A Phase 1 Dose Escalation Trial Evaluating the Safety and Pharmacokinetic Profile of BIO 300 Oral Powder in Healthy Volunteers

Short title: Phase 1 BIO 300 Oral Powder

Protocol Number: CL0106-01

National Clinical Trial (NCT) Identified Number: NCT04650555

Principal Investigator: Amy R. Eastenson, MD

IND Sponsor: Humanetics Corporation

Version Number: v3.0

07 June 2021

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials 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 Institutional Review Board (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. In addition, 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:	A Phase 1 Dose Escalation Trial Evaluating the Safety and Pharmacokinetic Profile of BIO 300 Oral Powder in Healthy Volunteers
Study Description:	<u>Single Ascending Dose:</u> Open-label, single-dose escalation in healthy volunteers. Each cohort will enroll 8 subjects of which 2 will be backups (1M/1F), so that at least 6 subjects (3M/3F) complete the protocol procedures. The pertinent safety data will be reviewed for each cohort before the next dose level cohort is started. Subjects will follow a diet low in soy isoflavones for 7 days before and 7 days after treatment and will fast at least 8 h before dosing. The test article will be administered on day 1 and the initial dose will be one BIO 300 Oral Powder sachet, 500 mg genistein. Subsequent doses will be 2x the previous cohort. The fourth, and final cohort, dose level will be TBD based on the safety and pharmacokinetic (PK) results from the previous 3 cohorts. Subjects will remain in the clinic 12 hours after dosing for observations and blood sample collection for clinical lab assessment, PK, and pharmacodynamics (PD). Subjects will remain fasted for 4 hours after the test article administration. Subjects will be provided a standardized low soy meal after the 4-hour blood draw and after the 8-hour blood draw. Subjects will return to the clinic on day 2, 3 and 8 after dosing for blood sampling and/or observations as detailed in the schedule of events. Subjects may not miss any clinic visits. At the conclusion of the study, data will be analyzed from all cohorts to determine safety and PK. PD samples will be stored until the completion of all phase 1 studies, and then sent for RNA sequencing and data analysis.

Multiple Single Dose:
Open-label, single dose given daily for 6 days in healthy volunteers. A single cohort will enroll 14 subjects (7M/7F) of which 4 will be backups (2M/2F), so that at least 8 subjects (4M/4F) complete the protocol procedures. Subjects will follow a diet low in soy isoflavones for 7 days before treatment, during the 6 days of treatment and 7 days after treatment. Subjects will fast at least 8 h before the first dose, 3rd dose and the 6th dose. The test article will be administered starting on day 1 and the dose used in this study will be determined based on safety and PK analysis from the single ascending dose study. Subjects will be administered test article daily during their schedule clinic visits. Subjects will remain in the clinic 4 hours after the first dose and 12 hours after the 6th dose for observations and blood sample collection for clinical lab assessment, PK and PD. Subjects will remain fasted for 4 hours after the test article administration on days 1 and 6. On the 6th day, subjects will be provided a standardized low soy meal after the 4-hour blood draw and after the 8-hour blood draw. Blood sampling and/or observations will be performed on dosing days 1-6 as described in the schedule of events. Subjects will return to the clinic on days 7, 8 and 13 after initial dosing for blood sampling and/or observations as detailed in the schedule of events. Subjects may not miss any clinic visits. At the conclusion of the study, data will be analyzed to determine safety and PK, and data will be analyzed from all cohorts to determine PD.

Objectives:

Primary Objectives:

- Determine the overall adverse event and PK profiles of single ascending doses of BIO 300 Oral Powder in healthy volunteers
- Determine the overall adverse event and PK profile of multiple doses of BIO 300 Oral Powder in healthy volunteers

Secondary Objectives:

- Determine the effects of single and multiple doses of BIO 300 Oral Powder on blood-based biomarkers
- Use a combination of the PK and PD profiles from the single and multiple doses of BIO 300 Oral powder to identify the putative BIO 300 Oral Powder human efficacious dose

Endpoints:

Primary
Evaluate the safety and pharmacokinetics of BIO 300 Oral Powder in Healthy Volunteers

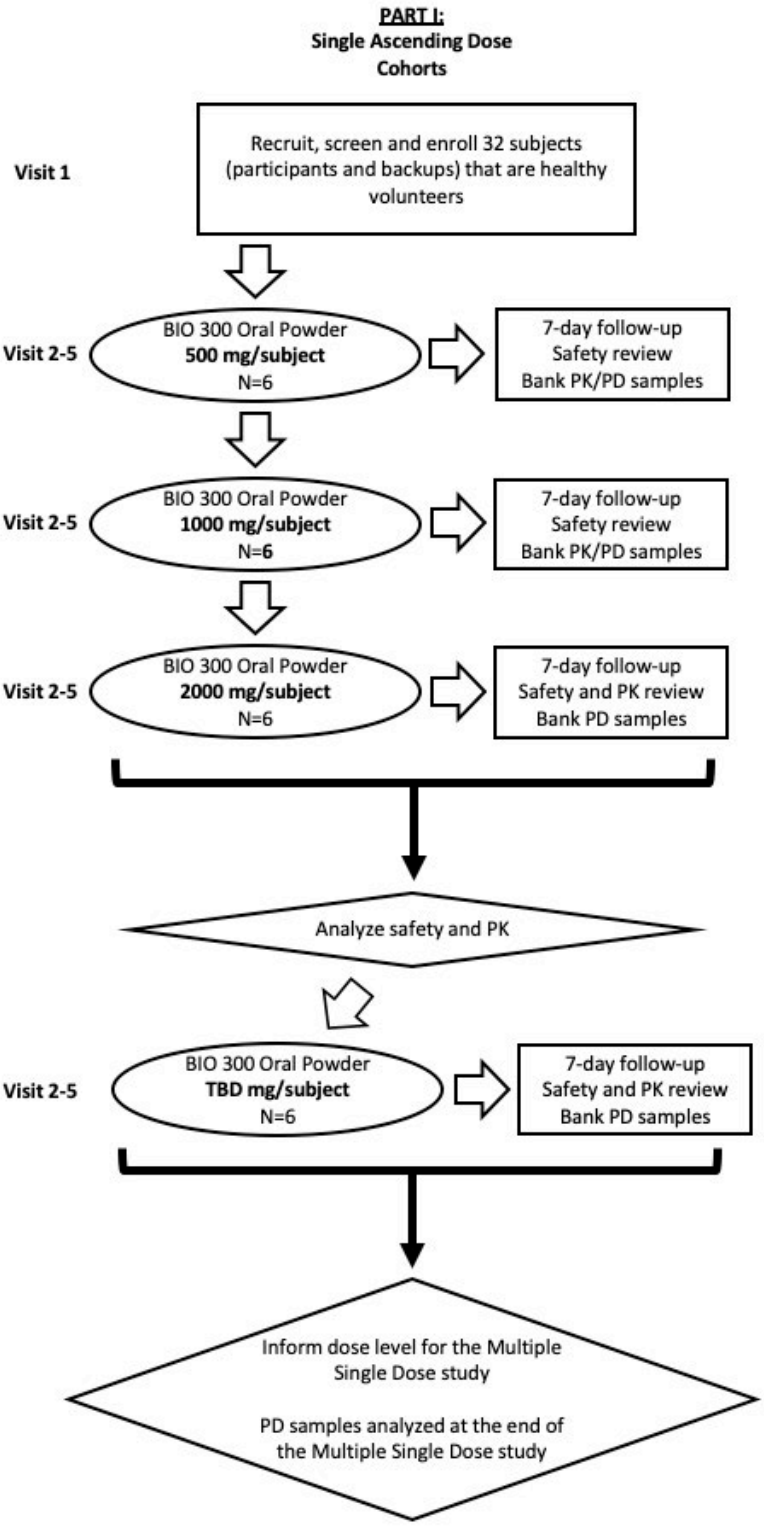
Secondary
Characterize the expression of blood-based biomarkers

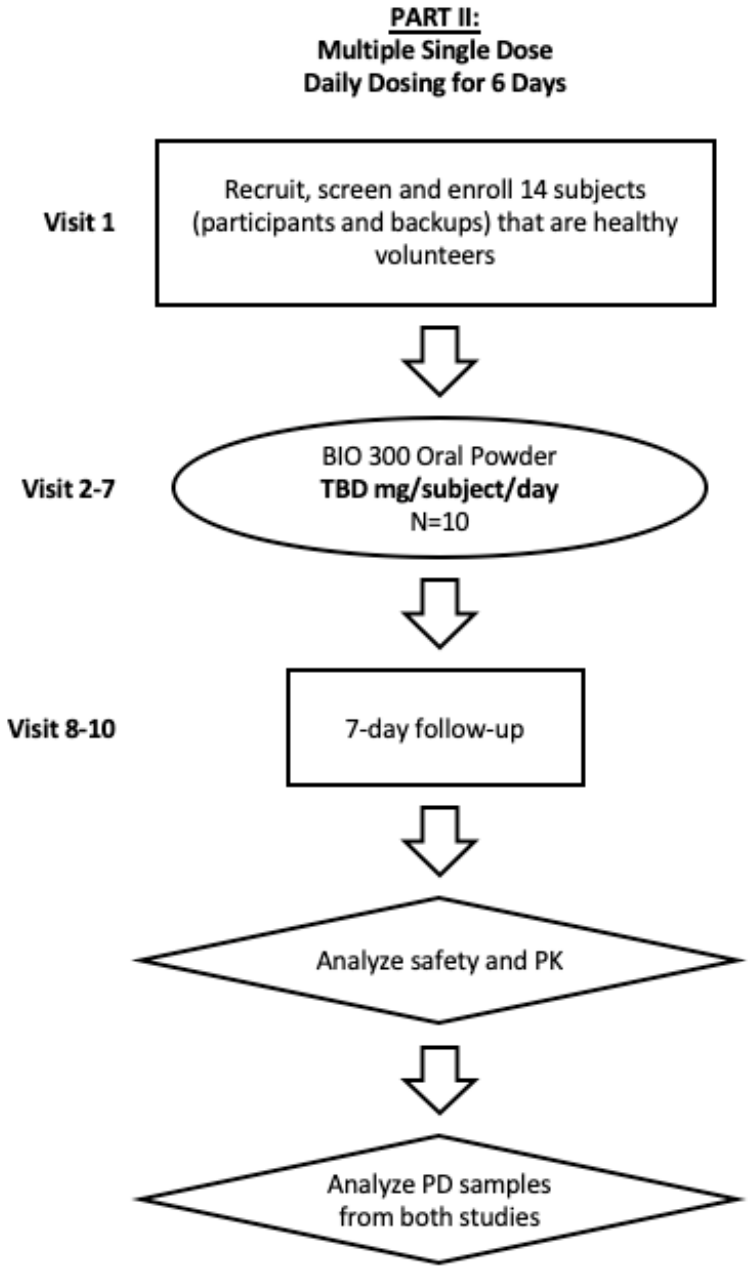
Study Population:

- 6 subjects/cohort (3M/3F) will be recruited for the single ascending dose study, and at least 6 (3M/3F) subjects/cohort will complete all aspects of the study. 2 additional subjects (1M/1F),

	will be screened, consented and available as backups for each cohort. • 10 (5M/5F) subjects will be recruited for the multiple single dose study, and at least 8 (4M/4F) subjects will complete all aspects of the study. 4 additional subjects (2M/2F) will be screened, consented and available as backups. • In total, at least 32 healthy volunteers who will complete all aspects of the trial.
Phase:	1
Description of Sites/Facilities Enrolling Participants:	Nucleus Network (formally Prism Clinical Research) 1000 Westgate Drive, #149 Saint Paul, MN 55114
Description of Study Intervention:	BIO 300 Oral Powder will be provided by Humanetics Corporation, Minneapolis, Minnesota. [redacted] The inactive ingredients include povidone K12 and sucralose powder. The vials are labeled with clinical study information including the lot number, storage instructions to store at controlled room temperature 15-30°C (59-86°F) and the statement "CAUTION: New Drug, limited by Federal law to investigational use."
Study Duration:	Approximately 8 months
Participant Duration:	The duration of study participation will be 35 days for Cohorts 1 – 4 (28-day screening period; Dosing on day 1; final follow-up visit on Day 8). The duration of study participation will be 41 days for Cohort 5 (28-day screening period; Dosing on days 1 - 6; final follow-up visit on day 13)

1.2 SCHEMA


PART I:
Single Ascending Dose
Cohorts
Visit 1
Recruit, screen and enroll 32 subjects (participants and backups) that are healthy volunteers
Visit 2-5
BIO 300 Oral Powder
500 mg/subject
N=6
7-day follow-up
Safety review
Bank PK/PD samples
Visit 2-5
BIO 300 Oral Powder
1000 mg/subject
N=6
7-day follow-up
Safety review
Bank PK/PD samples
Visit 2-5
BIO 300 Oral Powder
2000 mg/subject
N=6
7-day follow-up
Safety and PK review
Bank PD samples
Analyze safety and PK
Visit 2-5
BIO 300 Oral Powder
TBD mg/subject
N=6
7-day follow-up
Safety and PK review
Bank PD samples
Inform dose level for the Multiple Single Dose study
PD samples analyzed at the end of the Multiple Single Dose study


PART II:
Multiple Single Dose
Daily Dosing for 6 Days
Visit 1
Recruit, screen and enroll 14 subjects (participants and backups) that are healthy volunteers
Visit 2-7
BIO 300 Oral Powder
TBD mg/subject/day
N=10
Visit 8-10
7-day follow-up
Analyze safety and PK
Analyze PD samples from both studies

1.3 SCHEDULE OF ACTIVITIES (SOA)

Schedule of Events and Assessments														
	Single Ascending Dose Cohorts					Multiple Single Dose Cohort								
Visit Number	1	2	3	4	5	1	2	3	4	5-6	7	8	9	10
Day	**-28 to -8**	**1**	**2**	**3**	**8**	**-28 to -8**	**1**	**2**	**3**	**4-5**	**6**	**7**	**8**	**13**
Informed Consent	X					X								
Medical History	X					X								
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception Check	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[1]	X	X[8]	X	X	X	X	X[17]	X	X	X	X[8]	X	X	X
Calculation of BMI	X					X								
Physical Exam[2]	X			X	X	X			X		X			X
Drug Screen/Alcohol Testing	X	X				X	X							
Pregnancy test[3]	X	X			X	X	X							X
Hepatitis and HIV testing	X					X								
CBC with differential[4]	X			X	X	X			X		X			X
PT/INR, PTT	X			X	X	X			X		X			X
Serum chemistries and fasting lipid panel[5]	X			X	X	X			X		X			X
Urinalysis[6]	X				X	X					X			X
ECG[7]	X	X[9]	X	X	X	X	X[9]	X	X		X			X
Low isoflavone dietary counseling	X	X	X	X		X	X	X	X		X			
Administer BIO 300 Oral Powder		X					X	X	X	X	X			
PK		X[10]	X[11]	X[12]			X[13]				X[10]	X[11]	X[12]	
PD		X[14]	X[15]				X[14]				X[16]	X[15]		
Adverse Event Monitoring		X	X	X	X		X	X	X	X	X	X	X	X

Notes

1. Vital signs include height, weight, BMI, resting pulse, blood pressure, respiratory rate, and temperature. Subjects should be rested semi-recumbent for at least 5 min prior to collection.
2. Physical exams will assess the HEENT, lymphatic, cardiovascular, pulmonary, gastrointestinal, musculoskeletal, and neurological systems, and anything else deemed necessary by the Investigator.
3. Pregnancy test may be performed on urine or serum
4. CBC to include white blood cell count with differential, platelet count, red blood cell count, hemoglobin, and hematocrit
5. Serum chemistries to include total protein, albumin, sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, alkaline phosphatase, ALT, AST, uric acid, LDH, total and direct bilirubin, phosphorous, calcium, magnesium, amylase, lipase, total cholesterol, triglycerides, HDL. Subjects should fast at least 8 h prior to collection and blood will be drawn prior to test article administration.
6. Urinalysis to include pH, specific gravity, dipstick determinations of protein, glucose, ketones, blood and bilirubin and reflex microscopic exam (reflex only if any qualitative measurements or appearance return abnormal)
7. ECGs to be performed in triplicate with 5-minute intervals. Subjects should be rested supine for at least 5 minutes prior to collection.

8. Vital signs to be obtained within 1 hour prior to administration of BIO 300 Oral Powder and then approximately 30 minutes, 1, 2, 4, 6, 8, and 12 h following administration of BIO 300 Oral Powder
9. ECGs to be obtained within 1 h prior to BIO 300 Oral Powder administration and then approximately 1, 2, and 4 h following BIO 300 Oral Powder administration
10. Samples for PK assessment to be obtained just prior to BIO 300 Oral Powder administration and then 30 minutes, 1, 2, 4, 6, 8, and 12 h following BIO 300 Oral Powder administration. The time of the blood draw will be ±10 minutes of the nominal time.
11. Samples for PK assessment to be obtained 24 $\pm$ 2 h following administration of BIO 300 Oral Powder
12. Samples for PK assessment to be obtained 48 $\pm$ 4 h following administration of BIO 300 Oral Powder
13. Samples for PK assessment to be obtained just prior to administration of BIO 300 Oral Powder and then 30 minutes, 1, 2, and 4 h following BIO 300 Oral Powder administration. The time of the blood draw will be ±10 minutes of the nominal time.
14. Samples for PD assessment to be obtained -2 to 0 h before BIO 300 Oral Powder administration, and 1, 2, and 4 h following BIO 300 Oral Powder administration. The time of the blood draw will be ±10 minutes of the nominal time.
15. Samples for PD assessment to be obtained 24 $\pm$ 2 h following administration of BIO 300 Oral Powder
16. Samples for PD assessment to be -2 to 0 h before BIO 300 Oral Powder administration, and 4, 8, and 12 h following BIO 300 Oral Powder administration. The time of the blood draw will be ±10 minutes of the nominal time.
17. Vital signs to be obtained within 1 hour prior to administration of BIO 300 Oral Powder and then approximately 30 minutes, 1, 2, and 4 h following administration of BIO 300 Oral Powder

2 INTRODUCTION

2.1 BACKGROUND AND STUDY RATIONALE

The active ingredient in BIO 300 Oral Powder is genistein, a selective agonist of estrogen receptor beta (ERβ). ERβ activation promotes DNA repair, cell cycle regulation, and importantly, anti-inflammatory effects. This pleiotropic mechanism can partly be explained by ERβ's ability to repress expression and activation of nuclear factor kappa light-chain-enhancer of activated B cells (NF-κB), which is a master regulator that controls transcription of genes involved in the immune response and cell survival [1-3]. NF-κB is activated in response to radiation, infection or other immune stimuli, and in turn promotes expression of pro-inflammatory cytokines [reviewed in [4]].

Humanetics is developing BIO 300 for multiple clinical indications related to DNA damage and inflammation. The primary indication for BIO 300 Oral Powder is as a prophylactic medical countermeasure to increase survival in individuals exposed to myelosuppressive doses of ionizing radiation.

BIO 300 has been studied in a previous clinical trial (NCT02567799) as an aqueous oral nanosuspension (BIO 300 Oral Suspension). BIO 300 Oral Powder has been developed to facilitate a solid dosage form of BIO 300. The pharmacokinetics of BIO 300 Oral Powder are not fully known in humans, and the safety and maximum tolerated dose of this formulation is unknown. This phase 1 study is intended to methodically explore both safety and PK of this formulation in healthy human volunteers. In addition, blood-based biomarkers will be examined as part of an effort to develop a human dose conversion strategy under the FDA Animal Rule.

Refer to the Investigator's Brochure (IB) for more detail.

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

All study participants in this clinical trial will receive identical care and health assessments. This will be explained in detail at the time of consent to participate. Patient alternatives include the choice not to participate in this study, a decision that may mean no specific follow-up care.

[redacted]

Subjects with documented soy allergies should carefully consider taking BIO 300. Because BIO 300 is manufactured with synthetic genistein the risk of a soy-based allergic reaction is minimal. Although teratology studies were negative, it is not known if BIO 300 will cause harm when administered to pregnant women. If a patient becomes pregnant while taking BIO 300, the patient should be informed of potential hazards to the unborn fetus. For these reasons mothers who are nursing their children should be informed of potential hazards of taking BIO 300.

[redacted]

The following list summarizes the potential physical risks associated with participation in the proposed clinical study based upon known adverse events in previous clinical studies of BIO 300 at the proposed dose and dosing duration:

<u>Less Likely</u>

- Fatigue
- Constipation
- Diarrhea
- Dyspepsia
- Flatulence
- Anorexia
- Dysgeusia
- Increase in serum amylase
- Increase is serum lipase
- Decrease in the number of red blood cells
- Increase in blood pressure
- Lowering of the heart rate
- Increase in breathing rate
- Pain such as headaches, aches in muscles and joints and abdominal pain
- Change in appetite

- Bad taste in the mouth
- Breast changes like tenderness, enlargement, and discharge
- Change in menstrual cycle
- Fluid retention/swelling

Rare but serious

- Allergic reactions
- Increases in liver enzymes

[redacted]

2.2.2 KNOWN POTENTIAL BENEFITS

This is a phase 1 healthy volunteer study. There are no proposed benefits to the volunteers other than to participate in clinical research of an investigational drug.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

BIO 300 and its active ingredient, genistein, have shown an exceptional safety profile in previous human use. The likelihood of serious adverse events associated with the ingestion of BIO 300 Oral Powder in this study is low. Subjects will be closely monitored for adverse events and will be evaluated through clinic visits during the dosing period of BIO 300 Oral Powder. Risks will be identified in the Informed Consent and clearly presented to volunteers prior to enrollment. Subjects are free to withdraw from the study at any time.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Evaluate the safety and pharmacokinetics of BIO 300 Oral Powder in healthy volunteers.	• Safety assessments including vital signs, clinical chemistries, ECG, and spontaneous reporting of adverse events. • Pharmacokinetic profile of four dose levels and profile after six days of repeated dosing	Phase 1 safety and PK analysis endpoints.

