Title Page

Protocol Title:

A Randomized, Double-Blind, Single and Multiple Ascending Dose Study to Assess the Safety and Pharmacokinetics of ANA001 in Healthy Adults

Protocol Number: ANA001-002.02

Compound Number: ANA001

Short Title:

A single ascending dose (SAD) and multiple ascending dose (MAD) PK study of ANA001in healthy adults

Sponsor Name and Legal Registered Address:

ANA Therapeutics, Inc.
602 Bainbridge St.
Foster City, CA 94404 USA

Regulatory Agency Identifying Number(s):

IND #148459

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Version: 2.0

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that the information is *privileged* or *confidential* and may not be further disclosed by them. These restrictions on disclosure will apply equally to *all* future information supplied to you that is indicated as *privileged* or *confidential*.

INVESTIGATOR AGREEMENT

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations, as well as the "Guideline for Good Clinical Practice," International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure they are fully informed regarding the study drug and the conduct of the study.

Principal Investigator

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(Day Month Year)

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STUDY ADMINISTRATION

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Protocol Amendment History

Date	Description
24-Dec-20	**Amendment 1**
	The protocol is amended to address comments received by the FDA as follows: - Revising the Inclusion criteria pulse rate limits from 40 -100 bpm to 50 – 100 bpm - Providing reference laboratory values that will be used to determine if laboratory results are considered clinically significant - Providing a standard toxicity grading scale - Providing of detailed individual and dose level stopping criteria based upon the known safety profile and mechanism of action of ANA001 (niclosamide) - Limiting the total daily dose in the MAD portion of the protocol to 2000 mg
	Page 8. <u>MAD</u> Total daily doses ~~are anticipated to range between~~ will not exceed 2000 mg and ~~4500 mg~~ of ANA001.
	Page 18. Section 3.3 **Benefit/Risk Assessment** The current SAD/MAD study is designed to explore the safety and PK of dosing ~~greater than~~ **up to** ~~2000~~ **3000** mg/day as a single dose and **regimens not to exceed 2000 mg/day** as divided doses BID or TID.
	Page 20. <u>MAD</u> Total daily doses ~~are anticipated to range between~~ will not exceed 2000 mg ~~and 4500 mg~~ of ANA001.
	Page 21. Section 5.5 **Justification for Dose** The current study is designed to assess the safety of single doses of ANA001 ~~exceeding~~ up to 3000 ~~2,000~~ mg and multiple dosing regimens ~~up to~~ not to exceed 2000 mg daily divided either BID or TID.

Date	Description
24-Dec-20	**Amendment 1**
	Page 22. Section 6.1 **Inclusion Criteria** 6. Pulse rate between ~~40~~ 50 and 100 beats per minute (bpm)
	Page 23. Section 6.2 **Exclusion Criteria** Clinically significant abnormal values for hematology, clinical chemistry, or urinalysis at screening as ~~deemed appropriate by the Investigator~~ **assessed per Appendix 6.**
	Page 25. 7.2 **Dose Modification** ~~Following review of the safety and PK data of three SAD cohorts, a fourth cohort may be added, not to exceed 4500 mg.~~ Total daily doses ~~are anticipated to be between~~ will not exceed 2000 mg ~~and 4500 mg~~.
	Page 31. Section 9.1.4 **Clinical Safety Laboratory Assessments** The Investigator must review the laboratory report, document this review, and record any clinically relevant changes **(as per the reference laboratory values [Appendix 6])** occurring during the study in the AE section of the CRF. All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant ~~by the Investigator or medical monitor~~ **as per the reference laboratory values in Appendix 6.** If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant ~~by the Investigator~~ **as given in Appendix 6** (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.
	Page 33. Insertion of 9.3 **Stopping Rules in Response to SAE**

Date	Description
24-Dec-20	**Amendment 1**
	Dose-limiting toxicity AEs will be defined as Grade ≥3, treatment-emergent, treatment-related laboratory abnormalities (Appendix 6) or AEs per the grading system by US Department of Health and Human Services (CTCAE, Version 5.0). The following Stopping Criteria will be used: Clinical Findings: 1. Anaphylaxis or Grade ≥3 skin rash or pruritis 2. Grade ≥3 nausea, emesis or diarrhea Laboratory Findings: 1. Evidence of new onset of acute renal or hepatic failure, defined by increases in BUN, creatinine, or LFTs (AST, ALT, Alkaline phosphatase) that reflect new evidence of Grade 3 thresholds for liver function tests, for creatinine, and for electrolytes attributable to the administration of drug in the context of the Investigator's evaluation. 2. Evidence of acute infection or inflammation, defined by changes in the WBC and differential indices, attributable to the administration of drug in the context of the Investigator's evaluation. 3. Any "unexpected" Grade ≥3 Laboratory test result. If one of the above clinical or laboratory criteria for stopping occurs in any subject, further study recruitment and subject dosing will be halted until a full safety assessment can be completed. Unblinding of the affected subject will be performed and the PI and Sponsor will review the totality of clinical data and any other circumstances possibly related to the "Stopping Criteria" findings to determine if the study can be resumed, modified, or will be permanently terminated.
	Page 33. Section 9.3 **Treatment of Overdose**

Date	Description
24-Dec-20	**Amendment 1**
	For this study, any dose of ANA001 greater than ~~4500~~ **3000** mg within a 24-hour time period will be considered an overdose.
	Page 37. Section 11 **References** Inserted reference in relation to Stopping rules: **US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. Published: November 27, 2017.**
	Page 50. **Appendix 4** Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant ~~in the medical and scientific judgment of~~ **by** the Investigator **per Appendix 6** (i**.e.**, not related to progression of underlying disease).
	Insertion of **Appendix 6 Potentially Clinically Significant Laboratory Criteria**
	Editorial Changes
	Language in **bold** has been added to the document for clarification purposes. Minor formatting and typographical errors were corrected throughout the protocol.
	Page 7. Section 1 Synopsis and Page 15. Section 3.1 Study Rationale **ANA001 is a new formulation containing 250 mg niclosamide per capsule.** Although **other formulations containing** niclosamide (ANA001) **have** been studied for tapeworm infections and other potential human uses, limited systemic PK/PD data exists in the literature. To ensure proper systemic levels of niclosamide are achieved for therapeutic effect, a SAD/MAD study **with ANA001 capsules** is necessary.
	Page 7. Section 1 Synopsis ANA001 capsule **containing** 250 mg **niclosamide**, administered orally as 4, 6, 8 or 12 capsules with a light meal (500 to 750 cal) or snack.

Date	Description
24-Dec-20	**Amendment 1**
	All participants on active treatment who contributed at least one post dose **blood sample**, evaluable **for drug** PK concentration will be included in the PK analysis.
	Global change throughout protocol Replaced ‘postdose’ with ‘after dosing’ and ‘predose’ with ‘before dosing’ expect with analysis timepoints.
	Page 14. Section 3 Introduction Due to its pleiotropic pharmacologic activity, niclosamide has been and ~~is being~~ **continues to be** studied ~~in~~ **for** a variety of other clinical indications. COVID-19 ~~is~~ **results in** a cytokine release syndrome.
	Page 43. Appendix 1 Updated as per changes in text.

