

COVID-19 Vaccination Detoxication in Low Density Lipoprotein Cholesterol

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
9.4.2	Defining the actual primary efficacy endpoint, and adding some preliminary analyses.	Even though the participant's travel plans will shorten the primary efficacy endpoint by two days, the purpose of the endpoint can still be served.
9.4.2	Within the rationale of the null hypothesis, revisions to the study design and statistical analysis plan are made upon the UP from the start of the study.	The neurodivergent participant's case offered a new window for sebaceous immunobiology research. With the premises of clinical healing in the trial, the PI conceived various possible methods for further studies and study design under the primary purpose.

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

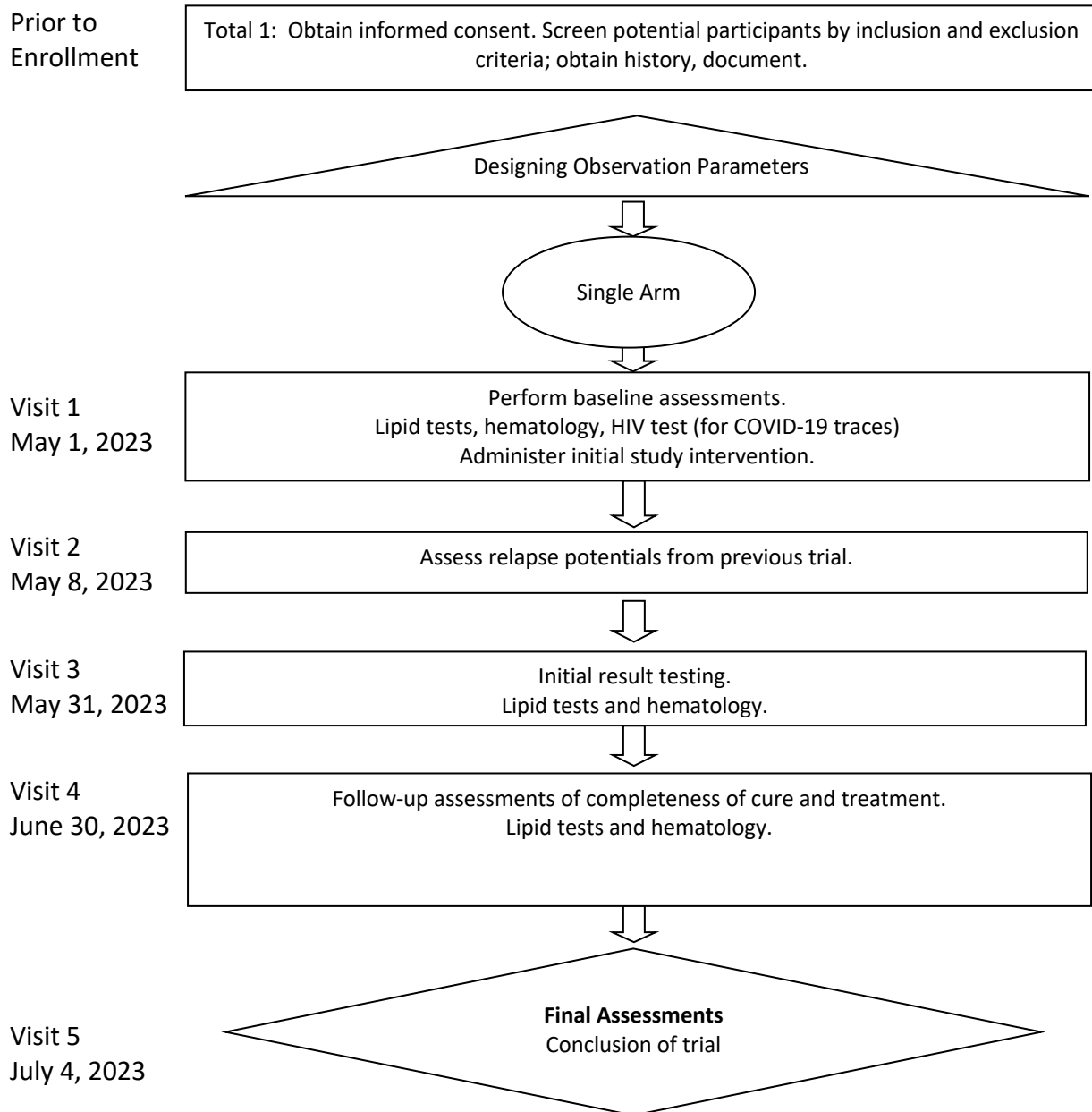
Title:	COVID-19 Vaccination Detoxification in Low Density Lipoprotein Cholesterol
Study Description:	The study hypothesizes that SARS-CoV-2 vaccination poisoning hibernates in human host in Low Density Lipoprotein Cholesterol (LDL-C). The clinical trial is a follow-up from the intervention trial with NCT number NCT05711810. It tests the use of Atorvastatin Calcium Tablets for detoxification and prevention of blood acidification, and the use of the Chinese herb compounded Anti-Viral Granules for the detoxification in the endocrine system.
Objectives:	<p>Primary Objective: Bypass the lipid degeneration activities in the blood system that can acidify the blood environment, and to detox the inactive or mildly active SARS-CoV-2 viruses and proteins out of the endocrine system and respiratory tract.</p> <p>Secondary Objectives: Observe and correlatively determine the functions and roles of chromatophores in immunology and immune reflex.</p>
Endpoints:	<p>Primary Endpoint: 7 days after the trial start as the observational window for emergent medicine preparedness.</p> <p>Secondary Endpoints: 30 days after the trial start for evaluation of effects.</p>
Study Population:	The sole participant trial takes place in Chongqing, mainland China. The participant, male, 35, Asian, has been intoxicated by COVID-19 vaccine and experienced severe cardiac adverse event. The study starts after the elimination of sudden death risks of the participant.
Phase:	2.
Description of Sites/Facilities Enrolling Participants:	The site is outside of the United States geographically. The participant is facilitated in his own residence in Chongqing, mainland China without restrictions to daily activities.