Secondary		
Characterize the expression of blood-based biomarkers	• Assessment of RNA changes related to single and multiple doses of BIO 300 Oral Powder.	Characterization of biomarkers relative to the mechanism of action that can be translated between species is a critical component of drug approval under the FDA Animal Rule.

4 STUDY DESIGN

4.1 OVERALL DESIGN

- Open label, single site phase 1 study in healthy volunteers who are equally distributed by sex.
- The study will include a single ascending dose (SAD) study in four cohorts and will be followed by a six-day multiple single dose study at either the highest dose or the maximum tolerated dose.
- There are no planned stratifications or sub-studies.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study is designed as a traditional phase 1 in healthy volunteers.

4.3 JUSTIFICATION FOR DOSE

The starting dose of BIO 300 Oral Powder in the SAD study will be 500 mg API (1 BIO 300 Oral Powder sachet). This dose of BIO 300 Oral Powder is predicted to provide a drug exposure that is ≤ 0.5 times that of 1500 mg of BIO 300 Oral Suspension, which has a previous history of safety in a phase 1b/2a study. The predicted drug exposure for BIO 300 Oral Powder is based on the AUC and C_{max} achieved in nonhuman primate studies using two dose levels of BIO 300 Oral Powder. Extrapolating drug exposure in NHPs to humans assumed a linear dose-response relationship and used the recommended guidance from FDA for estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. [redacted]

4.4 END OF STUDY DEFINITION

The study will be considered completed at the last subject, last visit per the Schedule of Activities as defined in Section 1.3. Upon monitoring of all study data and locking of the database, the study site will be closed. Following the closing of the study site, the Sponsor will analyze the study data per the plan in

Section 9 and prepare a final study report that will be submitted to the Investigational New Drug Application (IND).

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) Healthy adult non-smokers, 18-64 years old.
2) BMI 18-32 kg/m^2
3) No ingestion of prescription or over-the-counter medications (including dietary and herbal supplements) for 7 days prior to first dose of study drug and no planned use during study participation. Acetaminophen of up to 3 g/day and ibuprofen up to 1 g/day will be allowed at discretion of the Investigator.
4) At the discretion of the Investigator, blood routine, liver and kidney functions are within the controllable range.
    a. Adequate hepatic function as evidenced by ALT, AST or LDH < 1.25X ULN and bilirubin < 1.5X ULN for the reference lab.
    b. Adequate renal function as evidenced by a serum creatinine ≤ 1.5 X ULN for the reference laboratory OR a calculated creatinine clearance of ≥ 60 mL/min by the Cockcroft-Gault Equation.
    c. Adequate hematopoietic function as evidenced by white blood cells ≥ $3x10^9$ / L and platelets ≥ $100x10^9$ / L.
5) Female subjects of childbearing potential must have a negative pregnancy test within 72 hours of the start of treatment.
6) Subjects must agree to abstain from heterosexual intercourse or use a reliable method of contraception for 7 days after their last dose. Subjects using hormonal contraception are required to utilize condom/spermicide + additional barrier method for 7 days after their last dose.
7) Ability to read and provide written informed consent.
8) Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, dietary restrictions, and other study procedures.
9) No clinically significant abnormalities identified by medical history, physical examination, vital signs, ECG, and clinical laboratory tests in the opinion of the Investigator.

5.2 EXCLUSION CRITERIA

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

1) Any prior use of the study test article.
2) Any clinically significant weight loss any time in prior 4 weeks at discretion of Investigator based on medical history interview.
3) Subjects with any of the following are not eligible;
    a. Previous history of QTc prolongation resulting from “known-risk” medications (*www.Crediblemeds.org*) that required discontinuation of that medication;

   b. Congenital long QT syndrome, or 1st degree relative with unexplained sudden death under 40 years of age;
   c. Presence of left bundle branch block (LBBB);
   d. QTc with Fridericia's correction (QTcF) that is unmeasurable, or ≥ 480 msec on screening ECG. The average QTcF from the screening ECG (completed in triplicate) must be $<$ 480 msec in order for the subject to be eligible for the study.

4) Subjects must not have had a clinically significant cardiac event such as myocardial infarction (within 6 months prior to the first dose of the study treatment); uncontrolled/symptomatic congestive heart failure (New York Heart Association (NYHA) classification of heart disease, Class III or IV, see Appendix 3) within 6 months before entry; or the presence of any other uncontrolled cardiovascular conditions [unstable hypertension at discretion of Investigator or arrhythmia, unstable angina pectoris, or severe valvular heart disease, etc.] that, in the opinion of the Investigator, increases the risk of ventricular arrhythmia.
5) Subjects with a history of arrhythmia (multifocal premature ventricular contractions (PVCs), bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation) which is symptomatic or requires treatment (CTCAE Grade 3) or asymptomatic sustained ventricular tachycardia are not eligible. Subjects with atrial fibrillation with well-controlled ventricular rate are eligible at the discretion of the Investigator.
6) Psychiatric conditions, social situations or substance abuse that precludes the ability of the subject to cooperate with the requirements of the trial and protocol therapy at Investigator discretion.
7) Inability to refrain from alcohol consumption for 48 hours prior to day 1 and for the duration of the study. Illicit drugs, including THC, must be avoided from screen through the duration of the study.
8) Grade 2 or higher peripheral neuropathy.
9) Positive results for Hep B surface antigen, Hep C antibody, or HIV 1/2 antibody at screening visit.
10) Clinically significant immunodeficiency disorder in the opinion of the Investigator.
11) Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception.
12) Women who are breastfeeding are not eligible for this study.
13) Subjects that are vegan, vegetarian or consume a soy-rich diet.
14) Any history of systemic infection requiring hospitalization, systemic antibiotics, or as judged clinically significant by the investigator in the 3 months prior to day 1.
15) Any condition possibly affecting drug absorption (e.g., prior bariatric surgery, gastrectomy, intestinal resection). Participants who have undergone appendectomy or cholecystectomy are allowed so long as the surgery occurred more than 6 months prior to day 1.
16) Treatment with another investigational drug within 30 days or 5 half-lives (whichever is longer) proceeding Day 1.
17) Positive drug screen or alcohol test at screen and day 1 predose.
18) Blood donation of approximately 1 pint (500 ml) or more within 60 days of day 1; plasma donations within 14 days of day 1. Subjects must agree not to donate blood or plasma for the duration of the study and for 30 days following end of study procedures.
19) Inability to swallow powdered medication followed with water.
20) History of sensitivity to heparin or heparin-induced thrombocytopenia.
21) Considered by the Investigator to be unsuitable to participate in the study for any other reason.

5.3 LIFESTYLE CONSIDERATIONS

Participants will be counseled to adhere to a low isoflavone diet, such as those listed in **Appendix 1**, during the dosing and PK/PD assessment period. It is important for study participants to maintain a low isoflavone diet (e.g., low soy-diet) in order to accurately quantify study drug pharmacokinetics and drug exposure.

Contraception:

1) Women who are not able to get pregnant are not required to use birth control. To be considered not able to get pregnant, you must be
   a) postmenopausal for at least 12 months confirmed by hormone testing; ***or***
   b) surgically sterile
      - hysterectomy (surgical removal of uterus)
      - bilateral tubal ligation (tubes "tied")
      - removal of both ovaries and/or fallopian tubes
2) Women who are able to get pregnant must
   a) have a negative urine pregnancy test at screening and on admission to CRU; ***and***
   b) must be using, and agree to continue using, an effective method of contraception for at least 4 weeks prior to first study drug administration until 7 days after the last dose of study drug.

Effective methods of contraception include the following:

1) Total abstinence from sexual intercourse with a partner that may result in pregnancy
2) Sexual intercourse with a partner who has had a vasectomy
3) Non-Hormonal Intrauterine device
4) Double barrier contraception, i.e., condom and diaphragm, or condom or diaphragm with spermicidal gel or foam.
5) Women using hormonal contraception below must agree to use a barrier or other effective method of contraception during the study
   a) Combined (estrogen and progestogen containing) hormonal contraception
      - oral
      - intravaginal
      - transdermal
   b) Progestogen-only hormonal contraception
      - oral
      - injectable
      - implantable

Women must not donate ova (eggs) during the study and for at least 30 days after the last dose of study drug.

Male subjects who have not had a vasectomy and/or subjects who have had a vasectomy but have not had 2 post-surgery negative tests for sperm whose partners are not on a highly effective method of contraception (hormonal contraception is sufficient for female partners) must agree to use an acceptable method of contraception from time of first dose of study drug until 30 days after the last dose of the study drug, and must not donate sperm during the study and for at least 30 days after the last dose of study drug.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study due to their inability to meet inclusion or exclusion criteria or their decision to not consent to enrollment. 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).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment of subjects will be performed by the clinical site who maintains a robust database of healthy volunteers. The site will outreach to potential participants to encourage screening.

For optimal recruitment and retention, subject contact and convenience will be prioritized. Examples include providing effective subject information on the study, providing face-to-face meetings for discussing the study and questions, and ensuring the study design places no significant burden to being involved in the research study.

Subjects will be in contact with the study through clinical visits. Subject outreach will occur to encourage continued compliance and participation in clinic visits during the repeat dose study period.

6 STUDY INTERVENTION

The study intervention being investigated under this protocol is BIO 300 Oral Powder, an amorphous solid dispersion of synthetic genistein.

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

BIO 300 Oral Powder will be provided by Humanetics Corporation, Minneapolis, Minnesota. BIO 300 Oral Powder is an amorphous solid dispersion of genistein. It is packaged in single use foil sachets containing 500 mg genistein. It is a free-flowing pale orange to slightly tan powder.

6.1.2 DOSING AND ADMINISTRATION

Single Ascending Dose Cohorts:

Cohort 1 dose: one BIO 300 Oral Powder sachet, 500 mg genistein
Cohort 2 dose: two BIO 300 Oral Powder sachets, 1000 mg genistein (2X the dose of Cohort 1 in the absence of dose-limiting toxicity [DLT])
Cohort 3 dose: four BIO 300 Oral Powder sachets, 2000 mg genistein (2X the dose of Cohort 2 in the absence of DLT)
Cohort 4 dose: TBD based on the observed PK and AE profiles in the first 3 dose cohorts

All single dose cohorts will be administered the drug at the clinic under the supervision of the study personnel. Subjects will follow a diet low in soy isoflavones for 7 days before and 7 days after treatment and will fast at least 8 h before dosing. Subjects will remain fasted for 4 hours after the test article

administration. Subjects will remain in the clinic 12 hours after dosing. Subjects will be provided a standardized low soy meal after the 4-hour blood draw and after the 8-hour blood draw. The purpose of fasting is to standardize the effect of food on PK and PD markers.