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1. Synopsis

Protocol Title: A Randomized, Double-Blind, Single and Multiple Ascending Dose Study to Assess the Safety and Pharmacokinetics of ANA001 in Healthy Adults

Short Title: A single ascending dose (SAD) and multiple ascending dose (MAD) PK study of ANA001 in healthy adults

Rationale:

ANA001 is a new formulation containing 250 mg niclosamide per capsule. Although other formulations containing niclosamide (ANA001) have been studied for tapeworm infections and other potential human uses, limited systemic PK/PD data exists in the literature. To ensure proper systemic levels of niclosamide are achieved for therapeutic effect, a SAD/MAD study with ANA001 capsules is necessary.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess safety and tolerability of single oral daily doses of ANA001 (1000 mg, 2000 mg and 3000 mg) • To assess safety and tolerability of multiple daily oral doses (twice daily [BID] or thrice daily [TID]) of ANA001 for 7 days	• Incidence of adverse events (AEs), serious AEs (SAEs), study drug discontinuation due to an AE (MAD portion only), use of concomitant medications, and change from baseline in clinical laboratory tests, vital signs, electrocardiograms (ECG), and physical examinations
Secondary	
• To assess the PK of single and multiple doses of ANA001	• $AUC_{0\text{-}t}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$ (SAD only), C_{max}, t_{max}, $t_{1/2}$, CL/F, V_z/F

Overall Design:

This is a randomized, double-blind study to be conducted in two parts: single ascending dose (SAD) and multiple ascending dose (MAD). Potential participants for each part will undergo screening procedures within 30 days of enrolment.

<u>SAD</u>

On Day -1, eligible participants will be randomly assigned to active drug or placebo in an 8:2 ratio. On Day 1, following an overnight fast of at least 10 hours, participants will receive their assigned treatment (1000 mg, 2000 mg, or 3000 mg of ANA001) with a standardized light meal (500 to 750 cal). A baseline ECG will be performed at Screening and at 3 hours after dosing. Blood pressure and heart rate will be measured every 8 hours while confined to the clinic. Blood for PK will be collected before dosing and at 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hours after dosing. Participants will be discharged on Day 2 following the 24-hour PK sample and completion of clinical laboratory tests and physical examination. They will return on Day 7 (±2) for follow-up procedures including physical examination, laboratory tests, and assessment of AEs and concomitant medication use.

MAD

On Day -1, eligible participants will be randomly assigned to active drug or placebo in a 10:2 ratio on a BID (q12h) or TID (q8h) schedule, to be determined based on the PK results of the SAD cohorts. Total daily doses will not exceed 2000 mg of ANA001. On Days 1 through 7, participants will receive their assigned treatment in the morning with a standardized light meal (500 to 750 cal) following an overnight fast of at least 10 hours. Afternoon or evening doses will be given with a light snack. A baseline ECG will be performed at Screening and at 3 hours after the second dose on Day 7. Blood pressure and heart rate will be measured every 8 hours while confined to the clinic.

During BID dosing, blood for PK will be collected on Days 1 and 7 before dosing and at 0.5, 1, 2, 4, 6, 8, 10, and 12 hours after dosing. Blood samples will also be collected on Days 2, 4, 6, and 8 before dosing and before the 12 hour dose on Days 2, 4, and 6.

During TID dosing, blood for PK will be collected on Days 1 and 7 before dosing and at 0.5, 1, 2, 4, 6, and 8 hours after dosing. Blood samples will also be collected on Days 2, 4, 6, and 8 before dosing, and before the 8 hour dose on Days 2, 4, and 6, and before the 16 hour dose on Day 6.

Participants will be discharged on Day 8 following the last PK sample and completion of clinical laboratory tests and physical examination. They will return on Day 15 (±2) for follow-up procedures including physical examination, laboratory tests, and assessment of AEs and concomitant medication use.

Number of Participants:

A minimum of 30 participants will be enrolled in the SAD part and up to 36 participants in the MAD part. At least 3 participants of each sex will be included in each cohort.

Treatment Groups and Duration:

SAD

Cohort S1: 1000 mg (n=8) or placebo (n=2), single dose

Cohort S2: 2000 mg (n=8) or placebo (n=2), single dose

Cohort S3: 3000 mg (n=8) or placebo (n=2), single dose

MAD

Cohort M1: xx mg (n=9) or placebo (n=3) BID or TID for 7 days

Cohort M2: xx mg (n=9) or placebo (n=3) BID or TID for 7 days

Cohort M3: xx mg (n=9) or placebo (n=3) BID or TID for 7 days

Investigational Product, Dose, and Mode of Administration

ANA001 capsule containing 250 mg niclosamide, administered orally as 4, 6, 8 or 12 capsules with a light meal (500 to 750 cal) or snack.

Statistical Methods

Sample Size Determination:

Sample size was not based on statistical considerations.

Safety Analysis:

All participants who received at least one dose of study drug will be included in the safety analysis. Safety will be assessed by the incidence and frequency of AEs, and changes in physical examinations, vital signs, clinical laboratory tests, and ECGs. Results will be summarized using descriptive statistics (mean, standard deviation [SD], coefficient of variation [%CV], median, minimum, maximum).

Pharmacokinetic Analysis:

All participants on active treatment who contributed at least one post dose blood sample, evaluable for drug PK concentration will be included in the PK analysis. PK parameters, calculated using non-compartmental models, include $AUC_{0-\infty}$, AUC_{0-t}, AUC_{0-last}, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V_z/F. Results will be summarized using descriptive statistics (mean, standard deviation [SD], coefficient of variation [%CV], median, minimum, maximum). Plasma concentration-time profiles will be plotted.

2. Schedule of Activities (SoA)

Table 1 Schedule of Activities for SAD

	Screening	In-Patient		Discharge	Follow-up
Study Day	-30 to -2	-1	1	2	7±2
Study Procedures					
COVID Pre-screen informed consent	**X**				
Full study informed consent	X				
Medical history	X				
Prior medications	X				
Physical examination	X				
Abbreviated PE		X	X	X	X
Viral Serology (HIV, HCV, HBV)	X				
Urine alcohol and drug screen	X	X			
Inclusion / exclusion criteria	X	X			
Pregnancy test for WOCBP	X	X			
Randomization		X			
CPU Admission & Confinement		X	X		
CPU Discharge				X	
Drug Administration[a]			X		
Vital signs[b]	X	X	X	X	X
Height	X				
Weight	X	X			
ECG[c]	X		X		
Hematology	X	X		X	X

	Screening	In-Patient		Discharge	Follow-up
Study Day	-30 to -2	-1	1	2	7±2
Study Procedures					
Serum chemistry	X	X		X	X
Urinalysis	X			X	X
Pharmacokinetics[d]			X	X	
Adverse events		Continuous			
Concomitant medications		Continuous			