Description of Study Intervention: The intervention is taken orally with Atorvastatin Calcium Tablets 20 mg per night and Chinese herb compounded medicine Anti-Viral Granules 12 grams per day distributed in three times. Contaminant therapy is applicable and rescue medicine is prepared from the previous trial’s proven medicines.

Study Duration: 2 months.

Participant Duration: 1-2 month(s).

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Screening Day -1	Enrollment/B aseline Visit 1, Day 1	Study Visit 2 Day 7 +/-1 day	Study Visit 3 Day 30 +/- 1 day	Study Visit 4 Day 60 +/-1 day	Conclude Day 84 +/-1 day
Procedures						
Informed consent	X					
Demographics	X					
Medical history	X					
Administer study intervention		X ----- X				
Behavioral monitoring	X	X ----- X				X
Concomitant medication review		X ----- X				
Physical exam	X	X		X	X	
Performance status		X		X	X	X
Hematology		X		X	X	
Lipid tests		X		X	X	
Adverse event review and evaluation	X	X ----- X				

2 INTRODUCTION

2.1 STUDY RATIONALE

LDL-C's correlations to COVID-19 vaccine injuries incentivized further studies on the roles of chromatophores in human physiology. The rationale for the study design is informed both by the oxidative stress symptoms of the participant in the previous interventional trial with the ClinicalTrial.gov number NCT05711810, and sebaceous immunobiology (1-3). Ethnic differences in COVID-19 pathogenic risks have raised more awareness on the potential immunological roles of chromatophores against viral pathogens with correlations to bacteria, i.e., inflammation (4).

Evidence suggests chromatophores may be involved in natural detoxification and the human immune reflexes. The phenomenon was observed in proton motive force (PMF) dynamics with relation to adenosine triphosphatase (ATPase) (5). There is no current study on the biochemical correlations to the experimented photochemical oxidation of succinate by chromatophores from *Rhodospirillum rubrum* (6).

Vaccine poisoning entry path and LDL-C's correlations to COVID-19 prognosis and severity call for sebaceous immunobiology studies. Evidence emergence from the pilot interventional trial seeded the null hypothesis, that SARS-CoV-2 vaccination poisoning hibernates in human host in LDL-C, for another clinical trial after the elimination of sudden death risks of the participant (7-9).

