NCT05482867

Exploratory Open-Label Study for the Development of a Method to Detect Dendritic Cell Recruitment in Alzheimer's Disease (DC RAD)

STATISTICAL ANALYSIS PLAN

PROTOCOL: ICG-001

Exploratory Open-Label Study for the Development of a Method to Detect Dendritic Cell Recruitment in Alzheimer's Disease (DC RAD)

SPONSOR: MindImmune Therapeutics, Inc.
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PRODUCT: Indocyanine Green (ICG)

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2 AMENDMENT HISTORY

3 LIST OF ABBREVIATIONS

Abbreviation	Term
AD	Alzheimer's Disease
AE	Adverse event
BAL	Breath alcohol level
CR3	Complement receptor 3
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CRF	Case report form
CRO	Contract Research Organization
CSR	Clinical study report
DBP	Diastolic blood pressure
DC	Dendritic Cells
ECG	Electrocardiogram
MedDRA	Medical Dictionary for Regulatory Activities
MHIS	Modified Hachinski Ischemia Scale
mg	milligram
mmHg	millimeters of mercury
MMSE	Mini Mental State Examination
NIRS	Near Infrared Spectroscopy
PBMC	Peripheral Blood Mononuclear Cells
SAE	Serious adverse events
SAP	Statistical analysis plan
SD	Standard deviation
TEAE	Treatment-emergent adverse events

4 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analysis for the protocol titled "Exploratory Open-Label Study for the Development of a Method to Detect Dendritic Cell Recruitment in Alzheimer's Disease (DC RAD)" (Version 4.0 dated 13 June 2023). Mock shells will be produced as a separate working document to facilitate programming of Tables, Figures, and Listings (TFLs) according to the SAP. The SAP is to be interpreted in conjunction with the protocol, and supersedes the statistical considerations identified in the protocol. If the final clinical study report contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the clinical study report (CSR).

On June 13th, 2023 the ICG-001 protocol was amended due to 5 subjects experiencing adverse events related to the use of sterile water to reconstitute ICGreen. The proposed change is to use Dextrose 5% in water (D5W) solution as the dilutant/infusion vehicle. Two additional cohorts of 3 subjects each were planned. Starting with Cohort 2a: 3 subjects were enrolled and monitored for dose limiting AE's. If none were observed then Cohort 3a would enroll 3 healthy elderly subjects. If no dose limiting AE's are observed then the D5W would be adopted as the infusion vehicle for the remainder of the study.

5 STUDY OBJECTIVES

Biomarker Proof of Concept Part 1

- Characterize indocyanine green (ICG) labeling of peripheral immune phagocytic cells in healthy adult subjects.

Biomarker Proof of Concept Part 2

- Determine the presence of ICG in the brain of adult subjects diagnosed with Alzheimer's disease (AD).

Safety and Tolerability

- Examine the safety and tolerability of ICG infusion in normal healthy adult volunteers, normal healthy elderly volunteers, and in AD subjects.

6 STUDY DESIGN

6.1 DURATION OF STUDY

Study duration is approximately 45 days, including 29 days from the time of Screening at Day -28 up to and including dosing at Day 0, and 16 days following dosing to telephone follow-up.

6.2 NUMBER OF SUBJECTS

The total number of subjects planned is 51 volunteers, including 18 healthy adults (ages 21 to 55; 5 in Cohort 1, 10 in Cohort 2 and 3 in Cohort 2a) 18 healthy elderly adults (ages 65 to 90; 15 Cohort 3 and 3 in Cohort 3a) and 15 AD subjects (ages 50-90; Cohort 4).