WOCBP = woman of child-bearing potential

a.) Administered with Standardized light meal

b.) Blood pressure and heart rate supine for 3 to 5 mins and every 8 hours during CPU confinement

c.) Supine for 5 mins at Screening and 3 hours after dosing

d.) 4 mL before dosing and 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hr after dosing

Table 2 Schedule of Activities for MAD

	Screening	Confinement/Treatment Period								Discharge	Follow-up
Study Day	-30 to -2	-1	1	2	3	4	5	6	7	8	D15±2
Study Procedures											
COVID Pre-screen ICF	**X**										
Full study informed consent	X										
Medical history	X										
Prior medications	X										
Physical examination	X										
Abbreviated PE		X		X			X			X	X
Viral Serology (HIV, HCV, HBV)	X										

	Screening	Confinement/Treatment Period								Discharge	Follow-up
Study Day	-30 to -2	-1	1	2	3	4	5	6	7	8	D15±2
Study Procedures											
COVID Surveillance (ELISA)		+ *Swab*			X			X			
Urine alcohol and drug screen	X	X									
Pregnancy test for WOCBP	X	X									
Inclusion / exclusion criteria	X	X									
Randomization		X									
CPU Admission & Confinement		X	X	X	X	X	X	X	X		
CPU Discharge										X	
Drug Administration[a]			X	X	X	X	X	X	X		
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Weight	X										
ECG[c]	X								X		
Hematology	X	X		X			X			X	X
Serum chemistry	X	X		X			X			X	X
Urinalysis	X			X			X			X	X
Pharmacokinetics[d]			X	X	X	X	X	X	X	X	
Adverse events		Continuous									
Concomitant medications		Continuous									

WOCBP = woman of child-bearing potential
a.) Administered with standardized light meal (500 to 750 cal) in AM and light snack (PM) if BID (q12h) or TID (q8h) daily on days 1 through 6 and a single AM dose on day 7
b.) Blood pressure and heart rate supine for 3 to 5 mins and every 8 hours during confinement
c.) Supine for 5 mins at Screening and at 3 hours after second dose on Day 7
d.) see Table 3

Table 3 Schedule of PK Sampling for MAD

	PK Sampling (4 mL) Study Day BID Dosing							
Time (hr)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Pre-dose	X[a]	X[a]		X[a]		X[a]	X[a]	X[a]
0.5	X						X	
1	X						X	
2	X						X	
4	X						X	
6	X						X	
8	X						X	
10	X						X	
12	X	X[a]		X[a]		X[a]	X[a]	
	PK Sampling (4 mL) Study Day TID Dosing							
Time (hr)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Pre-dose	X[a]	X[a]		X[a]		X[a]	X[a]	X[a]
0.5	X						X	
1	X						X	
2	X						X	
4	X						X	
6	X						X	
8	X	X[a]		X[a]		X[a]	X[a]	

[a] Pre-dose

3. Introduction

Niclosamide is a chlorinated salicylanilide with anthelmintic, antiviral and anti-inflammatory activity being developed as a potential treatment for COVID-19. Niclosamide was discovered in 1958, and was approved by the Food and Drug Administration (FDA) in 1982 under New Drug Application (NDA) 018669 (Bayer Pharmaceuticals) for the treatment of tapeworm infections, although it has since been voluntarily discontinued from marketing in the United States by Bayer. Niclosamide is approved in several other countries for the treatment of tapeworm infections and is on the World Health Organization's List of Essential Medicines. Due to its pleiotropic pharmacologic activity, niclosamide has been and continues to be studied for a variety of other clinical indications.

ANA Therapeutics is developing ANA001, an orally administered niclosamide formulation containing 250 mg niclosamide per capsule, to treat adult patients with coronavirus disease of 2019 (COVID-19). COVID-19 results in a cytokine release syndrome (Hirano and Murakami, 2020) that is associated – amongst others - with acute respiratory distress syndrome (ARDS), a widespread inflammation in the lungs, and increased blood clotting. Niclosamide is a promising oral therapeutic which has both antiviral and anti-inflammatory properties and a long history of safety in humans.

Niclosamide has broad *in vitro* antiviral activity (Fan *et al*., 2019, Andersen *et al*., 2019, Jurgeit *et al*., 2012, Mazzon *et al*., 2019, Xu *et al*., 2020, Wu *et al*., 2004, Wen *et al*., 2007, Gassen *et al*., 2019) including activity against severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) with a half-maximal inhibitory concentration (IC_{50}) of 0.15-0.28 µM (49-92 ng/mL) (Shi, 2020, unpublished data, Jeon *et al*., 2020, Gassen *et al*., 2020). Additionally, niclosamide has *in vitro* anti-inflammatory properties due to its inhibition of nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) and signal transducer and activator of transcription 3 (STAT3), two main drivers to induce the expression of proinflammatory cytokines. NF-κB and STAT3 were inhibited by niclosamide with an IC_{50} of 0.125 µM (40.9 ng/mL) (Jin *et al*., 2010) and 0.25 µM (81.8 ng/mL), respectively (Ren *et al*., 2010). In addition, a recent *in vitro* study showed that niclosamide works as a potent bronchodilator that relaxed histamine induced constriction of mouse tracheal rings and human bronchial rings with a half-maximal effective concentration (EC_{50}) of 124 ng/mL (0.4 µM) and 240 ng/mL (0.7 µM), respectively (Miner *et al*., 2019).

PK data available in the literature show significant variability. A single dose of 2000 mg reaches maximal systemic serum concentrations in humans of 0.76 µM to 18.3 µM (249 to 5986 ng/mL) (Andrews et al., 1982). A study with prostate cancer patients showed that 149-182 ng/mL (0.46-0.56 µM) become available after a single oral dose of 1000 mg (Schweizer et al., 2018). These studies strongly suggest that the dose regimen foreseen for clinical development – between 1000 mg BID, 1000 mg TID and 2000 mg BID - will provide sufficient systemic and intracellular drug levels for effective antiviral and anti-inflammatory activity. However, there is a need for well characterized PK data to support dose selection in COVID-19 and other indications.

As niclosamide was approved by FDA to treat tapeworms in humans, it has a well-understood clinical safety profile on oral administration at 2000 mg daily for up to 7 days. In addition, it has been studied in clinical trials in oncology and several other indications, and two other Sponsors have recently initiated trials of niclosamide in COVID-19 patients. This Investigational New Drug Application represents the first clinical use of ANA001 capsules, thus there is no previous clinical data to report for this formulation of niclosamide.