The null hypothesis implies that SARS-CoV-2 acidification strategizes oxidizing the endocytic domain for getting out of hibernation and entering the host's upper immune system, and the respiratory and neurological pathogenesis partially result from hypoxia (10). The alternative hypothesis of the trial is separated into two parts: 1) COVID-19 vaccine injury can be detoxicated by inducing lipid degeneration outside of the blood system and in the sebaceous immunobiology level, therefore, the clinical medicine design; 2) spike protein platelet binding and / or further pathogenic activities depend on reactive oxygen species (ROS) (11). The objective for the alternative hypothesis is to bypass the lipid degeneration activities in the blood system that can acidify the blood environment, and to detox the inactive or mildly active viruses and proteins out of the endocrine system and respiratory tract. Due to the limited

availability of medicines, the antiviral drug's effect in the combination is unclear, and proton pump inhibitor will be discretely continued from the previous trial.

Since the participant's neurodiverse conditions are mainly associated with the vagus nerve and oxidization is also associated with the symptom emergence with the ATPase readjustments, the order of symptom disappearance between neurological conditions and vaccine detoxification can further narrow down the causal inference between sebaceous immunobiology and oxidization stress. Since platelet binding must proceed after initial rapid acidification in SARS-CoV-2 entry, it is highly likely that the correlation exists between oxidization and symptomatic autism spectrum disorder (ASD). The behavioral studies in the new trial therefore, may be able to contribute new knowledge on neurodiversity's implications to immunology and immune reflex. The differences in the rates of recovery between from detoxification and from neurodiverse symptoms for the ADS indicators will then evidence the correlative role of chromatophores in immunology and the immune reflex.

2.2 BACKGROUND

It has been traced that SARS-CoV-2 entered the participant's blood system already after the second vaccine shot, but the spike proteins did not bind to platelet at that time. The evidence was collected from the hematology and HIV-test included physical examination of the participant days rightly after the second vaccine shot, where minor chemiluminescence was detected but did not at the conclusion of the previous interventional trial (12, 13). The evidence suggests endocytic fusogenicity did not happen during the vaccination, but caused the pericarditis symptoms that informed the medical intervention (14). Furthermore, the participant's neurodiverse conditions did not symptomatically emerge and never symptomatically emerged before until after the intervention during worsened acidification, which suggests a correlation between the respiratory immune reflex and nervous system. Its continued symptoms after the stabilization of cardiac conditions imply that sebaceous immunobiology can be more associated with the neurological responses than the leukocyte disorders.

The ASD symptoms are seen as independent variable, and sebaceous changes under medication are seen as dependent variable. The severity of the first emergence of SARS-CoV between 2002 and 2003 in Guangzhou, PRC was deceitfully kept from the global society by the PRC government, and its potential roles in neurodegenerative disease associated clinical trials remain questionable (15-17). It is possible that the sebum and chromatophores regulate the ROS across the immune system and have an influence on immune reflex. The inference from the analysis may not be able to be determined by the clinical trial's study design, but the correlative evidences may accumulate just as the detail in its possible correlations with PMF (5, 18). Even though lipids are generally considered non-polar, they may have a polar activity with the ROS and PMF correlations that influence the physiological complex and viral infection patterns. Further studies into the molecular diffusion and kinetics via density and ions may shed new light on the questions involving chromatophores.

Cytokine storms in COVID-19 lung fibrosis could have resulted from ROS concentration in the immunological tract (19, 20). Albeit SARS-CoV series' spike proteins target across the immunological duality in human physiology, both's targeting features in human physiology concentrate on ROS-rich areas. With Spike 1 protein's angiotensin-converting enzyme (ACE) 2 targeting that takes a faster route across the blood-brain barrier through the carotid artery, the immune tract's less defense filtering from stem cells could have led to the respiratory symptoms that constitute the long mis-categorization of the virus.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There are inherent long-range risks for strokes and epilepsies for the participant from the COVID-19 vaccine poisoning / toxication. The risks are associated with the relapses of cardiac adverse events risks with the potentially hibernating viral loads in the participant’s system.

The known risks for atorvastatin oral intake mainly reside with muscle and liver problems, and increased blood sugar (21).

2.3.2 KNOWN POTENTIAL BENEFITS

The clinical trial may potentially prolong the long-range risks. If detoxication is achieved, the long-range risks from the incident can be potentially eliminated.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