6.3 DESIGN

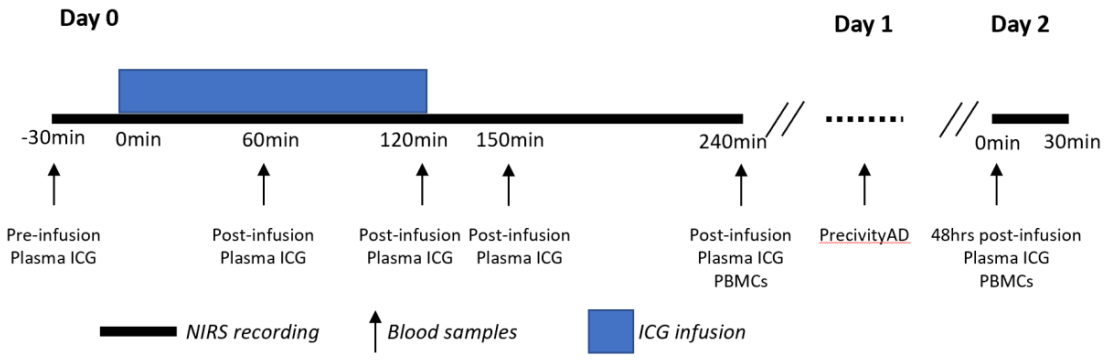
This proof-of-concept study is designed to determine if human phagocytic cells can be labeled with the near-infrared dye ICG in the periphery and the presence of ICG-labeled cells can then be detected 48 hours later in the cerebral cortex by near infrared spectroscopy (NIRS).

To develop a method to detect dendritic cell recruitment in Alzheimer's disease (DC RAD), this study is designed in 2 parts. The first part is to characterize the efficacy of intravenous infusion of indocyanine green (ICG) for labeling of peripheral immune phagocytic cells in healthy adult subjects. The second part is designed to determine the presence of ICG-labeled cells in the brain of adult subjects diagnosed with AD.

In the first part of the study, ICG will be delivered by intravenous infusion to healthy subjects to verify that peripheral immune phagocytic cells, of which DCs are a subset, can be labeled with ICG. Labeling will be confirmed by analysis of the PBMC fraction. If ICG labeling of phagocytic cells is confirmed, then in the second part of the study the presence of ICG in brain of AD subjects, putatively carried in by ICG-labeled cells, will be investigated by NIRS using the INVOS 7100 cerebral oximeter.

For all subjects, the study will follow the timeline shown in Figure 1.

Figure 1. Study Timeline



On Day 0, NIRS recording will commence and continue throughout a 270-minute session. All times measures are relative to the initiation of the ICG infusion. All timed measures on Day 0 and Day 2 are to be completed within ± 5-minute window; vital signs will be completed within a +/- 7-minute window. Following baseline recording from 30 minutes pre-infusion to minute 0, an intravenous infusion of ICG will commence and be maintained from minute 0 to minute 120 (120 minutes duration). After cessation of the infusion, NIRS recording will continue until minute 240. Blood samples will be drawn relative to the start of infusion at 30 minutes pre-

infusion, and at minutes 60, 120, 150, and 240 post-infusion. All blood samples will be assayed for plasma ICG concentration. For Cohorts 3 and 4 (healthy elderly and AD subjects), a separate blood sample collected on Day 1 will be used for assay for biomarkers predictive of brain amyloid deposition-relevant pathologies using the PrecivityAD™ test (see protocol). An additional blood sample will be collected at the 240-minute timepoint, coinciding with the end of the NIRS recording. This sample will be used to determine the presence of ICG-labeled cells. Procedure for the preparation of the PBMC Fraction is included in the protocol. Subjects will remain in the clinic for approximately 48 hours.

Approximately 48 hours after ICG infusion, blood samples will be drawn and an NIRS recording will be made for 30 minutes. Subjects will be discharged at the end of the 30-minute recording. One of the Day 2 blood samples will be used for assay of plasma ICG level, and a separate blood sample will be used for isolation of PBMCs for determination of the percentage of cells labeled with ICG. The procedure for PBMC isolation is in the study protocol.

Cohort 1, healthy adults (n = 5), will receive an ICG infusion of 1 mg/min. If no dose limiting adverse effects are observed in Cohort 1, then Cohort 2, healthy adults (n = 10), will receive an ICG infusion of 2 mg/min. If there are no dose limiting adverse events and there is evidence of ICG-labeling of PBMCs, the 2 mg/min infusion rate will be used for the remainder of the study.