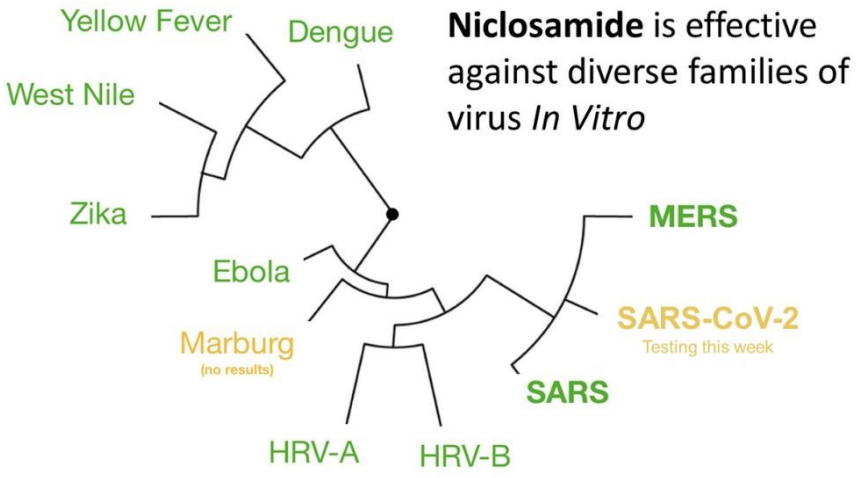
3.1. Study Rationale

ANA001 is a new formulation containing 250 mg niclosamide per capsule. Although other niclosamide formulations have been studied for tapeworm infections and other potential human uses, limited systemic PK/PD data exists in the literature. To ensure proper systemic levels of niclosamide are achieved for therapeutic effect, a SAD/MAD study with ANA001 capsules is necessary.

3.2. Background

Niclosamide has broad *in vitro* antiviral activity (Fan *et al*., 2019, Andersen *et al*., 2019, Jurgeit *et al*., 2012, Mazzon *et al*., 2019, Xu *et al*., 2020, Wu *et al*., 2004, Wen *et al*., 2007, Gassen *et al*., 2019) including activity against coronaviruses (Figure 1). Three initial publications have demonstrated that niclosamide inhibited replication of both SARS-CoV at concentrations of ≥1.56 µM (≥510 ng/mL) (Wu *et al*., 2004) and 40 µM (13,084 ng/mL) (Wen *et al*., 2007) and Middle East respiratory syndrome (MERS)-CoV with an IC_{50} of 0.32 µM (105 ng/mL) (Gassen *et al*., 2019).

Figure 1 Phylogenetic Tree Showing Antiviral Effects of Niclosamide Against Various Virus Families



Source: Adapted from Xu *et al* 2020.

SARS-CoV, MERS-CoV and SARS-CoV-2 share 86% homology (Wilder-Smith *et al*., 2020) and three recent studies have confirmed the *in vitro* antiviral efficacy of niclosamide against SARSCoV-2. The reported IC_{50} values were 0.15 µM (49 ng/mL) (Shi, 2020, unpublished data), 0.28 µM (92 ng/mL) (Jeon *et al*., 2020) and 0.17 µM (56 ng/mL) (Gassen *et al*., 2020).

Furthermore, it was shown that pretreating cells for 24 h with 5 µM (1636 ng/mL) niclosamide followed by drug washout and viral infection reduced SARS-CoV-2 replication significantly (Gassen *et al*., 2020). This indicates that niclosamide has potential as a prophylactic COVID-19 treatment and that serum concentrations may not need to continuously exceed *in vitro* inhibitory levels to be effective.

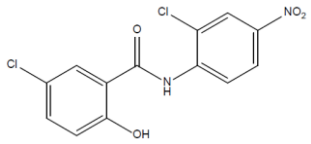
3.2.1. Chemical Name/Structure

USAN: Niclosamide

IUPAC: 5-Chloro-N-(2-chloro-4- nitrophenyl)-2-hydroxybenzamid

Molecular formula: $C_{13}H_8Cl_2N_2O_4$

Molecular weight: 327.1 g/mol



3.2.2. Nonclinical Studies

Nonclinical Pharmacology

In an *in vitro* study, Vero E6 cells were infected with a SARS-CoV-2 reporter virus. This virus has a luciferase gene engineered into its genome and when cells are infected with such a reporter virus, they express luciferase that can be quantified to measure viral replication. Increasing concentrations of niclosamide were added to Vero E6 cells together with reporter SARS-CoV-2. Twenty-four hours post-infection, infected cells were assayed for luciferase activity. The antiviral IC_{50} of niclosamide was 0.15 µM (49 ng/mL) (Shi, 2020, unpublished data).

In a separate *in vitro* study, 50 FDA-approved drugs were screened for their ability to inhibit SARS-CoV-2 replication. Vero cells were infected with SARS-CoV-2 in the absence and presence of various drug concentrations. 24 hours post infection, cells were scored by immunofluorescence analysis with an antibody specific for the viral N protein of SARS-CoV-2 to generate dose-response curves for each compound tested. Niclosamide demonstrated an IC_{50} of 0.28 µM (92 ng/mL). In the same assay, the IC_{50} values of remdesivir, chloroquine and lopinavir were 11.41 µM (3732 ng/mL), 7.28 µM (2381 ng/mL) and 9.12 µM (2983 ng/mL), respectively (Jeon *et al*., 2020).

In an additional *in vitro* study, VeroFM cells were infected with SARS-CoV-2 and treated with increasing concentrations of niclosamide. 48 hours post infection, plaque forming units were determined by plaque assay. The antiviral IC_{50} of niclosamide was 0.17 µM (56 ng/mL).

Furthermore, pretreating VeroFM cells for 24 h with 5 µM niclosamide significantly reduced viral replication (Gassen *et al*., 2020).

Nonclinical Toxicology

Oral toxicology studies for NDA 018669 evaluated niclosamide in mice, rats, rabbits, dogs, and cats. Single dose studies included doses as high as 5000 mg/kg in rats without any lethality (reviewed in Andrews *et al*., 1982). A repeat dose study with dogs showed that single oral doses of 6000 mg/kg for 8 consecutive days, followed by 4500 mg/kg for another 24 consecutive days were tolerated well with no signs of intoxication (reviewed in Andrews *et al*., 1982). Other repeat dose studies in rabbits, cats or dogs with doses that were 2-5 times the human therapeutic dose and lasted 11, 12, and 84-96 days were non toxic, based on routine laboratory tests and toxicology. Male cats were noted to have a mild reduction in white blood cells (WBC), and dogs showed a tendency toward watery stools, but otherwise adverse treatment effects were not evident. Other studies reported that doses of 250 mg/kg may cause vomiting in dogs and cats. The conclusion of these studies was that niclosamide was a low risk for dosing orally in humans at the standard therapeutic regimen of 2000 mg/day (BAYER NDA 018669; Summary Basis for Approval (SBA)).

3.2.3. Safety

Between 1971 and 1978, niclosamide was administered to 6365 patients under a US IND. Doses were up to and including 2000 mg/day for 7 days. There were 2385 evaluable patients, of which 13.3% reported side effects, all of which were mild or moderate, with none requiring treatment discontinuation. These included nausea/emesis in 4.1%, abdominal discomfort/loss of appetite in 3.4%, diarrhea in 1.6%, drowsiness/dizziness/headache in 1.4%, and skin rash/pruritis in 0.3% of patients (NDA 018669 Review Documentation).