With the participant’s recovery from cardiac adverse events, Trimetazidine Hydrochloride has been introduced as concomitant medicine to reduce the risks in muscle problems. The participant’s liver functioning is intact, but there is a mild risk from the participant’s continuous participation in the two trials continuously with long-term medicine administration. However, this risk is milder from the severity of the non-clinical long-range risks. The participant does not have a history of diabetes nor apparent risks thereof. The prostate function of the participant is intact and it is predicted uric acid levels may increase. Urological infections of COVID-19 may increase during the clinical trial resulted from increased blood sugar risks. Therefore, dosage adjustment on the main trial medicine will be conducted and monitored according to the blood pressure of the participant. The potential adverse event is leveraged against the low blood pressure risks in the rescue medicine from the previous interventional trial. Therefore, the immediate risks are optimal for the prevention of long-range risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective is to reaffirm the conclusion of the previous trial, and the safety of the current trial.	The primary endpoint will reaffirm the conclusion of the previous trial that the null hypothesis is based upon. The null hypothesis’ correctness will determine the possible efficacy of the clinical design. It then informs the possible behavioral tendencies of the participant during the trial period, and its implications to the testing of the alternative hypothesis.	The primary endpoint is mainly chosen for discretion in participant’s safety in health.
Secondary		
The secondary objective is to assess the efficiency of the clinical	The secondary endpoint is designed to obtain the objective data results on the clinical design. The data,	The secondary endpoint is chosen based on the time

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
design, and to determine if further treatments are needed.	compared with the historic data and data from the last trial will provide a better picture of the pathogenic developments in the participant's system. The immune reflex and sebaceous-blood-brain barriers will be assessed with the data analysis.	projection for the treatment to take relatively lasting effects.
Tertiary/Exploratory		
Tertiary objective is to evaluate the lasting effects of the intervention.	The tertiary endpoint's objective data will help evaluating if COVID-19 vaccine poisoning can be detoxicated for good.	The tertiary endpoint is designed to assess the relapse possibilities after the intervention.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The study is designed to seize the opportunity window of the participant's stabilized conditions to bypass the lipid degeneration activities in the blood system, which can acidify the blood environment, and to detox the inactive or mildly active viruses and proteins out of the endocrine system and respiratory tract.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The design is selected as active drug. Evidence from the participant's historic data and previous trial have narrowed down the case's pathogenesis with comparison to natural infection paths with regard to LDL-C levels (7).

4.3 JUSTIFICATION FOR DOSE

Starting dose for Atorvastatin Calcium Tablets is set at the highest approved safe dose of 20 mg per day. The dose is advantageous for the efficiency, and the safety from risks is ensured by the concomitant therapy.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form

2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, unpregnant and not planning pregnancy at least 1 month after the anticipated trial conclusion, aged 18 to 65
4. In good general health as evidenced by medical history and COVID-19 vaccinated
5. Ability to take oral medication and be willing to adhere to the COVID-19 Vaccination Detoxification regimen
6. Agreement to adhere to Lifestyle Considerations (see section 5.3) throughout study duration

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Has known liver problems
2. Diagnosed or have high risks for diabetes
3. Currently experiencing cardiac problems
4. Have known history of muscular dystrophy or related diseases and nutrition deficiency
5. Currently experiencing scurvy, leukemia, cancer, or similar blood-borne diseases
6. Pregnancy or lactation.

5.3 LIFESTYLE CONSIDERATIONS

It is advised that the participant take more fiber and protein-based food and avoid high sugar foods, including beverages. Whether coffees are continued to be prohibited will be determined after the primary endpoint. Excessive physical exercises should be avoided.

5.4 SCREEN FAILURES

Not applicable.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The participation followed from the interventional trial NCT05711810.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The main intervention in the study is Atorvastatin Calcium Tablets taken orally 20 mg per night. The dosage can be reduced to 10 mg or 5 mg per night according to the participant's actual tolerance of the medication. Anti-Viral Granules (12 grams per day) or other respiratory antiviral medicines is administered to assist the detoxification process. PPIs are taken 30 mg per day for discretion on the detoxification process' influence to transmembrane binding of the viruses. Blood pressure and heart rate are monitored for immune responses during detoxification.

6.1.2 DOSING AND ADMINISTRATION

All interventions are administered orally. The dosage is designed with the maximum for approved safe use for the statistical advantage where no sign of current virus activation is present.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The study intervention will be acquired locally by the sponsor and provided to the Principle Investigator (PI).

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The PI will properly label the medicines for the participant's handling and administration.

6.2.3 PRODUCT STORAGE AND STABILITY

The participant will be responsible for the appropriate storage of the medicines for daily intake.

6.2.4 PREPARATION

Not applicable.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

The participant will self-report to the PI on a weekly basis for the compliance of trial procedures.