Cohort 3, healthy elderly adults, will receive an ICG infusion of 2 mg/min and a sample will be taken on Day 1 for the PrecivityAD™ biomarker test. The first 5 subjects will serve as a satellite group. If no dose limiting adverse effects are observed in the satellite group, then a further 10 healthy elderly subjects will receive a 2 mg/min ICG infusion (n = 15 total for Cohort 3).

Two additional Cohorts (Cohorts 2a and 3a) will be added for IV infusion safety testing, with the change in infusion solution from Sterile Water to Dextrose 5% in water (D5W). Three (3) additional healthy adults (Cohort 2a) at 2 mg/min of ICG infusion and three (3) additional healthy elderly adults (Cohort 3a) at 2 mg/min of ICG infusion will be conducted. If no dose limiting adverse events are reported and there is evidence of ICG-labeling of PBMCs the trial will advance to Cohort 4 dosing.

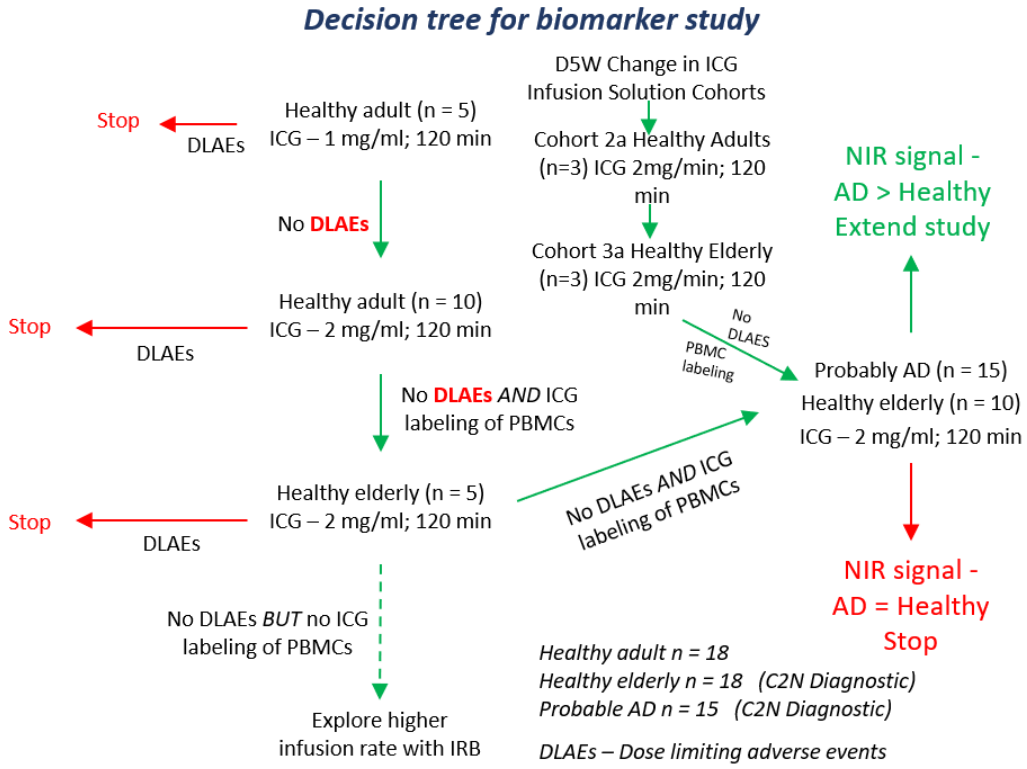
Cohort 4, AD subjects, will receive an ICG infusion of 2 mg/min, and a sample on Day 1 will be taken for the PrecivityAD™ biomarker test. The first 5 subjects will serve as a satellite group. If no dose limiting adverse effects are observed, then a further 10 AD subjects will receive a 2 mg/min ICG infusion (n = 15 total for Cohort 4). Recruitment of AD subjects will begin after three (3) subjects are dosed in Cohort 2a and three (3) subjects are dosed in Cohort 3a without any dose limiting adverse if there are no dose limiting adverse effects observed in the satellite group of healthy elderly.