In addition, according to the Safety Review of Niclosamide, Pyrantel, Triclabendazole and Oxamniquine report of the World Health Organization (WHO), there have been 84 reported adverse drug reactions related to niclosamide between 1975 and 2004 in the WHO database. They include 173 reports from 16 countries and the most common reactions are related to skin and appendages (41 reports), gastrointestinal tract (37 reports), cardiovascular system (28 reports) and anaphylactic reactions (9 reports).

Niclosamide was approved as a pregnancy class B drug and is thus safe to use during pregnancy.

Summarized below are safety assessment findings reported in the available literature:

- Prostate cancer patients received 500 mg and 1000 mg of niclosamide orally thrice per day for 15 days. TID regimens of >500 mg PO per day suggested the potential for DLT, however these findings are confounded by coadministration of antineoplastic treatment associated with a similar range of GI disturbances and occurred after niclosamide was dosed for >7 days (Schweizer *et al*., 2018).
- Colorectal cancer patients received 2000 mg of niclosamide orally once per day until disease progression or toxicity (up to four months). No adverse side effects were reported (Burock *et al*., 2020).

- 2000 mg niclosamide/person did not result in hematological changes (Andrews *et al*., 1982).
- No induction of methemoglobinemia was observed in men after oral administration of 30 mg/kg b.w. (~2000 mg/person) (Andrews *et al*., 1982).
- Men and women received 1000 mg niclosamide once or twice per person; children (6-15 years of age) received 750-1000 mg/person; neither scenario resulted in signs of intoxication (Andrews *et al*., 1982).
- In a Phase I study, adults were divided into two groups (niclosamide and placebo). Study participants received 2000 mg/day for 3 days with a repeat course 6 days later. Transitory reactions, such as loose stools and stomach aches were reported (Andrews *et al*., 1982).
- No dermal sensitizing effect was observed upon topical administration (Andrews *et al*., 1982).

At the established doses, most adverse events were transitory and generally mild to moderate.

3.3. Benefit/Risk Assessment

Niclosamide is approved for dosing up to 2000 mg PO daily for 7 days. There is limited safety and PK data in humans receiving more than 2000 mg as a single dose and/or more frequently than once daily. The current SAD/MAD study is designed to explore the safety and PK of dosing up to 3000 mg/day as a single dose and regimens not to exceed 2000 mg/day as divided doses BID or TID. In light of the immediate pressing need for development of an effective and safe oral therapeutic that can prevent progression of COVID-19, the benefit to risk ratio for the study is anticipated to be justified.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of ANA001 may be found in the Investigator's Brochure.

4. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess safety and tolerability of single oral daily doses of ANA001 (1000 mg, 2000 mg and 3000 mg) • To assess safety and tolerability of multiple daily oral doses (twice daily [BID] or thrice daily [TID]) of ANA001 for 7 days	• Incidence of adverse events (AEs), serious AEs (SAEs), study drug discontinuation due to an AE (MAD portion only), use of concomitant medications, and change from baseline in clinical laboratory tests, vital signs, electrocardiograms (ECG), and physical examinations
Secondary	
• To assess the PK of single and multiple doses of ANA001	• $AUC_{0\text{-}t}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$ (SAD only), C_{max}, t_{max}, $t_{1/2}$, CL/F, V_z/F

5. Study Design

5.1. Overall Design

This is a randomized, double-blind study to be conducted in two parts: single ascending dose (SAD) and multiple ascending dose (MAD). Potential participants for each part will undergo screening procedures within 30 days of enrolment.

SAD

On Day -1, eligible participants will be randomly assigned to active drug or placebo in an 8:2 ratio. On Day 1, following an overnight fast of at least 10 hours, participants will receive their assigned treatment (1000 mg, 2000 mg, or 3000 mg of ANA001) with a standardized light meal (500 to 750 cal). A baseline ECG will be performed at Screening and at 3 hours after dosing. Blood pressure and heart rate will be measured every 8 hours while confined to the clinic. Blood for PK will be collected before dosing and at 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hours after dosing. Participants will be discharged on Day 2 following the 24-hour PK sample and completion of clinical laboratory tests and physical examination. They will return on Day 7 (±2) for follow-up procedures including physical examination, laboratory tests, and assessment of AEs and concomitant medication use.

MAD

On Day -1, eligible participants will be randomly assigned to active drug or placebo in a 9:3 ratio on a BID (q12h) or TID (q8h) schedule, to be determined based on the PK results of the SAD cohorts. Total daily doses will not exceed 2000 mg of ANA001. On Days 1 through 7, participants will receive their assigned treatment in the morning with a standardized light meal (500 to 750 cal) following an overnight fast of at least 10 hours. Afternoon or evening doses will be given with a light snack. A baseline ECG will be performed at Screening and at 3 hours after the second dose on Day 7. Blood pressure and heart rate will be measured every 8 hours while confined to the clinic.

During BID dosing, blood for PK will be collected on Days 1 and 7 before dosing and at 0.5, 1, 2, 4, 6, 8, 10, and 12 hours after dosing. Blood samples will also be collected on Days 2, 4, 6, and 8 before dosing and before the 12 hour dose on Days 2, 4, and 6.

During TID dosing, blood for PK will be collected on Days 1 and 7 before dosing and at 0.5, 1, 2, 4, 6, and 8 hours after dosing. Blood samples will also be collected on Days 2, 4, 6, and 8 before dosing, before the 8 hour dose on Days 2, 4, and 6, and before the 16 hour dose on Day 6.

Participants will be discharged on Day 8 following the last PK sample and completion of clinical laboratory tests and physical examination. They will return on Day 15 (±2) for follow-up procedures including physical examination, laboratory tests, and assessment of AEs and concomitant medication use.

5.2. Participant and Study Completion

A minimum of 30 participants will be enrolled in the SAD part and up to 36 participants in the MAD part. At least 3 participants of each sex will be included in each cohort.

5.3. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

Sequential timing of the ascending dose cohorts will allow early stopping if serious or unanticipated safety signals are observed at any dose level.

5.5. Justification for Dose

Niclosamide was approved by FDA to treat tapeworms in humans and has a well understood clinical safety profile with oral administration at 2000 mg daily for up to 7 days. Furthermore, a single dose of 2000 mg reaches maximal systemic serum concentrations in humans of 0.76 µM to 18.3 µM (249 ng/mL to 5986 ng/mL) (Andrews et al., 1982). A study with prostate cancer patients showed that 149 ng/mL to 182 ng/mL (0.46 µM to 0.56 µM) become available after a single oral dose of 1000 mg (Schweizer et al., 2018). In a very recent study, colorectal cancer patients received 2000 mg of niclosamide orally once a day until disease progression or toxicity (up to four months). Plasma levels mainly peaked 240 minutes after the first niclosamide administration with a median C_{max} of 2.03 µM (665 ng/mL) (Burock et al., 2020). The lower bounds of the reported C_{max} values fall within the effective in vitro ranges of niclosamide as an antiviral agent (0.15-0.28 µM, 49-92 ng/mL) (Shi, 2020, unpublished results; Jeon *et al*., 2020, Gassen *et al*., 2020) and an anti-inflammatory drug that inhibits NF-kB and STAT3 at 0.13 µM (42.5 ng/mL) (Jin *et al*., 2010) and 0.25 µM (81.8 ng/mL) (Ren *et al*., 2010), respectively.