6.5 CONCOMITANT THERAPY

With recovery from the previous interventional trial, Trimetazidine Hydrochloride 60 mg per day (total) in 3 times is used with cefixime 200 mg per day (total) in 2 times for stabilizing the cardiac conditions. Sertraline Hydrochloride 50 mg per day is used to maintain the ASD symptoms. PPI 30 mg per day is taken for discretionary purposes.

6.5.1 RESCUE MEDICINE

The study site will supply cardiac rescue medication that will be provided by the sponsor. The following rescue medications may be used: Sacubitril Valsartan Sodium Tablets, beta blockers, and / or ACE inhibitors.

Although the use of rescue medications is allowable at any time during the study, the use of rescue medications should be delayed, if possible, for at least 10 hours following the administration of Atorvastatin Calcium Tablets. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from COVID-19 Vaccine Detoxification does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- AE(s) that caused the decision;
- Causal inference on the AE(s);
- Retrospective data analysis.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention for 7 days.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 1 scheduled visit and is unable to be contacted by the study site staff.

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

- The site will attempt to contact the participant and reschedule the missed visit within 7 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will 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 or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Due to the limitations for hematology and lipid test frequencies, efficacy assessments can only be conducted at scheduled endpoints.

8.2 SAFETY AND OTHER ASSESSMENTS

Safety assessments are designed for the primary endpoint. It will be assessed with the monitoring of the participant’s blood pressure, and physiological ASD symptoms.

Historic hematology data assessment in the previous trial compared to the baseline from the second vaccine shot is performed and seen in the table below. The historic statistics suggest hematocrit is inversely correlated to viral immune attacks in the blood system, and viral binding applies both to leukocyte and red blood cells. This could be contributed by its influence to eosinophil numbers and percentage in the leukocyte’s acidification environment (22). Red blood cell and its CV and standard deviation suggest the receptor treatment was successful in dispersing the red blood cells from the binding activities with possible apoptosis, accompanied by increased mononucleosis percentage in leukocytes. The ROS’ role is seen in the corpuscular changes, while total hemoglobin result’s indication on leukocyte variance suggests oxidative stress is positively related to viral infection activities. Reduced oxidative stress positively contributes to the increased basophil percentage in leukocytes even when its absolute number decreases, suggesting reduced acid blood environment in recovery from the previous trial. The historic data support the study design and safety considerations.

Indicator	Peak	ACE	Placebo	Ramipril	ACE Receptor	Unit
Δ Leukocyte#	1840	2620	1670	5060	980	per μL
Δ Neutrophils#	1220	1490	-70	3260	140	per μL
Δ Lymphocyte#	390	590	1190	1100	460	per μL
Δ Mononucleosis#	60	150	80	400	130	per μL
Δ Eosinophil#	170	380	450	280	240	per μL
Δ Basophil#	0	10	20	20	10	per μL
Δ Neutrophils%	1.1	-1.3	-13.4	1.3	-6.2	%
Δ Lymphocyte%	-1.1	-1	9.2	-1.9	2.7	%
Δ Mononucleosis%	-0.4	0.2	0	1.3	1.1	%
Δ Eosinophil%	0.4	2.1	4	-0.7	2.2	%
Δ Basophil%	0	0	0.2	0	0.2	%
Δ Platelet Count	-45	-14	-15	-28	-10	10 ³ /μL
Δ Plateletcrit	0	0.03	0.02	0.01	0.02	%
Δ Platelet Distribution Width	0.7	0.3	0.3	0.6	0.3	fL
Δ Mean Platelet Volume	3.2	2.4	1.9	2.4	1.9	fL
Δ Red Blood Cell	40	-60	140	-330	-560	10 ³ /μL
Δ Red Blood Cell - CV	-1.2	-1.4	-1.5	-1	-0.8	%
Δ Red Blood Cell σ	5.3	4.6	1.7	4.4	5.9	fL
Δ Total Hemoglobin	6	6	11	-5	-7	g/L
Δ Hematocrit	3.1	2	3.6	-1.9	-2.6	%
Δ Mean Corpuscular Volume	5.2	5.1	4.3	2.2	5.2	fL
Δ Mean Corpuscular Hemoglobin	0.9	1.5	1.2	1.1	2.3	pg
Δ MCHC	-10	-3	-3	3	5	g/L

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant’s condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Any AEs will be directed reported to the PI by the participant.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

The PI will be responsible for Informing the participant on the evaluations of moderate and serious AEs.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

Not applicable.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC/study sponsor within 1 day of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution’s written reporting procedures), the supporting agency head (or designee), and the OHRP within 7 days of the IRB’s receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Statistical hypotheses are tested with relation to symptomatic behavioral signs. The symptomatic signs’ healing will determine the primary alternative hypothesis, and before or after the lipid and hematological recovery will determine the secondary alternative hypothesis.