Baseline data will be collected to include urine analysis, urine drug screen, urine pregnancy, clinical laboratory tests, vital signs, physical examination finding, and ECG. Any abnormal vital

sign measurement, clinical laboratory test, physical examination finding, or ECG parameter deemed clinically significant by the investigator will be repeated, including test results obtained on Day 0, Day 1 and the final study day (Day 2) or upon early termination.

For any test abnormality deemed clinically significant, repeat analysis will be performed during the follow-up period and until the value returns to baseline (or within normal limits) or the investigator deems the abnormality to be stable and no longer of clinical concern**.**

Figure 2. Decision Tree for Biomarker Study



6.4 SCHEDULE OF EVENTS

Table 1. Schedule of Visits and Assessments

Visit	Screening[1]	Dosing and Measurements[2]	24 hours[2]	48 hours and Early Termination[2]	Telephone Follow-up
Day	-28 to -1	0	1	2 and ET	Day 7-16
Informed Consent[1]	X				
Inclusion/Exclusion Criteria[3]	X	X			
Demographics	X				
Medical and Psychiatric History	X				
Concomitant Medications	X	X	X	X	X
Suicide Screening	X			X	
12 – Lead ECG[4]	X	X		X	
Physical Exam[5,6]	X			X	
Safety labs[7]	X	X	X	X	
Urine Pregnancy testing	X				
Vital Signs Measurements[8,9]	X	X		X	
HIV Testing	X				
AE Monitoring	X	X	X	X	X
Urine Toxicology/BAL[10]	X	X			
Urinalysis[11]	X	X	X	X	
PrecivityAD™ test [12]			X		
MMSE [13]	X				
MHIS [14]	X				
Administration of ICG by Infusion[15]		X			
Scan by near infrared spectroscopy (NIRS) [16]		X		X	
Analytical measurement of labeled cells (PBMC) [17]		X		X	
ICG Concentration Levels [18]		X		X	

Notes:

1. All procedures must be completed after signing informed consent.
2. All timed measurements and procedures on Day 0, Day 1, and Day 2 are to be completed within a ± 5-minute window; vital signs will be completed within a +/- 7 minute window.

3. Inclusion/Exclusion criteria evaluated at Screening and Day 0.
4. ECG will be performed at Screening, Day 0 within 30 minutes pre-infusion and within 30 minutes of the end of the ICG infusion allowing a +5 minute window and on Day 2 after completion of the 30 minute NIRs recording prior to discharge.
5. The Physical Exam will be performed at Screening and on Day 2 prior to discharge.
6. Height to be collected at Screening only. Weight to be collected at Screening only.
7. On Day 0, after dosing and completion of NIRs, on Day 1 and on Day 2 a Hematology, and Serum Chemistry including fractionated bilirubin are to be collected.
8. Vital sign measurements will include measurement of oxygen saturation. Oxygen saturation will be collected at screening and prior to the NIRs recording Day 0 only. Resting vital signs (SBP, DBP and HR) will be taken upon having the subject sitting/semi-recumbent or supine/recumbent position for 5 min at Screening, on Day 0 immediately prior to the start of the NIRs recording, and immediately after the start of the ICG infusion, and at 30min, 90min, 120min, 150min, 210min, and 240min after the start of infusion, and prior to discharge on Day 2.
9. Orthostatic measurement of systolic, diastolic blood pressure and heart rate will be measured after the subject has been standing for a total of 5 minutes. On Day 0, the orthostatic measurements will be taken prior to the start of the NIRs recording, at 30 minutes after the start of the ICG infusion and 240 minutes after the start of ICG infusion. If the first measurement of any vital signs (SBP, DBP and pulse) shows the following, vital signs will be measured again in triplicate (same arm, separated by at least 1 minute) for SBP <90 mmHg, DBP <60 mmHg, and pulse <60 bpm. No upper limit will be set as the investigator or designee may repeat any vital sign at their discretion.
10. Urine drug testing will include opioids (fentanyl), buprenorphine, methadone, benzodiazepines, cocaine (benzoylecgonine), amphetamines, and other drugs. Breath alcohol levels (BAL) will be assessed at Screening and Day 0 prior to start of NIRs recording.
11. At Screening, Day 0, after dosing and completion of NIRs, Day 1 and on Day 2 a Urinalysis is to be collected.
12. PrecivityAD™ test to be drawn on Cohorts 3 and 4 only anytime on Day 1
13. Mini Mental State Examination (MMSE) to be completed only for Cohorts 3 and 4
14. Modified Hachinski Ischemia Scale (MHIS) to be completed only for Cohort 4
15. Administration of ICG will be done on Day 0 after all pre-dose procedures, 30mins relative to the start of the NIRs recording.
16. Day 0 all timed measurements and procedures are relative to the start of the ICG infusion. On Day 2, the 30min NIRs recording begins 48hrs after the start of the ICG infusion on Day 0.
17. Analytical measurement of labeled cells (PBMC) are measured on Day 0 at 240 minutes (relative to the start of ICG infusion)) and on Day 2 (48 hrs. after the start of the ICG infusion).
18. ICG levels will be drawn on Day 0 (relative to the start of ICG infusion) at 30 minutes pre-infusion and at minutes 60, 120, 150, and 240 post-infusion and on Day 2 (48hrs after the start of the ICG infusion).