Multiple Single Dose Cohort:
The cohort 5 dose will be dosed daily for 6 consecutive days at the highest dose or the maximum tolerated dose from the Single Ascending Dose cohorts. Subjects will consume the test article each day within +/- 2 hours of time when the first dose was administered and not within 1 hour before or after eating. The Day 6 dose will be administered during clinic visit 7 so that PK and PD blood draws can be timed after the dose.
Drinking of room temperature water only, (up to 240 mL) will be encouraged following administration of each BIO 300 Oral Powder sachet.

Subjects will follow a diet low in soy isoflavones for 7 days before treatment, during the 6 days of treatment and 7 days after treatment. Subjects will fast at least 8 h before the first dose, 3rd dose and the 6th dose. Subjects will remain in the clinic 4 h after the first dose and 12 hours after the 6th dose. Subjects will remain fasted for 4 hours after the test article administration on days 1 and 6. On the 6th day, subjects will be provided a standardized low soy meal after the 4-hour blood draw and after the 8-hour blood draw. The purpose of fasting is to standardize the effect of food on PK and PD markers.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

BIO 300 Oral Powder will be supplied to the investigational site pharmacy in foil sachets, each containing 500 mg of genistein. Sachets will be bulk packed in cardboard boxes and will be labeled as a new drug for investigational use only. All dosing cohorts will be administered whole sachets for dosing (e.g., 1 sachet for the 500 mg cohort).

Study drug used during the trial will be on an ICH compliant stability study with appropriate retest intervals. Any expired or out-of-spec drug product will be quarantined by the pharmacy and will be disposed upon full drug accountability monitoring and instruction by the Sponsor.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Description and Composition

The drug product, BIO 300 Oral Powder, is an amorphous solid dispersion (ASD) [redacted] The composition of BIO 300 Oral Powder is shown in **Table 6.2.2.1**.

Table 6.2.2.1 BIO 300 Oral Powder quantitative composition

Component	Function	Reference to Quality Standard	Amount (mg/g)

Genistein (Bonistein®)	Active Ingredient (API)	In-house	[redacted]
Polyvinylpyrrolidone K12	Carrier/Stabilizer	USP	[redacted]
Sucralose	Sweetener	NF	[redacted]

The ASD/sucralose mixture is filled into 1.5”x2.5” high barrier, multi-layer low-density polyethylene (LDPE)/foil, individual dosing sachets. The drug product contact surface of the sachet is comprised of linear low-density polyethylene (LLDPE). [redacted]

The drug product is labelled for investigational use only.

6.2.3 PRODUCT STORAGE AND STABILITY

BIO 300 Oral Powder is to be stored at 15-30°C, at ambient relative humidity by the study site pharmacy. The sachets should be stored in their original packaging until dispensed. Protection from light is not required. The sachets will be stored at the study facility and will be dispensed according to the study protocol. An extra supply of the BIO 300 Oral Powder study drug will be available in the event additional sachets are needed once the study is underway.

6.2.4 PREPARATION

The steps for preparing and dispensing BIO 300 Oral Powder are as follows:

1) Prepare the subject identifier label to each sachet.
2) Holding the sachet from the top (end with V grooves), gently swing back and forth to force all powder to the bottom of sachet.
3) Tear the top off the sachet being careful not to spill any powder.
4) Pour entire contents of sachet into mouth.
5) Immediately consume up to 8 oz. of water.
6) Inspect sachet to ensure all powder was dispensed. If not, take any residual powder immediately.
7) Follow steps 3 and 4 if more than 1 sachet is required. You may space the time between sachets but consume all within a 5 minute period.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is an open label, non-randomized phase 1 trial.

6.4 STUDY INTERVENTION COMPLIANCE

Adherence to the protocol will be assessed by documenting study visits. Study intervention compliance will be assessed by accounting for the number of returned empty sachets.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications, and supplements.

6.5.1 PERMITTED SURPPORTIVE THERAPY

All supportive therapy for optimal medical care will be given during the study period at the discretion of the subject's attending physician(s) within the parameters of the protocol and documented on the site's source documents as concomitant medication.

6.5.2 NON-PERMITTED SURPPORTIVE THERAPY

Though no data have shown that any concomitant medications will interfere with BIO 300 Oral Powder, it is advisable that subjects do not take any other medication(s) 1 hour before or after a dose of BIO 300 Oral Powder. Concomitant medications will be collected for all subjects from the screening visit through the end of the study.

<u>The following drugs are not permitted during the study protocol:</u>

Anti-pulmonary fibrosis therapeutics, (*e.g.,* imatinib, nintedanib, pirfenidone, penicillamine, colchicine, and tumor necrosis factor alpha blocker), anti-cytokine release syndrome therapeutics (*e.g.,* anakinra, sarilumab, siltuximab, tocilizumab and/or lenzilumab), biologics used to treat asthma (*e.g.,* omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab), and all systemic corticosteroids.

If a subject receives any of the listed non-permitted supportive therapies, this will constitute as a major protocol deviation.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 STOPPING CRITERIA FOR DISCONTINUATION OF THE STUDY INTERVENTION

Discontinuation of a subject and early stopping of the study intervention will be based on the following unacceptable adverse events (AEs) and must be attributable to the investigational drug BIO 300 Oral Powder (i.e., possibly, probably or definitely related to the study drug) to constitute a Dose-Limiting Toxicity (DLT).

- Non-hematologic toxicities of Grade 3 or higher, with the following exceptions:
  - anorexia
  - fatigue
  - infection without neutropenia

  - Grade 3 AST/ALT elevations ≤ 7 days
  - Grade 3 or 4 electrolyte abnormalities that are corrected to Grade 2 or less in less than 48 hours.
- Occurrence of a VTE (DVT or pulmonary embolism).

7.2 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from BIO 300 Oral Powder does not mean discontinuation from the study, and the 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 Principal 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).

7.3 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request. The Principal Investigator may discontinue or withdraw a subject from the study for the following reasons:

- Pregnancy (see **Section 8.4.8**). Women of childbearing potential must perform a pregnancy test in case of delayed menstruation and stop treatment immediately in case of positive result.
- Significant study intervention non-compliance.
- Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness that, in the opinion of the Principal Investigator, indicates that continued participation in the study is not in the best interest of the participant.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- If the participant withdraws their informed consent.

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.

7.4 LOST TO FOLLOW-UP

For both the Single Ascending Dose and the Multiple Single Dose studies a subject will be considered lost to follow-up if he or she fails to return for a single 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 as soon as possible that same day 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.
- If the missed visit consists of timed blood draws for PK and PD, that subject will be immediately considered lost to follow up and may be replaced.
- Should the subject be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

For both the Single Ascending Dose and Multiple Single Dose studies, subjects that are lost to follow up may be replaced. For the Single Ascending Dose study, and at least 6 (3M/3F) subjects/cohort will complete all aspects of the study. For the Multiple Single Dose study at least 8 (4M/4F) subjects will complete all aspects of the study.

7.5 DOSE ESCALATION CRITERIA

A Safety Monitoring Committee (SMC) consisting of a Humanetics representative, the Medical Monitor and Principal Investigator, or their recognized delegates will review all available data. The determination for escalation to the next Cohort will require, at a minimum, a review of all safety data of 6 subjects in the previous SAD Cohort through at least Day 3. Decisions to proceed with dose escalations, adding additional subjects to the current Cohort, and possible dose adjustments will be made following this review with the Medical Monitor and Principal Investigator agreeing with the decision. Whether additional information such as PK or PD data may be needed before a decision to escalate can also be determined by the SMC. The primary responsibility of the SMC is to regularly monitor the overall safety of patients enrolled in the study, while protecting the scientific integrity of the study data. Dose escalation criteria will be the following:

- Dose escalation may occur if no more than 2 subjects in a 6-subject cohort experiences a dose-limiting toxicity (DLT, as defined below).
- If 3 DLTs occur (3/6 subjects), an additional 2 subjects will be treated with the same dose.
- If no additional DLTs occur (3/8 subjects), dose escalation may proceed.
- The study sponsor will temporarily cease enrollment for evaluation if in any given cohort 4/8 subjects experience DLTs attributable to BIO 300 Oral Powder as the MTD (maximum tolerated dose) will have been exceeded and no further dose escalation will occur.

DLT is any grade 3 or grade 4 adverse event listed in the draft FDA document entitled "*Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*."

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 CRITERIA FOR EVALUATION

Safety:
The safety profile of BIO 300 Oral Powder will be based on the results of CBC with differential, coagulation parameters, serum chemistries, urinalysis, ECGs, and vital signs the reporting of adverse events.

Pharmacokinetics:
Blood samples will be collected at multiple timepoints after BIO 300 Oral Powder administration and processed for serum isolation. Serum concentrations of genistein aglycone will be measured from PK parameters (C_{max}, T_{max}, clearance, $AUC_{(0\text{-}24;0\text{-}48;0\text{-}INF)}$, volume of distribution, $T_{1/2}$ and drug accumulation index) which will be calculated using standard procedures and statistical analyses.

Pharmacodynamics:
Blood samples will be collected at multiple timepoints in PAXgene tubes after BIO 300 Oral Powder administration. It will be subjected to RNA sequencing to explore biomarkers which may be predictive of BIO 300 Oral Powder effectiveness.

8.2 SAFETY AND OTHER ASSESSMENTS

Physical Exam – Examination of the participant's cardiovascular, HEENT, lymphatic, pulmonary, gastrointestinal, musculoskeletal, and neurological systems.

Vital Signs – Vital signs will record the patient's height, weight and BMI. They will also measure heart rate, blood pressure (systolic and diastolic), respiratory rate, and body temperature.

Electrocardiogram – ECGs occur during the screening visit, on visit 2 (1 hr before, 1hr after, 2 hrs after and 4 hrs after BIO 300 Oral Powder dose), and visits 3-5 for the SAD phase. ECGs will occur during the screening visit, visit 2 (1 hr before, 1hr after, 2 hrs after and 4 hrs after BIO 300 Oral Powder dose), visits 3-4, visit 7 and visit 10 for the multiple single dose phase. ECGs will be digitally read locally at the study site. ECGs will be completed in triplicate and the average will be used to determine if the study subject has an abnormal reading.

QTc Interval Prolongation – Fridericia-corrected QTc (QTcF) interval from all subjects in both the SAD and the multiple single dose studies will be used to evaluate QTcF interval prolongation. QTcF prolongation will be determined by evaluating ECG at baseline (pre-dose) and at multiple time points around the predicted C_{max} of BIO 300 Oral Powder (ECG timepoints listed above). QTcF intervals will be reported for each dosing cohort as a mean and standard deviation. The upper limit for QTcF interval prolongation will be >480 ms or absolute QTcF change from baseline of >30 ms with a 95% confidence interval. The relationship between drug exposure and mean QTcF interval change will be evaluated in the SAD study using both C_{max} and AUC. Any adverse events that may signal a potential proarrhythmic effect will be carefully monitored (e.g., Torsade de pointes, sudden death, ventricular tachycardia, seizures, etc.).