These studies strongly suggest that the dose regimens between 1000 mg BID to 2000 mg BID or 1000 mg TID to 1500 mg TID will provide sufficient systemic and intracellular drug levels for effective antiviral and anti-inflammatory activity. The current study is designed to assess the safety of single doses of niclosamide up to 3000 mg and multiple dosing regimens not to exceed 2000 mg daily divided BID or TID. The PK data from this study will be used to refine the optimum dose and frequency of administration to achieve antiviral and anti-inflammatory activity in humans.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Signed the COVID and study informed consent forms as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
2. Man or woman, 18 to 65 years of age inclusive at the time of signing the informed consent form
3. Overtly healthy as determined by medical evaluation including medical history, physical examination, clinical laboratory tests
4. Body mass index (BMI) within 18 to 30.0 kg/m^2 (inclusive) and body weight not less than 50 kg
5. Blood pressure (after supine for 5 minutes) at Screening and Day -1 between 90 and 140 mmHg systolic, inclusive, and no higher than 90 mmHg diastolic.
6. A 12-lead electrocardiogram (ECG) at Screening consistent with normal cardiac conduction and function, including:
   - Sinus rhythm
   - Pulse rate between 50 and 100 beats per minute (bpm)
   - QTc interval 450 milliseconds (QT interval corrected using Fridericia correction method [QTcF])
   - QRS interval of <120 milliseconds
   - PR interval <200 milliseconds
   - Morphology consistent with healthy cardiac conduction and function
7. Non-smoker or ex-smoker for >12 months
8. If male, must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 30 days (a spermatogenesis cycle) after the last dose of study treatment and refrain from donating sperm during this period
9. If female, is not pregnant (see Appendix 5), not breastfeeding, and meets at least one of the following conditions:

   Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

   OR

A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 30 days (one menstrual cycle) after the last dose of study treatment.

Note: Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting will take place during an unscheduled visit in the screening phase.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has a history of or current clinically significant medical illness including but not limited to: cardiac arrhythmias or other cardiac disease; hematologic disease; coagulation disorders (including any abnormal bleeding or blood dyscrasias); lipid abnormalities; significant pulmonary disease, including bronchospastic respiratory disease; diabetes mellitus; hepatic or renal insufficiency (creatinine clearance below 60 mL/min); thyroid disease; neurologic or psychiatric disease; infection; or any other illness that the Investigator considers should exclude the subject or that could interfere with the interpretation of the study results.
2. Has known allergy to niclosamide or salicylate-containing medications.
3. Clinically significant abnormal values for hematology, clinical chemistry, or urinalysis at screening as assessed per Appendix 6
4. Clinically significant abnormal physical examination, vital signs or 12 lead ECG at screening as deemed appropriate by the Investigator
5. Has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV; has a history of hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at Screening.
6. History of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria within 5 years before screening or positive test result(s) for alcohol and/or drugs of abuse at screening and admission
7. Has received an investigational drug or used an invasive investigational medical device within 1 month or within a period less than 10 times the drug's half-life, whichever is longer, before Day 1.
8. Has preplanned surgery or procedures that would interfere with the conduct of the study
9. Is an employee of the Investigator or study site, with direct involvement in the proposed study or other studies under the direction of that Investigator or study site, as well as family members of the employees or the Investigator

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

1. Participants will refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 3 days before the start of study treatment until after the final dose.

6.3.2. Caffeine, Alcohol, and Tobacco

1. Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final pharmacokinetic (PK) blood sample.

2. Participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK blood sample.

3. Use of tobacco products will not be allowed during the study.

6.3.3. Activity

1. Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Study Treatment Name:	**ANA001**	**Placebo**
Dosage formulation:	Size 0 capsule	Size 0 capsule
Unit dose strength(s)/ Dosage level(s):	250 mg/capsule	NA
Route of Administration	oral	oral
Dosing instructions:	4, 6, 8, or 12 capsules with light meal or snack[a]	4, 6, 8, or 12 capsules with light meal or snack[a]
Packaging and Labeling	Bulk bottle	
Storage conditions	Capsules (ANA001 or matching placebo) should be stored at controlled room temperature (20-25 °C) out of direct sunlight.	
Manufacturer	ANA Therapeutics, Inc.	

[a] 500 to 750 cal

7.2. Dose Modification

The dose(s) and schedule (BID or TID) in the MAD part will be determined following review of the safety and PK data from the SAD part. Total daily doses will not exceed 2000 mg.

7.3. Method of Treatment Assignment

Within each cohort, participants will be randomly assigned to active drug or placebo as they qualify for the study using a computer-generated randomization.

7.4. Blinding

Participants will be randomly assigned to receive study treatment. Investigators will remain blinded to each participant's assigned study treatment throughout the course of the study. In order to maintain this blind, an otherwise uninvolved 3rd party (e.g., site pharmacist) will be responsible for the dispensation of all study treatment and will endeavor to ensure that there are no differences in time taken to dispense following randomization.

7.5. Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

Participants will receive study treatment under the direct supervision of the Investigator or designee. A hand- and mouth check will be done to ensure that the participants swallowed the drugs.

7.7. Concomitant Therapy

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

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

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

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

Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the Investigator.

7.7.1. Rescue Medicine

No rescue medication will be provided.

7.8. Treatment after the End of the Study

Participants will not receive study drug (ANA001 or matching placebo) after the end of the study.

8. Discontinuation/Withdrawal Criteria

8.1. Discontinuation of Study Treatment

An unexpected AE related to study drug could lead to temporary or permanent discontinuation of a participant's study treatment, as determined by the Medical Monitor or Investigator.

8.2. Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

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

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

See SoA (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Participants who withdraw will not be replaced.

8.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Volume of Blood to be Collected From Each Subject - SAD

Type of Sample	Volume per Sample (mL)	No. of Samples/ Subject	Total Volume of Blood (mL)[a]
Safety (including screening and post treatment assessments)			
- Hematology	4	4	16
- Serum chemistry	8.5	4	34
serology (HIV, hepatitis)	8.5	1	8.5
serum β-hCG pregnancy test	3	1	3
Pharmacokinetic samples - SAD	4	10	40
Total – SAD			101.5

[a] Calculated as number of samples multiplied by amount of blood per sample.