6.5 TREATMENT

ICG is a specific near infrared dye used to label peripheral immune phagocytic cells. ICG, as a solution in D5W, will be administered by study site personnel by IV infusion at 1 mg or 2 mg per minute using an infusion pump. Table 2 presents study cohorts and corresponding treatments.

Subjects in Cohort 2a and 3a will receive ICG, as a solution in D5W. Starting with Cohort 2a: 3 subjects were enrolled and monitored for dose limiting AE's. If none were observed then Cohort 3a would enroll 3 healthy elderly subjects. If no dose limiting AE's are observed then the D5W would be adopted as the infusion vehicle for the remainder of the study.

Table 2. Study Cohorts and Dosing Scheme

Cohort	Demographic	Number of subjects	ICG infusion rate
1	Healthy Adults	5	1 mg/min
2	Healthy Adults	10	2 mg/min
3	Healthy Elderly	15	2 mg/min
2a	Healthy Adults	3	2 mg/min
3a	Healthy Elderly	3	2 mg/min
4	AD patients	15	2 mg/min

6.6 EFFICACY ENDPOINTS

- Percentage of PBMCs labeled with ICG at the end of Day 0 and the beginning of Day 2
- Plasma ICG concentrations change from infusion (as measured by NIRS) determined from blood samples collected on Day 0: 30 minutes before start of the infusion (background), 60 and 120 minutes after the start of the infusion, and 30 and 120 minutes after the end of the infusion
- Difference in NIRS signal over the background signal from hemoglobin during infusion and 48 hours after infusion compared to baseline and between healthy adults and subjects with AD
- Correlation between NIRS signal after cessation of ICG infusion and results of the PrecivityAD™ screen.

6.7 SAFETY ENDPOINTS

- Vital signs (change from baseline)
- Adverse Events (AEs)
- 12-lead ECGs (change from baseline)
- Clinical laboratory tests (change from baseline)

6.7.1 ADVERSE EVENTS

AE verbatim terms will be collected at each study visit. The start date of the event stop, date of the event (if known), severity, relationship to study drug, seriousness, outcome, and action taken for each verbatim term will also be collected. All verbatim terms will be coded using the

most current version of Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization. AEs and serious AEs (SAEs) should be collected for a subject starting from signing of the informed consent until the subject's last study visit. This includes follow-up visit, early termination, or last regularly scheduled study visit. Safety data analyses will be conducted on all subjects who have started at least 1 infusion of ICG. The number and percentage of subjects experiencing 1 or more AEs will be summarized by infusion rate, relationship to ICG, and severity. Listings of subjects who withdraw from the study due to an AE, SAE, and/or death or lack of treatment effect will be presented.

6.7.2 PHYSICAL EXAMINATION

A standard physical examination will be performed at Screening and study Day 2 or Early Termination Visit. The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim physical examinations will be performed at the investigator's discretion, if necessary, to evaluate AEs or clinical laboratory abnormalities.