Complete Blood Count – Blood sampling for the laboratory parameters will be performed during the screening and BIO 300 Oral Powder treatment period according to the study schedule (**Section 1.3**). A complete blood count with differential will evaluate hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count.

Serum Chemistry and Fasting Lipid Panel – Blood serum will be used to evaluate the blood chemistry parameters. Serum chemistries to include total protein, albumin, sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, alkaline phosphatase, ALT, AST, uric acid, LDH, total and direct bilirubin, phosphorous, calcium, magnesium, amylase, lipase, total cholesterol, triglycerides, HDL. Subjects will fast at least 8 h prior to blood collection for serum chemistries.

PTT/INR – Prothrombin Time (PTT) is a test that evaluates a subject's ability to appropriately form blood clots. The International Normalized Ratio (INR) is a calculation based on results of the PTT that is used to monitor individuals who are being treated with the blood-thinning medication.

Pregnancy Test – Tests will occur at screening, day 1 and during the final visit (SAD, day 8, visit 5; Multiple Single Dose, day 13, visit 10). Tests will use urine or serum for determination of β-HCG.

Viral Testing – Test will occur at screening for both studies. Tests will utilize blood for analysis of the Hepatitis B surface antigen, Hepatitis C antibody, and HIV1 and HIV2 antibody.

Urinalysis – To include pH, specific gravity, dipstick determinations of protein, glucose, ketones and bilirubin, blood and reflex microscopic exam (reflex only if any qualitative measurements or appearance return abnormal)

Concomitant Medications – A record of concomitant medications will be collected for all subjects from the screening visit through BIO 300 Oral Powder treatment and the one-week follow-up phase.

Assessment of Adverse Events – All adverse events (AEs) will be collected from the time the subject takes their first dose of BIO 300 Oral Powder until 7 days after their last dose of BIO 300 Oral Powder. AEs will be documented and submitted to the Sponsor. Any serious AEs (SAEs) will be documented and reported to the Sponsor within 24 hours of awareness (see **Section 8.3**).

Blood-Based Biomarkers – Whole blood will be collected for biomarker analysis. Blood will be collected pre-dose, at several time points around the predicted C_{max} of BIO 300 Oral Powder. The collected samples will be subject to RNA extraction and next-generation RNA sequencing on the Illumina HiSeq platform with paired-end sequencing. [redacted]

8.3 BLOOD SAMPLING FOR PHARMACOKINETICS, SAFETY AND BIOMARKERS

Blood will be collected from all subjects to monitor BIO 300 Oral Powder pharmacokinetics, safety, and biomarkers. At each visit where blood sampling occurs, whole blood and serum may be collected for pharmacokinetics, complete blood counts (CBC) with differential, serum chemistry, clotting (PT/INR, PTT) and RNA extraction. A summary of blood draws for safety and biomarkers can be found in **Section 1.3 Schedule of Activities**. Below is an overview of the details of the blood collection summarized by visit.

For blood draws, whole blood will be collected in one 3 cc lavender top blood collection tubes for CBC analysis and two PAXgene blood RNA tubes for RNA isolation. The PAXgene tubes will be stored at -70°C until they are shipped to a Sponsor-designated laboratory for RNA extraction and processing. Blood will also be collected in one 3.5 mL SST collection tube for serum isolation to be used for serum chemistry and 1x 3cc red top blood collection tube for serum isolation to be used for BIO 300 Oral Powder PK analysis. Blood used for serum will be allowed to clot 20-30 minutes and then centrifuged at room temperature for 10-15 minutes. Collected serum will be frozen at -70°C. All blood and serum will be shipped to the sponsor-designated bioanalytical lab for analysis. Additionally, at screening, blood will be collected into another 3.5 mL SST collection tube, and a 3 mL EDTA collection tube to be used for viral testing. Specific blood draw volume requirements for the procedures listed below are detailed in **Section 8.3.1** and **Section 8.3.2**.

Single Ascending Dose

Visit 1 (Screening)

At the screening visit, blood will be collected to acquire the subject's baseline blood counts and serum chemistries, and for viral testing. If a pregnancy test is required for the subject, either a serum or urine test will be done at this time. These test results will assist in determining the subject's ability to be included in the trial (see **Section 5.1 Inclusion Criteria**).

Visit 2 (Day 1)

All subjects will have their blood collected for serum as described above. Serum samples will be collected for pharmacokinetics just prior to and following administration of a single dose of BIO 300 Oral Powder at 30 minutes, 1, 2, 4, 6, 8, and 12 hours. The time of the blood draw will be ±10 minutes of the nominal time. Subjects will be given a standardized low-soy meal after the 4 h blood draw and 2 h after the 6 h blood draw. Whole blood will be collected as described above for RNA isolation prior to a single dose BIO 300 Oral Powder administration, and at 1, 2 and 4 hours after administration.

Visit 3 (Day 2)

All subjects will have blood serum collected for PK 24 ± 2 hrs after BIO 300 Oral Powder dosing. Whole blood will also be collected for RNA isolation 24 ± 2 hrs after BIO 300 Oral Powder dosing.

Visit 4 (Day 3)

All subjects will have a whole blood and serum collected for CBC, PT/INR, PTT, 48 ± 4 hrs PK and serum chemistry as described above.

Visit 5 (Day 8)

All subjects will have a whole blood and serum collected for CBC, PT/INR, PTT and serum chemistry as described above.

Multiple Single Dose

Visit 1 (Screening)

At the screening visit, blood will be collected to acquire the subject's baseline blood counts, serum chemistries, PT/INR, PPT, and viral testing. If a pregnancy test is required for the subject, either a serum or urine test will be done at this time. These test results will assist in determining the subject's ability to be included in the trial (see **Section 5.1 Inclusion Criteria**).

Visit 2 (Day 1)

All subjects will have their blood collected for serum as described above. Serum samples will be collected for pharmacokinetics just prior to and following administration of a single dose of BIO 300 Oral Powder at 30 minutes, 1, 2 and 4 hours. The time of the blood draw will be ±10 minutes of the nominal time. Whole blood will be collected as described above for RNA extraction prior to a single dose BIO 300 Oral Powder administration, and at 1, 2 and 4 hours after administration.

Visit 4 (Day 3)

All subjects will have a whole blood and serum collected for CBC, serum chemistry, and PT/INR, PPT as described above.

Visit 5 and 6 (Days 4 and 5)

All volunteers will have their vital signs performed and will be administer a single dose of BIO 300 Oral Powder at the research unit.

Visit 7 (Day 6)

All subjects will have their blood collected for serum as described above. Serum samples will be collected for pharmacokinetics just prior to and following administration of a single dose of BIO 300 Oral Powder at 30 minutes, 1, 2, 4, 6, 8, and 12 hours. The time of the blood draw will be ±10 minutes of the nominal time. Subjects will be given a standardized low-soy meal after the 4 hr blood draw and 2 hours after the 6-hour blood draw. Serum will also be used for serum chemistry analysis. Whole blood will be collected as described above for RNA extraction prior to a single dose BIO 300 Oral Powder administration, and at 4, 8 and 12 hours after administration. Whole blood will also be collected for CBC analysis.

Visit 8 (Day 7)

All subjects will have blood serum collected for PK 24 ± 2 hrs after BIO 300 Oral Powder dosing. Whole blood will also be collected for RNA extraction 24 ± 2 hrs after BIO 300 Oral Powder dosing.

Visit 9 (Day 8)

All subjects will have blood serum collected for PK 48 ± 4 hrs after BIO 300 Oral Powder dosing.

Visit 10 (Day 13)

All subjects will have a whole blood and serum collected for CBC, serum chemistry, and PT/INR, PPT as described above.

8.3.1 SINGLE ASCENDING DOSE SUBJECT BLOOD VOLUME REQUIREMENTS

	Blood volume (mL) required					
Visit Number	**1**	**2**	**3**	**4**	**5**	
	Screening	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**TOTAL**
CBC (Lavender top whole blood)	3			3	3	9
Serum Chemistry (SST)	3.5			3.5	3.5	10.5
PT/INR PTT (SST)	2.7			2.7	2.7	8.1
Viral Testing (SST and EDTA)	6.5					6.5
BIO 300 Oral Powder PK (Red top serum)		24 (3cc x 8 draws)	3	3		30
BIO 300 Oral Powder PD (RNA) (PAXgene tube)		20 (5mL x 4 draws)	5			25
Waste associated with use of heparin lock		8				8
Subtotals	9.2	52	8	12.2	9.2	
STUDY TOTAL						97.1

8.3.2 MULTIPLE SINGLE DOSE SUBJECT BLOOD VOLUME REQUIREMENTS

	Blood volume (mL) required										
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
	Screening	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 13**	**TOTAL**
CBC (Lavender top whole blood)	3			3			3			3	12
Serum Chemistry SST)	3.5			3.5			3.5			3.5	14
PT/INR PTT (SST)	2.7			2.7			2.7			2.7	10.8
Viral Testing (SST and EDTA)	6.5										6.5

BIO 300 Oral Powder PK (Red top serum)		15 (3cc x 5 draws)					24 (3cc x 8 draws)	3	3		45
BIO 300 Oral Powder PD (RNA) (PAXgene tube)		20 (5mL x 4 draws)					20 (5mL x 4 draws)	5			45
Waste associated with use of heparin lock		5					8				13
Subtotals	11	40		11			63	8	3	11	
STUDY TOTAL											146.3

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite) (ICH, E2A, E6).

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

SAEs that fit any one of the criteria in the SAE definition below must be reported to the Sponsor within 24 hours of awareness of the event.

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the Principal Investigator or Sponsor, it results in any of the following outcomes:

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 SEVERITY OF EVENT

For adverse events (AEs), guidelines based on the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials will be used to describe severity. The guidance provides a toxicity grading scale (grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, potentially life threatening) for clinical and laboratory abnormalities. For AE

terminology, the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used, and AE system organ classification will follow the Medical Dictatory for Regulatory Activities (MedDRA).

8.4.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (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.

- **Definite** – 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 event must be pharmacologically or phenomenologically definitive.
- **Probable** – 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.
- **Possible** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). 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** – 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).
- **Unrelated** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology.

8.4.3.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (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. The final determination of expectedness will be determined by the Medical Monitor in consultation with the Principal Investigator.

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

The occurrence of an adverse event (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 case report form (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, or after they are screened, but before they are administered the first dose of study drug, 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.

Delegated study personnel will record AEs with start dates occurring any time after the first dose of study intervention is administered through the end of the study. SAEs will be recorded with start dates occurring any time after informed consent is obtained through the end of the study. 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. Documentation of the serious event will be reported on the Serious Adverse Event CRF and submitted to the Sponsor within 24 hours of awareness.

8.4.5 ADVERSE EVENT REPORTING

The notification process to the study Sponsor of all safety data begins with the completion and submission of the appropriate CRFs or in the case of an initial serious event reporting, by phone.