Volume of Blood to be Collected From Each Subject - MAD

Type of Sample	Volume per Sample (mL)	No. of Samples/ Subject	Total Volume of Blood (mL)[a]
Safety (including screening and post treatment assessments)			
- Hematology	4	6	64
- Serum chemistry	8.5	6	51
serology (HIV, hepatitis)	8.5	1	8.5
serum β-hCG pregnancy test	3	1	3
Pharmacokinetic samples – MAD (BID/TID)	4	25/28	100/112
Total – BID			226.5
Total - TID			238.5

[a] Calculated as number of samples multiplied by amount of blood per sample.

Approximately 102 mL of blood will be collected during the SAD part. During the MAD, approximately 227 mL will be collected following BID dosing and 239 mL during TID dosing.

9.1. Safety Assessments

Safety assessments include incidence and frequency of AEs/SAEs, study drug discontinuation due to an AE (MAD portion only), use of concomitant medications, and changes from baseline in clinical laboratory tests, vital signs, electrocardiograms (ECG), and physical examinations.

9.1.1. Physical Examinations

A complete physical examination, conducted at screening, will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal, and Neurological systems. Height and weight will also be measured and recorded.

A brief physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal systems.

9.1.2. Vital Signs

Vital signs should be taken in a quiet setting without distractions (e.g., television, cell phones) and before any blood collections.

Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed with a completely automated device after 3 to 5 minutes rest in a supine position. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements will be measured after 3 to 5 minutes rest in a supine position.

9.1.3. Electrocardiograms

A single ECG will be obtained for screening and at 3 hours after dosing during the SAD portion of the study and at Screening and 3 hours after dosing on Day 7 during the MAD portion. An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals will be used.

9.1.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 2) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes (as per the reference laboratory values [Appendix 6]) occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant as per the reference laboratory values in Appendix 6.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant as given in Appendix 6 (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study.

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

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

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

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

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until 30 days after the last dose.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.3. Stopping Rules in Response to SAEs or Other Events

Dose-limiting toxicity AEs will be defined as Grade ≥3, treatment-emergent, treatment-related laboratory abnormalities (Appendix 6) or AEs per the grading system by US Department of Health and Human Services (CTCAE, Version 5.0)The following Stopping Criteria will be used:

Clinical Findings:

1. Anaphylaxis or Grade ≥3 skin rash or pruritis
2. Grade ≥3 nausea, emesis or diarrhea

Laboratory Findings:

1. Evidence of new onset of acute renal or hepatic failure, defined by increases in BUN, creatinine, or LFTs (AST, ALT, Alkaline phosphatase) that reflect new evidence of Grade 3 thresholds for liver function tests, for creatinine, and for electrolytes attributable to the administration of drug in the context of the Investigator's evaluation.
2. Evidence of acute infection or inflammation, defined by changes in the WBC and differential, attributable to the administration of drug in the context of the Investigator's evaluation.
3. Any "unexpected" Grade ≥3 laboratory test result.

If one of the above clinical or laboratory criteria for stopping occurs in any subject, further study recruitment and subject dosing will be halted until a full safety assessment can be completed. Unblinding of the affected subject will be performed and the PI and Sponsor will review the totality of clinical data and any other circumstances possibly related to the "Stopping Criteria" findings to determine if the study can be resumed, modified, or will be permanently terminated.

9.4. Treatment of Overdose

For this study, any dose of ANA001 greater than 3000 mg within a 24-hour time period will be considered an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until ANA001 can no longer be detected systemically (at least 7 days).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.5. Pharmacokinetics

Whole blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of ANA001 as specified in the SoA (Section 2). Additional samples may be collected during the study if warranted and agreed upon between the Investigator and the Sponsor.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

The following PK parameters for ANA001 will be estimated using actual sample collection times:

C_{max}	maximum plasma concentration during a dosing interval
C_{min}	minimum plasma concentration during a dosing interval
t_{max}	time to reach the maximum plasma concentration
AUC_t	area under the plasma concentration-time curve from time 0 to time t after dosing
$AUC_{0\text{-last}}$	area under the plasma concentration-time curve from time 0 to time the last quantifiable concentration
$AUC_{0\text{-}\infty}$	area under the plasma concentration-time curve from time 0 to infinity
$t_{1/2}$	elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$
CL/F	Systemic clearance
V_z/F	Volume of distribution

9.6. Medical Resource Utilization and Health Economics

Not applicable.

10. Statistical Considerations

10.1. Sample Size Determination

Sample size was not based on statistical considerations.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Safety	All participants randomly assigned to study treatment and who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
Pharmacokinetic	All participants randomly assigned to study treatment, who take at least 1 dose of study treatment, and contribute at least 1 post-dose evaluable PK sample. Participants will be analyzed according to the dose they actually received.

10.3. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.3.1. Safety Analyses

All safety analyses will be performed on the Safety Population. Safety parameters will include frequency of treatment-emergent AEs (TEAEs), SAEs, study drug discontinuation due to an AE (MAD portion only), concomitant medication use, and changes from baseline in clinical laboratory results, vital signs, ECG, and physical examinations. TEAEs are defined as AEs that started or worsened after dosing. Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities. A list of participants who have SAEs and who discontinue from the study due to an AE will be provided. Treatment-emergent AEs will be summarized by system organ class and preferred term for each dose level.

Individual results of laboratory tests (chemistry, hematology, and urinalysis) will be listed and summarized. Baseline, post-dose, and change from baseline to post-dose laboratory data will be summarized by dose. Individual results of vital signs will be listed and summarized. Observed values and changes from baseline in vital signs will be summarized by dose. Individual results of ECG parameters from the 12-lead safety ECGs will be listed and changes from baseline will be

summarized by dose. Physical examination findings and concomitant medication use will be presented in data listings.

10.3.2. Pharmacokinetic Analyses

The non-compartmental PK analyses will be described in the Statistical Analysis Plan finalized before database lock. Plasma concentrations of ANA001 will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus actual time points will be presented in listings. Pharmacokinetic parameters of ANA001 will be summarized by dose using descriptive statistics. Individual PK parameters will be presented in a data listing. Dose proportionality will be assessed graphically and using the power model.