6.7.3 VITAL SIGN MEASUREMENTS

Resting vital signs, including systolic, diastolic blood pressure and heart rate (measured as pulse) will be measured after the subject has been in a sitting/semi-recumbent or supine/recumbent position for at least 5 minutes at the time points specified in the Schedule of Assessments Table 1.

Orthostatic measurement of systolic, diastolic blood pressure and heart rate will be measured after the subject has been standing for a total of 5 minutes. On Day 0, the orthostatic measurements will be taken prior to the start of the NIRS recording, at 30 min after the start of infusion, and 240 min after the start of the ICG infusion.

If the first measurement of any vital signs (SBP, DBP and pulse) shows the following, vital signs will be measured again in triplicate (same arm, separated by at least 1 minute) for SBP <90 mmHg, DBP <60 mmHg, and pulse <60 bpm. No upper limit will be set as the investigator or designee may repeat any vital sign at their discretion.

6.7.4 12-LEAD ELECTROCARDIOGRAM

A 12-lead ECG with rhythm strip will be performed at Screening, Day 0 within 30 minutes pre-infusion and within 30 minutes of the end of the ICG infusion; on Day 2 after the completion of the 30-minute of NIRS recording before discharge.

6.7.5 CLINICAL LABORATORY TESTING

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Visits and Assessments (Table 1).

Hematology:	Consists of complete blood count (hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, and platelet count)

Serology:	HIV
Serum chemistry:	Includes blood urea nitrogen, creatinine, total bilirubin, fractionated bilirubin, alkaline phosphatase, aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), alanine aminotransferase (serum glutamic pyruvic transaminase), glucose, albumin, total protein, HbA1C, lipase, amylase, and eGFR.
Urinalysis:	Includes pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, leukocytes, urobilinogen, microscopic urine analysis if dipstick positive
Urine pregnancy test	Conducted for females of childbearing potential only
Urine drug screen	Opioids, (fentanyl), buprenorphine, methadone, benzodiazepines, cocaine (benzoylecgonine), amphetamines, and other drugs. Results of the UDS for Inclusion/Exclusion is for the PI to determine if the subject if eligible.
Breath alcohol level	Conducted at Screening and prior to the start of NIRS monitoring on Day 0.

6.7.6 PLASMA ICG

The plasma ICG concentrations during the ICG intravenous infusion and the degree to which ICG has been eliminated from plasma after the infusion will be determined from blood samples collected on Day 0 30 minutes before start of the infusion (background), 60 and 120 minutes after the start of the infusion, and 30 and 120 minutes after the end of the infusion. Descriptive statistics and change from baseline by cohort will be summarized.

6.7.7 NEAR INFRARED SPECTROSCOPY

The presence of ICG labeled cells in brain will be inferred from the detection of an increase in absorbance of near infrared light at 805 nm measured using the INVOS 7100 cerebral oximeter. Descriptive statistics and change from baseline will be summarized.

6.7.8 PBMC LABELING

Peripheral blood mononuclear cells (PBMCs) will be isolated from the blood samples and the percentage of cells labeled with ICG determined by appropriate analytical methods. Descriptive statistics will be summarized.

6.7.9 PRECIVITYAD™ TEST

A plasma sample will be taken from each subject in Cohorts 3 and 4 and assayed for biomarkers predictive of brain amyloid deposition using the PrecivityAD™ test. Descriptive statistics will be summarized by cohort for each biomarker.

6.7.10 CONCOMITANT MEDICATIONS

Concomitant medications will be reviewed and documented during Screening, Day 0 through Day 2, and at the Telephone Follow-up visit.

7 STATISTICAL ANALYSES

7.1 GENERAL CONSIDERATIONS

All analysis dataset preparations and statistical analysis will be performed using SAS® version 9.4 or higher.

When reporting descriptive statistics, the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, and one more decimal place than raw data will be presented for mean and standard deviation. Two decimal places will be given for percentages and four decimal places will be given for proportions.

Continuous variables will be summarized by treatment using descriptive statistics (sample size, mean, median, standard deviation, minimum, and maximum). For categorical variables, frequencies and percentages will be presented by treatment.

Baseline is defined as the last measure prior to infusion on Day 0.