- Primary Efficacy Endpoint: Null hypothesis is proven if no relapse.

The null hypothesis is based on the immune reflex’s associations with the symptomatic signs of the participant. With the cease of cardiac medicines, the stable blood pressure will evidence the recovery of the participant’s immune reflex from Spike 2 proteins. Cardiac contraction ache is associated with the immune responses to the mildly active spike proteins in the blood system, and the headache symptom ought to decrease as the conditioned cardiac responses wear off. If not at the primary efficacy endpoint, mild neurological infection during the previous trial cannot be eliminated completely, and the association of neurological responses in vagus nerve to sebaceous immunobiology is established. Headache symptom’s positive correlations with cardiac contraction ache will largely eliminate neurological infection from the previous trial, and increase the possibilities of the headache’s correlations with sebaceous immunobiology. The two’s correlations to stingy skin (skin responses) will further enhance the null and alternative hypotheses’ validities. It is predicted that if the headache symptom does not wear off on the primary efficacy endpoint, the other two symptomatic signs will not wear off before the primary efficacy point.

- Secondary Efficacy Endpoint: Alternative hypotheses are proven with the symptomatic signs’ disappearance time with relation to the lowered LDL-C and platelet binding.

Truth table on the behavioral observations’ correlations to hypotheses testing is seen below. The order of the symptomatic signs’ healing sequence will further determine the details and subsidiary truth values.

	Healing	Before or After	Null Hypothesis	Alternative Hypothesis 1	Alternative Hypothesis 2

Symptomatic Signs	F	-	-	F	-
	F	A	F	F	-
	T	B	T	T	F
	T	A	T	T	T

Symptomatic Signs	Degree	Healing	Time	Before or After	Order
Headache	Mild	T			
Cardiac contraction ache	Mild				
Stingy skin	Mild				

9.2 SAMPLE SIZE DETERMINATION

The upper threshold for diastolic blood pressure (DBP) in the primary efficacy endpoint is set at 80 mmHg, systolic blood pressure (SBP) at 115 mmHg, and heart rate (HR) at 90 beats per minute with 5% Type I error rate.

The indicators are defined as discrete random variable with the ranges of between 60 and 80 mmHg, 90 and 115 mmHg, and 60 and 90 beats per minute, respectively. Therefore, each sample will have a probability of $\frac{1}{3}$ falling below, within, and above the ranges. Power level is set with 90% for the statistics where the variance within the range is less than the value of 10. The baseline is tested at SBP/DBP/HR in 110/67/58.

Sampling frequency will be reduced after the primary efficacy endpoint, and the sample size will be reduced. However, at least 5 samples each week are still required after the primary efficacy endpoint, and the secondary efficacy endpoint's data will be merged with the primary.

9.3 POPULATIONS FOR ANALYSES

Apart from blood pressure and heart rate sample analyses, hematology and lipid analyses will be performed with relation to the participant's historic data.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Hematology and lipid test data will be analyzed qualitatively with quantitative features. The preliminary analyses on the historic data and trial start baseline data are seen in **Sections 8.2** and **9.4.5**.

General results on blood pressure and heart rate will be reported with standard deviation. Variance of the discrete random variable(s) will be calculated with the formula $var(X) = \sum(x - \mu)^2 p_x(x)$ (23). Statistical testing is seen in **Section 9.2**.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Due to the participant's travel plans, monitoring data collection will be suspended at midnight of May 6, 2023, and constitute as the *de facto* primary efficacy endpoint.

At the first three days, the participant's heart rate has still been experiencing turbulences, positively correlated to SBP's reaching in upper threshold. The phenomenon suggests that infection is still

happening in the participant's internal system, but the immune responses have recovered substantially from the last trial. The participant's migraine symptoms have become milder, and are sometimes shifted to sores identified to be located around the cervical plexus (24). The association of cervical nerve C1 and C2 to the vagus nerve, with C1's connection to the geniohyoid and the thyrohyoid and C1 & C2's connection in the rectus tract, reaffirms the introduction of PPI in the previous trial and reduces the possibilities of neurological infections from the previous trial by qualitative assessment (25, 26). The first shift of the headache to the cervical plexus happened after the participant's experience in months in excreting solid feces. It is possible that the participant's headache and previous migraine AE resulted from the previous study design's purposes in accelerating the natural respiratory excretion with medicine-induced internal oscillation. Burdens from the immune system through the cervical plexus inferentially explain the asthma-like and migraine AEs. The initial signs corroborate with the null hypothesis.