10.3.3. Interim Analyses

Data from the SAD Cohorts S1 through S3 will be summarized and evaluated to determine the doses and schedule to be used in a potential 4th SAD cohort and the BID and TID MAD cohorts. The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

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12. Appendices

Appendix 1: Abbreviations and Terms

ANA	ANA Therapeutics, Incorporated
API	Active pharmaceutical ingredient
ARDS	Acute respiratory distress syndrome
AUC	Area under curve
BID	Twice daily
BSL	Bio-safety Level
CL	Clearance
Cmax	Maximum serum concentration
CoV	Coronavirus
COVID-19	Coronavirus disease of 2019
CYP	Cytochrome P450
DG	Dose group
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DMSO	Dimethylsulfoxide
DP	Drug product
DS	Drug substance
EC50	Half-maximal effective concentration
ECMO	Extracorporeal membrane oxygenation
IC50	Half-maximal inhibitory concentration
FDA	Food and Drug Administration
GI	Gastrointestinal
GLP	Good laboratory practice

HDPE	high-density polyethylene
HTD	Human therapeutic dose
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IL	Interleukin
LD50	Half-maximal lethal dose
LLN	Lower limit of normal
MERS	Middle East respiratory syndrome
MRT	Mean residence time
NA	Not applicable
NDA	New drug application
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PBS	Phosphate buffered saline
PK	Pharmacokinetic
PO	By mouth
PVA	Polyvinyl alcohol
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SBA	Summary basis for approval
STAT	Signal transducers and activators of transcription
SUSAR	Suspected unexpected serious adverse reaction
t1/2	Elimination half-life
TID	Thrice daily
tmax	Time take to reach Cmax

TMEM16A	Transmembrane member 16A
TNF-α	Tumor necrosis factor-alpha
ULN	Upper limit of normal
VSS	Volume of distribution at steady state
WBC	White blood cell
WHO	World Health Organization

Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the local laboratory.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 4 Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="4">Hematology</td><td>Platelet Count</td><td rowspan="4">RBC Indices:
MCV
MCH
% Reticulocytes</td><td rowspan="4">WBC Count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td>RBC Count</td></tr>
<tr><td>Hemoglobin</td></tr>
<tr><td>Hematocrit</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td>BUN
Calcium
Creatinine</td><td>Glucose
Potassium
Sodium</td><td>Total and direct bilirubin
Total Protein</td></tr>
<tr><td colspan="3">Aspartate Aminotransferase (AST)
Alanine Aminotransferase (ALT)
Alkaline phosphatase</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="3">• Specific gravity
• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
• Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Other Screening Tests</td><td colspan="3">• Urine alcohol and drug screens (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)
• Serum human chorionic gonadotropin (hCG) pregnancy test at Screening and urine pregnancy test on Day -1 for women of childbearing potential
• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody or specify other tests)</td></tr>
</table>

Investigators must document their review of each laboratory safety report.

Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

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

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR

50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

A clinical study report will be prepared with reference to ICH Guidance E3 to include:

- details of where the study was carried out,
- dates of the start and completion of each period of the study,
- details of the investigational product (IP) and a statement of production will be provided by ANA Therapeutics, Inc.,
- a statement confirming that the applicable IRB/IEC gave written approval for the study in accordance with local regulations,
- a demographic listing for all participants,
- a list of all AEs according to IP,
- details of any occurrences which may be of significance to the study outcome,
- details of all operations, calculations and transformations performed on the reported data,
- the SAP and report will be produced by ANA Therapeutics, Inc. or their agents and will be incorporated into the final report,
- all data from any withdrawn participant not included in the statistical analysis,

- a scientific interpretation of the results,
- a description of the study methods used.

Consideration will be given to any comments on a draft report. The report will incorporate the analytical and statistical results and methods produced by the Sponsor or their agents. A final report will be prepared to contain all those sections in the draft and a statement of compliance covering all the areas of the study conducted at the investigational site and the report, with GCP. The report will be issued under the Sponsor's responsibility.

Where required by the applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results. The Sponsor will also provide the Investigator with the full summary of study results.

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study treatment development

Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of an Adverse Event (AE)

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant by the Investigator per Appendix 6 (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

Recording and AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to ANA Therapeutics in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by ANA Therapeutics. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to ANA Therapeutics.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to ANA Therapeutics. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** ANA Therapeutics**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by ANA Therapeutics to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide ANA Therapeutics with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the ANA Therapeutics within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to ANA Therapeutics via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to ANA Therapeutics will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or by telephone.
- Contacts for SAE reporting can be found in the Study Manual.

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Study Manual.

Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

- Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following [during the protocol-defined time frame in Section 6.1]:

Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 5 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration [during the protocol-defined time frame]

Refrain from donating sperm for the duration of the study and for 30 days after the last dose of study treatment.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 5.

Table 5: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study treatment

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive pregnancy test.

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive active study treatment.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Investigator as described in Section 9.2. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study

Appendix 6: Potentially Clinically Significant Laboratory Criteria

(Local Laboratory Results)

Parameter	SI Unit	Lower Limit	Higher Limit	% Decrease from Bio-safety Level (BSL)	% Increase from BSL
CHEMISTRY					
Blood Urea Nitrogen (BUN)	mmol/L	NA	>1.5 *ULN	NA	>100
Creatinine	mg/dL	NA	>1.5 *ULN	NA	>50
Sodium	mmol/L	<0.85 *LLN	>1.1 *ULN	>10	>10
Potassium	µmol/L	<0.8 *LLN	>1.2 *ULN	>20	>20
Chloride	mmol/L	<0.8 *LLN	>1.2 *ULN	>20	>20
Carbon Dioxide (Bicarbonate)	mmol/L	<0.7 *LLN	>1.3 *ULN	>40	>40
Glucose	mmol/L	<0.6 *LLN	>3.0 *ULN	>40	>200
Total Bilirubin	mg/dL	NA	>2.5 *ULN	NA	>150
Direct Bilirubin	mg/dL	NA	>1.5 *ULN	NA	>150
Alkaline Phosphatase	U/L	<0.5 *LLN	>2.0 *ULN	>80	>100
Aspartate Aminotransferase (AST)	U/L	NA	>3.0 *ULN	NA	>200
Alanine Aminotransferase (ALT)	U/L	NA	>3.0 *ULN	NA	>200
HEMATOLOGY					
Hematocrit	Ratio	<0.8 *LLN	>1.3 *ULN	>20	>30
Hemoglobin	g/L	<0.8 *LLN	>1.3 *ULN	>20	>30
Platelet Count	10^9/L	<0.65 *LLN	>1.5 *ULN	>50	>100
White Blood Cell Count	10^9/L	<0.65 *LLN	>1.6 *ULN	>60	>100
Neutrophils, absolute cell count	10^9/L	<0.65 *LLN	>1.6 *ULN	>75	>100

Parameter	**SI Unit**	**Lower Limit**	**Higher Limit**	**% Decrease from Bio-safety Level (BSL)**	**% Increase from BSL**
Lymphocytes, absolute count	10^9/L	<0.25 *LLN	>1.5 *ULN	>75	>100
Eosinophils, absolute count	10^9/L	NA	>4.0 *ULN	NA	>300
Monocytes, absolute count	10^9/L	NA	>4.0 *ULN	NA	>300
Basophils, absolute count	10^9/L	NA	>4.0 *ULN	NA	>300
COAGULATION					
Partial Thromboplastin Time (aPTT)	sec	<0.5 *LLN	>2.0 *ULN	>100	>100
Prothrombin Time (PT)	sec	<0.5 *LLN	>2.0 *ULN	>100	>100
International Normalized Ratio (INR)	Ratio	<0.5 *LLN	>2.0 *ULN	>100	>100

LLN: Lower limit of normal value provided by the local laboratory

ULN: Upper limit of normal value provided by the local laboratory