Listings of CSR Appendix 16.2 will include all the subject data points collected or derived for analyses. Data listings will be provided for all subjects up to the point of study completion or discontinuation.

7.2 SAMPLE SIZE DETERMINATION

No formal sample size calculations have been performed. Decisions regarding safety will be made by comparing the known profiles and likelihood of relatedness to the treatment and/or unexpected results.

7.3 STUDY DATA

The study data to be analyzed include all clinical data captured by the case report form (eCRF) or otherwise centrally, including safety lab data. The database will be locked prior to the final analyses.

7.4 MISSING DATA

No imputations will be performed for missing data unless stated otherwise.

7.5 ANALYSIS POPULATION

The following analysis populations are planned:

- Safety Population: All subjects who receive study drug.
- Full Analysis Set (FAS): All subjects in the Safety Population who have at least one plasma ICG level or PBMCs.

7.6 TREATMENT GROUPS

Analyses will be conducted by Cohort (1, 2, 2a, 3, 3a, and 4) and by ICG infusion rate: 1 mg/min or 2 mg/min.

Six cohorts will be enrolled in succession. Cohort 1, healthy adults (n = 5), will receive an ICG infusion of 1 mg/min. If no dose limiting adverse effects are observed in Cohort 1, then Cohort 2, healthy adults (n = 10), will receive an ICG infusion of 2 mg/min. If there are no dose limiting adverse events and there is evidence of ICG-labeling of PBMCs, the 2 mg/min infusion rate will be used for the remainder of the study.

Cohort 3, healthy elderly adults, will receive an ICG infusion of 2 mg/min and a sample will be taken on Day 1 for the PrecivityAD™ biomarker test. The first 5 subjects will serve as a satellite group. If no dose limiting adverse effects are observed in the satellite group, then a further 10 healthy elderly adults will receive a 2 mg/min ICG infusion (n = 15 total for Cohort 3).

Two additional cohorts (Cohorts 2a and 3a) will be added for IV infusion safety testing, with the change in infusion from Sterile Water to Dextrose 5% in water. Three (3) additional healthy adults (Cohort 2a) at 2 mg/min of ICG infusion and three (3) additional healthy elderly adults (Cohort 3a) at 2 mg/min of ICG infusion will be conducted. If no dose limiting adverse events are reported and there is evidence of ICG-labeling of PBMCs the trial will advance to Cohort 4 dosing.

Cohort 4, AD patients, will receive an ICG infusion of 2 mg/min and a sample on Day 1 will be taken for the PrecivityAD™ biomarker test. The first 5 subjects will serve as a satellite group. If no dose limiting adverse effects are observed, then a further 10 AD patients will receive a 2 mg/min ICG infusion (n = 15 total for Cohort 4). Recruitment of AD patients will begin after three (3) subjects are dosed in Cohort 2a and three (3) subjects are dosed in Cohort 3a without any dose limiting adverse events and evidence of ICG-labeling of PBMCs is confirmed.

Cohorts 3 and 4 will be used for inferential statistics.

7.7 EFFICACY ENDPOINTS

- Percentage of PBMCs labeled with ICG at the end of Day 0 and the beginning of Day 2
- Plasma ICG concentrations change from infusion (as measured by NIRS) determined from blood samples collected on Day 0: 30 minutes before start of the infusion (background), 60 and 120 minutes after the start of the infusion, and 30 and 120 minutes after the end of the infusion.
- Difference in NIRS signal over the background signal from hemoglobin during infusion and 48 hours after infusion compared to baseline and between healthy adults and subjects with AD.
- Correlation between NIRS signal after cessation of ICG infusion and results of the PrecivityAD™ screen.

7.8 SAFETY ENDPOINTS

- Vital signs (change from baseline)

- Adverse Events (AEs)
- 12-lead ECGs (change from baseline)
- Clinical laboratory tests (change from baseline)

7.9 STATISTICAL HYPOTHESIS TESTS

This is an open-label and exploratory study. Therefore, no formal hypothesis tests will be conducted.

7.10 MULTIPLICITY ADJUSTMENT

No adjustments will be made for multiple comparisons.