Investigators are required to report promptly to the Sponsor any adverse events that may reasonably be regarded as caused by, or probably caused by, the drug. If the Adverse Event (AE) meets the Serious Adverse Event (SAE) criteria, the investigator is required to report the event to the Sponsor within 24 hours of awareness.

8.4.6 SERIOUS ADVERSE EVENT REPORTING

The Sponsor will notify the FDA, all participating investigators in a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected and any finding from tests in laboratory animals that suggests a significant risk for human subjects. The Sponsor will submit an IND safety report to the FDA and all participating investigators no later than 15 calendar days after the Sponsor determines that the suspected adverse reaction or other information qualifies for reporting. Unexpected fatal or life-threatening suspected adverse reactions will be reported to the FDA no later than 7 calendar days after the Sponsor's initial receipt of the information. If the FDA requests any additional data or information, the Sponsor will submit it to FDA as soon as possible, but no later than 15 calendar days after receiving the request.

8.4.7 EVENTS OF SPECIAL INTEREST

Subjects that experience any cardiovascular-related events, overdose on the study intervention, have any clinically significant laboratory test abnormalities, or become COVID-19 positive should be reported to the study Sponsor.

8.4.8 REPORTING OF PREGNANCY

Should a participant become pregnant during the study, the Principal Investigator will report this event to the study Sponsor and will create a plan to stop the study intervention as soon as possible. The Principal Investigator will communicate with the physician managing the pregnancy and the subject and pregnancy will be followed to term.

8.5 UNANTICIPATED PROBLEMS

8.5.1 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** 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 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.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The Principal Investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Sponsor. 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 serious adverse events (SAEs) will be reported to the IRB and to the study Sponsor in accordance with the sites policies and procedures and within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study Sponsor within one week 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 Office for Human Research Protections (OHRP) within 7 business days of the IRB's receipt of the report of the problem from the investigator.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Data analysis of the primary endpoints will be based on measurements of genistein aglycone (free genistein) serum concentrations (0-48 h). They will also be based on safety assessments which include blood counts, serum chemistries, urinalysis, ECGs, vital signs, and PTT/INR at the timepoints listed in the **SoA, Section 1.3**. "Baseline" will refer to measurements taken during the screening visit. If no "baseline" data exists from a parameter, then changes in the parameter time regression will be compared.

As this is a single dose escalation and multiple single dose trial evaluating the safety and pharmacokinetic profile of BIO 300 Oral Powder, the statistical hypotheses for the safety measurements is that there will be no change in safety measurements during BIO 300 Oral Powder dosing, and 7 days after the last BIO 300 Oral Powder dose.

For the secondary endpoint, the statistical hypothesis is that there will be a significant change in the level of expression of one or more genes that is attributable to BIO 300 Oral Powder dose.

9.2 SAMPLE SIZE DETERMINATION

The single ascending dose study consists of 4 cohorts, each with at least 6 subjects completing all aspects of the study, split evenly to include at least 3 females and 3 males. As such, 12 females and 12 males will participate for a total of 24 subjects. The multiple single dose study will include at least 8 subjects completing all aspects of the study, split evenly to include at least 4 females and 4 males. This is a sufficient number of subjects in each study to characterize the PK and PD of BIO 300 Oral Powder and to identify DLTs.

9.3 POPULATIONS FOR ANALYSES

All participants will be analyzed. The ITT dataset is the primary dataset for analysis. As a guide, analyses may include, but are not limited to, any or all of the following:

- Intention-to-Treat (ITT) Analysis Dataset: all participants
- Safety Analysis Dataset*:* participants who took at least one dose of BIO 300 Oral Powder

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

An independent statistician using standard statistical techniques will determine statistically significant differences in the trial measurement data. Statistical significance will be set at the nominal level of $p<0.05$. Plasma concentrations (genistein aglycone; free genistein) will be measured (AUC, C_{max}, T_{max}, $T_{1/2}$) and plasma kinetic rate will be calculated using standard procedures and statistical analyses (e.g., AUC using the linear trapezoidal formula and $T_{1/2}$ using linear regression). Data will be summarized by descriptive statistics (mean/medians and standard errors/confidence intervals for continuous response variables and distribution tables or histograms for discrete response variables).

Baseline characteristics will be compared using matched-pair t-tests. The computed change from baseline will be calculated for all measured variables and expressed as the mean change from baseline

and accompanying standard deviation (SD) of the change from baseline. Repeated measures ANOVA tests will be used to compare changes in scores for each variable between each treatment group. Matched pair t-tests will be used to compare the change scores within each treatment group. All data analyses will be conducted on the subjects who completed the study treatment periods and statistical significance will be set at $p<0.05$.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Blood counts, serum chemistry, urinalysis, ECGs, vital signs, and PTT/INR for the study cohorts will be reported as a mean ± SD at each of the timepoints listed in the **SoA, Section 1.3**. An analysis of covariance (ANCOVA) to compare the cohorts after adjusting for "baseline" (the adjustment covariate) will be completed. Analysis will be performed in individual subjects to identity changes in safety measurements relative to baseline, and between cohorts at the timepoints listed in the **SoA, Section 1.3** to identify any potential dose-response relationships.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For the secondary endpoint of RNA sequencing, statistical analysis will be used to detect differential expressed genes (DEGs). Analysis will be performed in individual subjects to identity DEGs relative to baseline, and between cohorts at the timepoints listed in the **SoA, Section 1.3** to identify dose-response relationships.

RNA samples will be sequenced using an Illumina HiSeq approach that will produce 20-30 million paired end reads per sample. Raw reads will be mapped to the human genome. Reads will be normalized as fragments per kilobase million (FPKM) and used to identify DEGs for biomarker evaluation.

9.4.4 SAFETY ANALYSES

All adverse events (AEs), including clinically significant laboratory abnormalities, will be collected in the site's source document, and reported on the AE case report form (CRF). Documentation of the serious event will be reported on the Serious Adverse Event (SAE) CRF and submitted to the Sponsor within 24 hours of awareness.

AEs will be identified using the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. The following information regarding each adverse event will be recorded:

- Assessment period
- Severity Grade (0-4)
- Attribution to study agent (relatedness)
- Date AE occurred
- Date AE resolved
- Whether or not the event was reported as an SAE
- Whether or not the participant dropped due to the event
- Action taken with study agent
- Outcome of the event
- Additional investigator comments

AEs will be summarized by study group and system organ class. Tables will include summaries of all AEs, all SAEs, all BIO 300 Oral Powder related AEs, all BIO 300 Oral Powder related SAEs, all Grade 3 or 4 AEs, and all AEs leading to death or study discontinuation.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics, such as subject age, vital signs, laboratory results, and BMI will be compared between the dosing cohorts using descriptive statistics. ANOVA analysis will be used to compare each parameter between the study cohorts at baseline.

9.4.6 PLANNED INTERIM ANALYSES

Following the 2000 mg single ascending dose cohort, safety and PK analysis will be completed to determine the dose for the final cohort of the single ascending dose study.

9.4.7 SUB-GROUP ANALYSES

No sub-group analysis is planned.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

All individual participant data will be listed by measure and timepoint.

9.4.9 EXPLORATORY ANALYSES

There are no exploratory analyses planned for this study.

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 informed consent form (ICF) is submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The environment where the process of consent is conducted will be private, confidential, and safe in order to facilitate a constructive dialogue between the prospective subject and the person(s) involved in obtaining consent. All prospective subjects must have the cognitive ability to provide legally effective informed consent. Individuals who do not have such ability (i.e., decisionally impaired persons) can only be enrolled in research through consent of their legally authorized representative (LAR). If there is any concern about an individual's cognitive ability an appropriate assessment should be performed by a qualified individual.

The informed consent will be presented and discussed with the prospective subject in a sequential manner utilizing the approved ICF as a guide. The presentation should be structured to facilitate a dialogue with reinforcement and elaboration of important information (e.g., the risks of the research). The person(s) involved in obtaining the subject's consent will constantly evaluate whether the process is

achieving the goal which is obtainment of legally effective informed consent from the subject. In addition to paying attention to general signs of information receptivity, the person obtaining consent may ask open-ended questions in order to identify points of confusion which require clarification.

A delayed consent procedure will be used in order to afford the subject the opportunity to discuss participation in the research with family, friends, counselors, or other confidants before they sign the ICF. If the individual is uncomfortable or anxious about participating in the research, they will be instructed to take the ICF home for further review and consideration before deciding whether or not to participate in the research.

The informed consent process will be documented by personnel qualified to attest the that the subject has provided legally effective informed consent. The individual documenting the process and the consenting subject will sign and date the ICF and indicate the time at which the ICF was signed. It is unacceptable for the person documenting consent to sign the ICF in advance of obtaining the subject's signature.

The informed consent document must be reviewed and approved by the IRB, any changes to the informed consent must be submitted to the IRB for approval prior to initiation.

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, Principal Investigator, funding agency, the Investigational New Drug (IND) Sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (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 Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

In order to maintain subject confidentiality, a subject number and initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor.

Participant confidentiality and privacy is strictly held in trust by the Principal Investigator, their staff, and the Sponsor(s) and their interventions. This confidentiality is extended to cover all aspects of 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 Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the 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 a site designated by the Sponsor. 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 staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Sponsor's designated site.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

*See also **Section 10.1.3, Confidentiality and Privacy** and **Section 10.1.9, Data Handling and Record Keeping**, for further information on future use of study records.*

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

There will be no storage of samples (e.g., whole blood or blood serum) for future new research. Storage of any samples (e.g., whole blood or blood serum) will solely be kept as reserves to be used for reanalysis if necessary. If samples are not used within 2 yrs they will be destroyed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator **Amy R. Eastenson, MD**	**Medical Monitor** **Carin Verduyn, MD**
Nucleus Network (Formally Prism Clinical Research)	Medical Monitoring Consultancy, LLC
1000 Westgate Drive, #149 Saint Paul, MN 55114	530 Payne Avenue Saint Paul, MN 55130
[redacted]	[redacted]

10.1.6 SAFETY OVERSIGHT

Safety oversight will be the responsibility of the Principal Investigator and the Medical Monitor.

10.1.7 CLINICAL MONITORING

Site monitoring will be 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 ICH GCP, and with applicable regulatory requirement(s).

Sponsor will monitor the progress of all clinical investigations being conducted under its IND based on the study specific Monitoring Plan, which shall be prepared by the Sponsor. If Sponsor discovers that a participating investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or other requirements the study Sponsor shall promptly either secure compliance or discontinue the investigator's participation in the investigation.

The Sponsor will review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the participating investigator. The notification process to the study Sponsor begins with the completion and submission of the appropriate CRFs. Investigators are required to report promptly to the Sponsor any adverse events that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse event meets the serious adverse event criteria, the investigator is required to report the event to the Sponsor within 24 hours of discovery.

Prompt review of the AE by the study Sponsor will be completed to determine if the AE meets any of the criteria for an AE to be reported to the FDA, Investigators, and/or Institutional Review Boards (IRB). Should an AE be determined by the study Sponsor to meet the criteria for a 7- or 15-day reportable event, the medical monitor will be notified promptly. The medical monitor will assist in writing the IND safety report with the study Sponsor. The Sponsor will submit all necessary reports to FDA regarding information relevant to the safety of the drug.

