | >3.0 x ULN or higher |
| Hematocrit (Male) - % | 33.0 -36.1 | 29.8 - 32.9 | < 29.8 |
| Hematocrit (Female) - % | 29.5 - 32.6 | 26.0 – 29.4 | < 26.0 |
| RBC (Male) – x $10^6$/uL | 3.9 - 4.1 | 3.4 - 3.8 | < 3.4 |

| Adverse Events* | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) |
|---|---|---|---|
| RBC (Female) – x $10^6$/uL | 3.5 - 3.7 | 3.0 - 3.4 | < 3.0 |
| Lymphocytes - cell/$mm^3$ decrease | 600- 799 | 500 – 599 | < 500 |
| Monocytes – cell/$mm^3$ increase | 1001-2000 | 2001-3000 | >3000 |
| Eosinophils - cell/$mm^3$ increase | 871 - 950 | 951 - 1700 | >1700 |
| Basophils - cell/$mm^3$ increase | 101 - 300 | 301 - 800 | > 800 |
| High Density Lipoproteins (HDL) Male – mg/dL | N/A | N/A | N/A |
| High Density Lipoproteins (HDL) Female – mg/dL | N/A | N/A | N/A |
| Total Carbon Dioxide – mEq/L | N/A | N/A | N/A |
| Total Cholesterol – mg/dL | N/A | N/A | N/A |
| Low Density Lipoprotein Cholesterol, Direct – mg/dL | N/A | N/A | N/A |
| Triglycerides – mg/dL | N/A | N/A | N/A |
| **Laboratory Adverse Events* (Urine)** | | | |
| Protein | 1+ | 2+ | >2+ |
| Glucose | 1+ | 2+ | >2+ |
| Blood (microscopic) - red blood cells per high power field (rbc/hpf)** | 3-10** | 11-50** | >50 and/or gross blood** |

*Abnormal laboratory values, performed as part of hematology, chemistry panel, or urinalysis but not listed in Appendix B, VT-1598 TOXICITY GRADING CRITERIA FOR NORMAL HUMAN SUBJECTS, will be evaluated by the study clinicians, recorded in the source document and, if clinically significant, considered AEs and graded according to the criterion described in Section 8.1.

| Adverse Events* | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) |
|---|---|---|---|

** Hematuria during active menses is considered not clinically significant.

| Vital Sign Adverse Events | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) |
|---|---|---|---|
| Fever<br>(°C)<br>(°F) | <br>38.0 – 38.4<br>100.4 – 101.1 | <br>38.5 – 38.9<br>101.2 – 102.0 | <br>39.0 – 40<br>102.1 – 104 |
| ECG – QTcF (ms) | > 30 but ≤60 above baseline | >60 above baseline to ≤500 | >500 |
| Tachycardia – (beats per minute) | 101 – 115 | 116 – 130 | >130 |
| Bradycardia – (beats per minute) | 50-54 if baseline >60 | 45-49 if baseline >60 | <45 if baseline >60 |
| | 45-50 if baseline ≤ 60 | 40-44 if baseline ≤ 60 | <40 if baseline ≤ 60 |
| Hypertension (systolic) – mmHg | 141 – 150 | 151 – 155 | >155 |
| Hypertension (diastolic) – mmHg | 91 – 95 | 96 – 100 | >100 |
| Hypotension (systolic) – mmHg | 85 – 89 | 80 – 84 | <80 |
| Respiratory Rate – breaths per minute | 17-20 | 21-25 | >25 |
| Nausea/vomiting | No to mild interference with activity or 1 to 2 episodes/24 hours | Moderate interference with activity or >2 episodes/24 hours | Prevents daily activity, requires outpatient IV hydration |
| Diarrhea | 2 - 4 loose stools or | 5-6 stools or 400 – 800 | 7 or more watery stools or >800gms/24 hours or |

| Vital Sign Adverse Events | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) |
|---|---|---|---|
| | < 400 gm/24 hours | gm/24 hours | requires outpatient IV hydration |
| Headache | No interference with activity | Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity | Significant; any use of narcotic pain reliever or prevents daily activity |
| Fatigue | No interference with activity | Some interference with activity | Significant; prevents daily activity |
| Adverse Events – Other | | | |
| Illness or clinical AE (as defined according to applicable regulations | No interference with activity | Some interference with activity, not requiring medical intervention | Prevents daily activity and requires medical intervention |