7.11 DEFINITION OF SUBGROUPS

No subgroup analyses are planned.

7.12 MAIN ANALYTICAL APPROACH

Descriptive observed and change-from-baseline values will be presented in summary tables.

8 PLANNED INTERIM ANALYSIS

Since this is an open-label study, MindImmune may examine data in an ongoing manner that is separate from the analyses outlined in this document. Mindimmune's analysis can be used to make decisions on the continuation of the study.

9 SUBJECT INFORMATION

9.1 DISPOSITION INFORMATION

Subject disposition will be analyzed using counts and percentages. The number and percentage of subjects screened, using the device, treated with randomized therapy, discontinued from the study and study treatment, as well as the primary reason for discontinuation will be analyzed and listed. The possible reasons for discontinuation include the following:

- Adverse Event
- Death
- Lost to Follow-up
- Non-Compliance
- Investigator Decision
- Study Terminated by Sponsor
- Pregnancy
- Withdrawal of Consent by Subject
- Other

9.2 PROTOCOL DEVIATIONS

All reported, important protocol deviations will be documented and included in the CSR.

9.3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and Baseline characteristics data will be summarized using descriptive statistics for the safety population.

9.3.1 DEMOGRAPHIC PARAMETERS AT SCREENING

- Age (years)
- Sex (Male, Female)
- Race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Other, Not Reported, Multiple)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Weight at Screening (kg)
- Height at Screening (cm)
- Body Mass Index (BMI) = Weight (kg) / [Height (m)]^2 rounded to 1 decimal.

9.4 MEDICAL HISTORY

Medical history terms will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA®). Medical history will be analyzed using descriptive statistics by MedDRA® SOC and PT for the safety population.

9.5 PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded using the most current version of the World Health Organization (WHO) drug dictionary available. Prior and concomitant medications will be listed by subject and summarized by treatment using anatomic therapeutic chemical (ATC) and preferred name for the safety population.

9.6 STUDY DRUG ADMINISTRATION

Treatment compliance and exposure will be summarized and listed by treatment for all subjects in the safety population.

10 SAFETY

10.1 ADVERSE EVENTS

AEs will be coded using the most current version of MedDRA®. A by-subject AE data listing, including verbatim term, PT, SOC, severity and relationship to study drug will be provided. The number of subjects experiencing treatment-emergent adverse events (TEAEs) and number of

individual TEAEs will be summarized by SOC and PT. TEAEs will also be summarized by severity and by relationship to study drug.

Safety data will be captured for any adverse event after administration of study test dose until the Follow Up visit or Early Termination Visit.

Subjects who report the same preferred term on multiple occasions will be counted once for the preferred term: under the highest severity when summarized by severity and under the closest relationship to study medication when summarized by relationship. If a subject reports multiple preferred terms for a system organ class, the subject will be counted only once for that system organ class.

The number and percentages of subjects who experience TEAEs will be summarized by labeled and actual dose (category) for the following:

- By system organ class and preferred term
- By severity/intensity, system organ class and preferred term
- By relationship to study drug, system organ class and preferred term
- Serious adverse events by system organ class and preferred term
- Serious adverse events by relationship to study drug, system organ class and preferred term
- Adverse events resulting in discontinuation of study medication by system organ class and preferred term
- Adverse events result in study medication dose interruption by system organ class and preferred term

By-subject listings will be provided for any deaths, serious adverse events and adverse events leading to discontinuation of treatment.

10.2 OTHER SAFETY ASSESSMENTS

By-subject listings will be provided for vital signs, ECGs, and laboratory assessments for each visit/timepoint. Summary statistics for observed and change-from-baseline values will be provided in tables.

11 OTHER ASSESSMENTS

By-subject listings will be provided for MMSE and MHIS.

12 CHANGES FROM PROTOCOL

There are no changes to any procedures outlined in the protocol.

13 TABLES, FIGURES, AND LISTINGS

A separate document containing the list of tables, figures, and listings (TFLs) to be included in the post-text Appendix 14 of the CSR will be provided. TFLs may be modified with Sponsor's approval and as deemed necessary without update to the SAP.