The study Sponsor will promptly investigate all safety information it receives. Should the Sponsor, in consultation with the Medical Monitor, determine that the investigational drug presents an unreasonable and significant risk to subjects, the study shall be discontinued. In this case, the study Sponsor will notify the FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance and assure the disposition of all stocks of the drug outstanding and furnish FDA with a full report of the Sponsor's actions.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion per its Standard Operating Procedures (SOPs).

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 SOPs, the monitor(s) 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 as appropriate and necessary.

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 Principal Investigator. The Principal 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 adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a study specific data capture system, a 21 CFR Part 11-compliant data capture system utilized by the Sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. 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.

Compliance with the study protocol and all study procedures will be assessed during each monitoring visit. A protocol deviation for this study is defined as any departure from the protocol whether pre-approved by the Sponsor or unplanned. Protocol deviations may be identified during monitoring visits or by the site either in anticipation of a deviation or upon discovery. The research site should complete a Protocol Deviation CRF and submit it to the Sponsor after review and signature by the investigator. Protocol deviations must be sent to the reviewing Institutional Review Board (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.

As specified in the Study Monitoring Plan, the Sponsor will review protocol deviations by site and overall to determine if there are any trends identified that may affect subject safety, data integrity and the impact on analysis and to determine if any actions need to be taken prevent continued deviations.

10.1.11 PUBLICATION AND DATA SHARING POLICY

Publication of clinical trial results will be consistent with the Sponsor's Publication Policy. The first publication in journal, or presentation at a congress, will be based on the consolidated data, analyzed as stipulated by the protocol and agreed upon by investigators.

The Sponsor intends to share all applicable data collected as part of this project with the DoD and the general scientific community. The data will be made as widely and freely available as possible through presentation at scientific conferences and publication of primary data in a peer-reviewed journal.

10.1.12 CONFLICT OF INTEREST POLICY

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.

10.2 ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ASD	Amorphous Spray Dried Dispersion
AST	Aspartate Aminotransferase
AUC	Area-Under-The-Curve
β-HCG	Human Chorionic Gonadotropin
BMI	Body mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CC	Cubic Centimeter
[redacted]	[redacted]
CFR	Code of Federal Regulations
C_{max}	Maximum (Peak) Concentration
CONSORT	Consolidated Standards of Reporting Trials

COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTPA	Computed Tomography Pulmonary Angiogram
DEG	Differentially Expressed Gene
DLT	Dose Limiting Toxicity
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ERβ	Estrogen Receptor Beta
FDA	US Food and Drug Administration
FPKM	Fragments Per Kilobase Million
[redacted]	[redacted]
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
g	Gram
HDL	High-Density Lipoprotein
HEENT	Head, Eyes, Ears, Nose and Throat
H/Hr	Hours
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
[redacted]	[redacted]
IND	Investigational New Drug Application
INR	International Normalized Ratio Based On PTT
IRB	Institutional Review Board
ITT	Intention-to-Treat
Kg	Kilogram
LAR	Legally Authorized Representative
LBBB	Left Bundle Branch Block
LDPE	Low-Density Polyethylene
LLDPE	Linear Low-Density Polyethylene
M^2	Square Meters
MedDRA	Medical Dictionary for Regulatory Activities
M/F	Male/Female
mg	Milligram
min	Minute
mL	Milliliter
msec	Millisecond
MOP	Manual of Procedures
MTD	Maximum Tolerated Dose
N	Number
NCT	National Clinical Trial

NF-κB	Nuclear Factor Kappa Light-Chain-Enhancer of Activated B Cells
[redacted]	[redacted]
NIH	National Institutes of Health
NF	National Formulary and Drug Standards Laboratory
NYHA	New York Heart Association
OHRP	Office for Human Research Protections
oz	Fluid Ounce
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PTT	Prothrombin Time
PVC	Premature Ventricular Contractions
QC	Quality Control
QTc	Corrected QT Interval
QTcF	QTc with Fridericia's Correction
RBC	Red Blood Cells
RNA	Ribonucleic Acid
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SD	Standard Deviation
SoA	Schedule of Assessments
SOP	Standard Operating Procedure
T1/2	Half-life
TBD	To Be Determined
T_{max}	Time to Reach C_{max}
[redacted]	[redacted]
UP	Unanticipated Problems
USP	United States Pharmacopeia
VTE	Venous Thromboembolism
w	Weight
WBC	White Blood Cells
Yrs	Years

10.3 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
0.5	17Sep2020	Initial Release	Initial Release
1.0	16Nov2020	Changed the biomarkers of interest, time period and frequency of AE reporting and reporting of pregnancy	Revised to include acute radiation syndrome relevant biomarkers, provide consistency with the Schedule Activities,

			and remove unnecessary language.
2.0	16Mar2021	Changed the blood draw times for PD (biomarkers) on day 6 of the multiple single dose study Added a pregnancy test to day 1 of the Multiple Single Dose Study Cohort	The original blood draw times were based on the predicted Cmax of BIO 300 Oral Powder from animal studies. The updated blood draw times are based on the actual Cmax from all 4 cohorts in the SAD study conducted under this protocol. Pregnancy test added to day 1 of the Multiple Single Dose Study Cohort to align with inclusion criteria requiring a negative pregnancy test within 72 hours of day 1.

11 REFERENCES

1. Hamalainen M, Nieminen R, Vuorela P, Heinonen M, Moilanen E. Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-kappaB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-kappaB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. Mediators of inflammation 2007;2007:45673.

2. Pons DG, Vilanova-Llompart J, Gaya-Bover A, et al. The phytoestrogen genistein affects inflammatory-related genes expression depending on the ERalpha/ERbeta ratio in breast cancer cells. Int J Food Sci Nutr 2019:1-9.

3. Liu J, Viswanadhapalli S, Garcia L, et al. Therapeutic utility of natural estrogen receptor beta agonists on ovarian cancer. Oncotarget 2017;8:50002-14.

4. Liu T, Zhang L, Joo D, Sun SC. NF-kappaB signaling in inflammation. Signal Transduct Target Ther 2017;2.

5. Chen Y, Xiao CQ, He YJ, et al. Genistein alters caffeine exposure in healthy female volunteers. European journal of clinical pharmacology 2011;67:347-53.

12 APPENDICES

APPENDIX 1: SOY RICH FOODS

The following is a list of soy rich foods that study participants should be counseled to avoid while participating in the study:

- Edamame
- Meat Alternatives containing soy protein or tofu, e.g.no meat hot dogs
- Miso
- Natto
- Nutritional drinks and bars with added soy protein
- Soymilk
- Soy cheese
- Soy ice cream
- Soy yogurt
- Soy Nuts
- Tempeh
- Textured Soy Protein
- Tofu
- Whole Soybeans

Use to the following links for additional information on soy rich foods:

http://www.ucsfhealth.org/education/a_guide_to_foods_rich_in_soy/

http://www.ars.usda.gov/SP2UserFiles/Place/80400525/Data/isoflav/Isoflav_R2.pdf

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1 Dose Escalation Trial Evaluating the Safety and Pharmacokinetic Profile of BIO 300 Oral Powder in Healthy Volunteers
Protocol Number:	CL0106-01
[redacted]	[redacted]
Investigational Agent:	BIO 300 Oral Powder
Phase of Development:	Phase 1
Sponsor:	Humanetics Corporation 7650 Edinborough Way, Suite 620 Edina, Minnesota 55435
Date of SAP:	December 28, 2020 (version 1.0)
Amendment History:	Original Version

Table of Contents

1. Introduction

Protocol Title: A Phase 1 Dose Escalation Trial Evaluating the Safety and Pharmacokinetic Profile of BIO 300 Oral Powder in Healthy Volunteers

Protocol Number: CL0106-01

[redacted]

Investigational Agent: BIO 300 Oral Powder

Phase of Development: Phase 1

Sponsor: Humanetics Corporation

Design: Open label, single site phase 1 study in healthy volunteers who are equally distributed by sex. The study will include a single ascending dose (SAD) study in four cohorts and will be followed by a six-day multiple single dose (MSD) study at either the highest dose or the maximum tolerated dose. There are no planned stratifications or sub-studies.

This Statistical Analysis Plan (SAP) details the planned methods for summarizing data collected in the clinical study conducted under Humanetics Corporation protocol CL0106-01. The current study protocol is identified as version 1.0 dated 16-Nov-2020.

Future protocol amendments (if any) will be reviewed to assess whether the changes necessitate modification of this SAP.

Since the study protocol is a companion document to this SAP, aspects in the protocol unrelated to statistical issues (e.g., patient eligibility criteria and detailed BIO 300 Oral Powder information) are not repeated here.

2. Study Objectives

2.1. Primary Objectives

- Determine the overall adverse event and pharmacokinetic (PK) profiles of single ascending doses of BIO 300 Oral Powder in healthy volunteers
- Determine the overall adverse event and PK profile of multiple doses of BIO 300 Oral Powder in healthy volunteers

2.2 Secondary Objectives

- Determine the effects of single and multiple doses of BIO 300 Oral Powder on blood-based biomarkers
- Use a combination of the PK and pharmacodynamic (PD) profiles from the single and multiple doses of BIO 300 Oral powder to identify the putative BIO 300 Oral Powder human efficacious dose

3. Study Endpoints

3.1. Primary Endpoint

- Evaluate the safety and pharmacokinetics of BIO 300 Oral Powder in Healthy Volunteers

3.2. Secondary Endpoint

- Characterize the expression of blood-based biomarkers

4. Sample Size

- 6 subjects/cohort (3M/3F) will be recruited for the single ascending dose study, and at least 6 (3M/3F) subjects/cohort will complete all aspects of the study. 2 additional subjects (1M/1F), will be screened, consented and available as backups for each cohort.
- 10 (5M/5F) subjects will be recruited for the multiple single dose study, and at least 8 (4M/4F) subjects will complete all aspects of the study. 4 additional subjects (2M/2F) will be screened, consented and available as backups.
- In total, at least 32 healthy volunteers who will complete all aspects of the trial.

The single ascending dose study consists of 4 cohorts, each with at least 6 subjects completing all aspects of the study, split evenly to include at least 3 females and 3 males. As such, 12 females and 12 males will participate for a total of 24 subjects. The multiple single dose study will include at least 8 subjects completing all aspects of the study, split evenly to include at least 4 females and 4 males. This is a sufficient number of subjects in each study to characterize the PK and PD of BIO 300 Oral Powder and to identify dose limiting toxicities (DLTs).

5. Analysis Populations

5.1. Intention-to-Treat Analysis Dataset

The Intention-to-Treat (ITT) analysis dataset will include all study participants

5.2. Safety Analysis Dataset

All study participants who receive at least one dose of BIO 300 Oral Powder. This analysis set will be used to summarize all safety endpoints.