At the night of the second day (one day before the solid excretion), the participant experienced mild stretching spasm, different from the contractive spasms during headache that risk of stroke. It could've been the electrolyte changes under the medication influence, and the positive sign indicates that the dose is appropriate. The participant ate fat food at the third night, and both the SBP and HR rose above the threshold, compared to the others that only either goes slightly high. It is unclear on nutrition influences on LDL-C and HDL-C ratios based on viral infection level, therefore, discretion has been informed to the participant to prohibit fat foods, apart from the avoidance of high sugar food. The participant reported nauseating feelings after the fat and oily diet, which never occurred in the previous trial. The trial currently does not have the conditions to further examine lipid dynamics' correlations with the nervous system.

The conditions may be contributed by ASD. Even though the participant is in need of dopamine, the associations with adrenaline may worsen the current trial's clinical results (27). Since Adderall is banned in mainland China, and black-market alternatives are both high priced and risky in quality, no further medical assistance can be provided with discretion (28). The nauseating feelings of the participant under the UP may be contributed by the mixed signaling between internal neurological needs and immunological needs (29). Another UP is the red cell pigmentation on the skin of the participant. The UP is mild compared to similar AEs after the first vaccine shot of the participant, and the pigmentation has been noticed by the needle wound from hematology. Further correlative observations will be needed to assess the implications to the detail functions of the null hypothesis.

The participant's conditions restabilized on the fourth day's morning. The PI proposed the possibility in using phentolamine to deal with the UP (30, 31). If the participant's DBP does not decrease and heart rate & SBP decreased by the use of phentolamine, statistical presumptions with ASD as independent variable are more concrete other than being weakened. The local availability of phentolamine only exists with injective forms in the local hospital. The hospital doctor suggested to the PI that the precision thinking is not usually clinically significant, and clinically passive discretion with minor behavioral intervention during the observation is more suitable. With the preparedness of rescue medicines, it is projected that the primary efficacy endpoint will not produce desired periodical result.

A separate review will be conducted by the PI on sebaceous immunobiology in further assessing the two clinical trials' shared participant's special case in ASD with immunology and neurology. This will further assist with the qualitative bases of the statistical analysis design, and its wider implications in neurotypical applications, apart from pure scientific values. Therefore, timeline for the primary efficacy point remains, but statistical analysis remains undecided.

There is a qualitative sign of the participant’s healing from headache, the previous migraine AE. Its healing is accompanied by the healing in cardiac contraction ache, which is a result from the last trial’s AE. The two symptoms healing is accompanied by the blood vessel reflex spasms that stimulate distress sensations that make the organs feel the inflow of ROS and improved breathing. At a relatively intense instance, involuntary abdomen contraction occurred. It could be possibly related to the activated pancreas activities, which was a consistent sign with pancreas pain under ACEI. The involuntary abdomen contraction is usually accompanied with prominent breathing reflex, and it is possible that this is a sign of the participant’s immune system’s recovery process competing for ROS with the pathogens.

The PI has conceived the phenomenon of the participant’s compared to neurotypical persons as adrenaline intolerance, with broader relevance to both neurology and immunobiology. The autoimmune pathogen recovery from the ASD case is seen as the psychiatrically typical study subject for the special case’s detailed implications to sebaceous immunobiology. Therefore, the purpose for the primary efficacy endpoint has been served under the null hypothesis, even though not for statistical analysis at the moment.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

<Insert text>

9.4.4 SAFETY ANALYSES

<Insert text>

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The baseline characteristics presume that the participant’s general healthy parameters are invariant from intoxication to detoxification, and the quotient of viral toxicants lies in the parameters in hematological and physical examinations. Therefore, the baseline is defined as the differentiated change of the parameters obtained at the start of trial to those from the historic data of the participant’s taken days after the second COVID-19 vaccination shot. The results descriptive statistics will be the differentiated change to the parameters obtained at the start of trial.

Indicator	Level	Unit	Indicator	Level	Unit
Δ Total Cholesterol	-0.01	mmol/L	Δ Triglycerides	2.48	mmol/L
Δ HDL-C	-0.04	mmol/L	Δ LDL-C	-0.18	mmol/L
Apolipoprotein A-I	1.35	g/L	Apolipoproteina B	0.83	g/L
Lipopoliproteina (a)	228	mg/L	Δ HIV (COVID-19)	-0.08	COI
Δ Leukocyte#	980	per μL	Δ Platelet Count	-10	10 ³ /μL
Δ Neutrophils#	140	per μL	Δ Plateletcrit	0.02	%
Δ Lymphocyte#	460	per μL	Δ Platelet Distribution Width	0.3	fL
Δ Mononucleosis#	130	per μL	Δ Mean Platelet Volume	1.9	fL
Δ Eosinophil#	240	per μL	Δ Red Blood Cell	-560	10 ³ /μL
Δ Basophil#	10	per μL	Δ Red Blood Cell - CV	-0.8	%
Δ Neutrophils%	-6.2	%	Δ Red Blood Cell σ	5.9	fL
Δ Lymphocyte%	2.7	%	Δ Total Hemoglobin	-7	g/L
Δ Mononucleosis%	1.1	%	Δ Hematocrit	-2.6	%
Δ Eosinophil%	2.2	%	Δ Mean Corpuscular Volume	5.2	fL
Δ Basophil%	0.2	%	Δ Mean Corpuscular Hemoglobin	2.3	pg

			Δ MCHC	5	g/L
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9.4.6 PLANNED INTERIM ANALYSES

The interim analyses planned mainly involve the secondary alternative hypothesis and safety analyses. **Sections 8.2** and **9.1** have outlined the planned interim analyses.

9.4.7 SUB-GROUP ANALYSES

The single arm trial falls into the Asian ethnic male sub-group. The qualitative experiment will provide the causal inference evidence with the specific sub-group.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Tabulation is performed after the primary efficacy endpoint and its analyses, and further tabulation for presentation in publications will be performed after the secondary efficacy endpoint.

9.4.9 EXPLORATORY ANALYSES

Exploratory analysis will put the sub-group's result into wider ethnic contexts from COVID-19 study references.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The consent materials are submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights

and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) or IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or FDA.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Open Science Framework. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management

systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Open Science Framework.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the PI's devices. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Open Science Framework, for use by other researchers including those outside of the study. Permission to transmit data to the Open Science Framework will be included in the informed consent.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the Open Science Framework.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Medical Monitor
<i>Rev. Yang I. Pachankis, PhD</i>	<i>Rev. Yang I. Pachankis, PhD</i>
<i>Independent</i>	<i>Independent</i>
<i>2-28-4 Dexinyuan, 1001 Biqing N Rd, Chongqing, 402762</i>	<i>2-28-4 Dexinyuan, 1001 Biqing N Rd, Chongqing, 402762</i>
<i>+86 18910566992</i>	<i>+86 18910566992</i>
<i>yang.pachankis@gmail.com</i>	<i>yang.pachankis@gmail.com</i>

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the PI.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The PI will conduct the monitoring as necessary for the study design;
- Independent audits will not be conducted.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into ClinicalTrials.gov. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

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

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to Program Official and sponsor. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive [PubMed Central](#) upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at [ClinicalTrials.gov](#), and results information from this trial will be submitted to [ClinicalTrials.gov](#). In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 1 year after the completion of the primary endpoint by visiting the Open Science Framework.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
ANCOVA	Analysis of Covariance
ASD	Autism Spectrum Disorder
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CV	Co-efficient of Variation
DBP	Diastolic Blood Pressure
DCC	Data Coordinating Center
DRE	Disease-Related Event
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISM	Independent Safety Monitor
LDL-C	Low-Density Lipoproteins - Cholesterol
HDL-C	High-Density Lipoproteins - Cholesterol
MCHC	Mean Corpuscular Hemoglobin Concentration
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
PPI	Proton-Pump Inhibitor
QA	Quality Assurance
QC	Quality Control
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV	Severe Acute Respiratory Syndrome associated Coronavirus
SBP	Systolic Blood Pressure
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure

UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
1.1	3 May 2023	ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S).	The actual primary efficacy endpoint is adjusted according to the participant’s activities.
1.2	4 May 2023	ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S).	The PI exchanged the SAP primary efficacy endpoint with qualitative analysis.

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