5.3. Pharmacokinetic (PK) Population

The PK Population will include all subjects who receive at least 1 dose of BIO 300 Oral Powder and have sufficient, valid serum samples to estimate key parameters for at least 1 of the days of sampling. PK summaries will be based on the PK population.

5.4. Pharmacodynamics (PD) Population

The PD Population will include all subjects who receive at least 1 dose of BIO 300 Oral Powder and have sufficient, valid serum samples to estimate key parameters for at least 1 of the days of sampling. PD summaries will be based on the PD population.

6. Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will review safety and PK data (when available) during the conduct of the study. After each cohort in the SAD study, the SMC will make decisions on proceeding with dose escalation, adding additional subjects to the current cohort, and possible dose adjustments. The SMC may also recommend stopping the study, suspending enrollment or significant changes to the dosing regimen and/or enrollment if warranted by safety data. The SMC will immediately communicate this recommendation to Humanetics for review and determination of a final decision. SMC data reviews are

not considered interim analyses and do not necessitate adjusting of the alpha level for multiple statistical hypothesis tests.

7. Statistical Methods

Unless stated otherwise, the term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation (STD), minimum (min), and maximum (max) and standard errors/confidence intervals for continuous response variables and distribution tables or histograms for discrete response variables. Min and max values will be rounded to the precision of the original value, means and medians will be rounded to 1 decimal place greater than the precision of the original value, and STDs will be rounded to 2 decimal places greater than the precision of the original value. Percentages will be rounded to the nearest whole number (zeros are not displayed) with values of "< 1%" and "> 99%" shown as necessary for values falling near the boundaries.

The computed change from baseline will be calculated for all measured variables and expressed as the mean change from baseline + STD of the change from baseline. Analysis of covariance will be used to compare dosage groups on "change from baseline" measures (with baseline measurement considered as an adjustment covariate).

Unless otherwise note, all data collected during the study will be included in data listings and will be sorted by study cohort, subject number and then by visit for each subject number.

7.1. Definitions

- Baseline is synonymous with screening, and the baseline value (or baseline result) is that measured during the screening visit prior to the first administration of BIO 300 Oral Powder.
- Day 1 is the first day of dosing with BIO 300 Oral Powder.
- Estimand is the estimated value for a parameter or, alternatively, a formula and/or description for how a parameter is estimated.
- Proportional months, defined for durations of time reported in months, are given by the formula

$$\text{months} = \frac{12}{365.25} \times \text{days}$$

- Shift table is a two-way frequency table pairing baseline value with the most extreme post-baseline result.

7.2. Missing Values

Given the small sample size, descriptive statistics and other analyses will be completed without replacing or imputing missing values.

7.3. Visit Windows

The study protocol defines a visit schedule based on the number of days since the first dose of BIO 300 Oral Powder (Day 1). All study participants will be instructed on when they need to return to the clinic in order to meet all scheduled assessments. Assessments outside of the scheduled visit window will be analyzed (by visit according to the clinical database) as if they occur within the visit window; that is, no data will be excluded if it is measured outside the visit window.

7.4. Interim Analysis

Following the third SAD cohort, PK analysis will be completed for all subjects (cohorts 1-3) and analyzed along with all safety data to determine the dose for the final cohort of the SAD study. No other interim analyses are planned. SMC data reviews are not considered interim analyses (see **Section 6**).

7.5. Significance level

An independent statistician using standard statistical techniques will determine statistically significant differences in the trial measurement data at the nominal 0.05 level of significance.

8. General Data Analyses

8.1. Subject Disposition

The numbers of subjects who were enrolled and dosed with BIO 300 Oral Powder will be summarized by frequency counts. Reasons for discontinuing BIO 300 Oral Powder and study completion status will be summarized as categorical variables (number and percentage of subjects in each category). Relevant data supporting these summaries will be listed by subject.

8.2. Protocol Deviations

Study inclusion/exclusion criteria violations and protocol deviations recorded in the clinical database, if any, will be summarized as categorical variables (number and percentage of subjects in each category). Relevant data supporting this summary will be listed by subject.

8.3. Baseline and Demographic Characteristics

Demographic and baseline characteristic data will be summarized with descriptive statistics for age, gender, race, ethnicity, height, weight, BMI, vital signs and laboratory results. ANOVA analysis will be used to compare each parameter between the study cohorts at baseline.

9. Endpoint Analyses

All observations available in the study database will be included in endpoint analysis regardless of subjects' aggregate exposure to BIO 300 Oral Powder, use of concomitant medications, or violations of the protocol. Relevant data supporting efficacy analyses will be listed by subject.

9.1. Analysis for Safety Endpoints

Safety data will include adverse events (AEs), safety laboratory (CBC/hematology, serum chemistry and urinalysis), pregnancy (if applicable), drug and alcohol tests test, physical exam, ECG, and vital signs. The proportion of subjects experiencing adverse events, serious adverse events, and DLTs will be summarized for each dosing cohort. See **Section 10** for more information on safety analysis.

9.2. Analysis for the Pharmacokinetic Profile

PK parameters will be estimated using nominal sampling times relative to each dose administration and nominal doses unless otherwise specified. Serum concentration values obtained at the predose time point will be used to estimate the concentration at time zero (baseline). Concentration values reported as not quantifiable (BLQ, <1.0 ng/mL) will be assigned a value of zero.

The area under the concentration vs. time curve (AUC) will be calculated using the linear trapezoidal method with linear interpolation. The AUC will not be calculated for PK profiles with less than 3 quantifiable concentrations of BIO 300 Oral Powder at separate time points. When practical, the terminal

elimination phase of each concentration versus time curve will be identified using at least three observed concentration values after Cmax, but not including Cmax. The slope of the terminal elimination phase will be determined using log linear regression on the unweighted concentration data. Parameters relying on the determination of the terminal elimination phase will not be reported if the coefficient of determination is less than 0.800, or if the extrapolation of the AUC to infinity represented more than 20% of the total area. The parameters Tmax, Cmax, AUC(0-t), AUC(0-inf) and T1/2 will be reported for each SAD cohort and for the MSD cohort on after the Day 6 dose of BIO 300 Oral Powder.

9.3. Analysis for Blood-Based Biomarkers

Blood-based biomarkers will be identified by extracting RNA from whole blood samples and performing transcriptome analysis to determine differential gene expression. Transcriptome analysis will be conducted by paired-end RNA sequencing. After investigating the quality of the raw sequencing data, sequence reads will be trimmed to remove possible adapter sequences and nucleotides with poor quality using Trimmomatic v.0.36. The trimmed reads will be mapped to the Homo sapiens reference genome available on ENSEMBL using the STAR aligner v.2.5.2b. The STAR aligner is a splice aligner that detects splice junctions and incorporates them to help align the entire read sequences. Binary Alignment Map (BAM) files will be generated as a result of this step. Unique gene hit counts will be calculated by using feature counts from the Subread package v.1.5.2. Only unique reads that fell within exon regions will be counted.

After extraction of gene hit counts, the gene hit counts table will be used for downstream differential expression analysis. Using DESeq2, a comparison of gene expression between the groups of samples will be performed. The Wald test will be used to generate p-values and Log2 fold changes. Genes with adjusted p-values < 0.05 and absolute log2 fold changes > 1 will be called as differentially expressed genes for each comparison. A gene ontology analysis will be performed on the statistically significant set of genes by implementing the software GeneSCF. The goa_human GO list will be used to cluster the set of genes based on their biological process and determine their statistical significance. A principal component analysis (PCA) will be performed using the "plotPCA" function within the DESeq2 R package. This plot will show the samples in a 2D plane spanned by their first two principal components. The top 500 genes, selected by highest row variance, will be used to generate the plot.

10. Safety Analyses

Summaries of safety endpoints will include data collected from the safety analysis dataset. Relevant data supporting safety analyses will be listed by subject.

10.1. Exposure to BIO 300 Oral Powder

For the SAD study, safety data will also be listed by cohort in order to analyze safety endpoints by dose level. For the MSD study, the number of BIO 300 Oral Powder doses will be calculated and summarized by the mean, standard deviation, median, minimum and maximum values.

10.2. Adverse Events

The FDA guidance entitled "*Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*" will be used to grade all AEs. All reported terms and descriptions for AEs will be coded using this FDA guidance and summarized with frequencies and percentages by treatment group, system organ classification (SOC) and preferred term.

All AEs will be included in comprehensive and cohort separated data listings. Additionally, AE summaries will be provided for the following:

- DLT
- Serious AEs (SAEs)
- All Grade 3 or 4 AEs
- AEs leading to discontinuation from the study
- AEs by severity using Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials grades
- AEs with 10% or higher incidence rates

For all AE summaries, events will be counted only once per subject by primary SOC and preferred term. When an AE occurs more than once for a subject, the maximum severity and causality will be used.

Partial start and end dates for adverse events will be replaced by calendar dates that maximize the duration of the adverse event. The following steps will be followed.

For a partial start date:

1. Replace a missing month with January
2. Replace a missing calendar day with the first of the month

For a partial end date:

1. Replace a missing month with December
2. Replace a missing calendar day with the last day of the month

An end date will not be estimated for adverse events marked continuing at the end of the study.

10.3. Clinical Laboratory Test Results

Subject minimum and maximum post-baseline laboratory values (and changes from baseline) for analytes measured on a continuous scale will be summarized by the mean, standard deviation, median, minimum and maximum values. The same statistics will be calculated to summarize laboratory test results by visit. Ordinal categorical test results with a corresponding Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials severity scale will be summarized using shift tables.

Urinalysis tests such as specific gravity and pH were collected only to assess a subjects' eligibility to participate in the study. No analyses are planned for urinalysis test results.

10.4. Vital Signs

Subject minimum and maximum post-baseline systolic and diastolic blood pressures, respiratory rate, pulse rate, temperature and body weight (and changes from baseline) will be summarized by the mean, standard deviation, median, minimum and maximum values. The same statistics will be calculated to summarize vital signs by visit.

10.5. Electrocardiograms

ECG QTc measurements will be summarized with descriptive statistics and time point with respect to BIO 300 Oral Powder administration. All ECG data will be displayed in a data listing.

11. Symbols and Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
AUC	Area Under the Curve
BAM	Binary Alignment Map
BLQ	Below the Limit of Quantitation
BMI	Body-Mass Index
CBC	Complete Blood Count
Cmax	Maximum (Peak) Serum Concentration
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
F	Female
FDA	U.S. Food and Drug Administration
ITT	Intent to Treat
Inf	Infinity
M	Male
Max	Maximum
Min	Minimum
mL	Milliliter
MSD	Multiple Single Dose
ng	Nanogram
PCA	Principal component analysis
PD	Pharmacodynamics
PK	Pharmacokinetics
QTc	Corrected QT Interval
RNA	Ribonucleic Acid
SAD	Single Ascending Dose
SAE	Serios Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOC	System Organ Classification
STD	Standard Deviation
t	time
T1/2	Half-Life
Tmax	Time to Reach Maximum (Peak) Serum Concentration