TITLE PAGE

Inhibikase Therapeutics

PROTOCOL NUMBER: IkT-148009-101

A Phase I, randomized Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) study to determine the safety, tolerability and pharmacokinetics (PK) of IkT-148009 in Older Adult and Elderly Healthy Volunteers with Extension into Parkinson's Patients

IND NUMBER: 138553

Investigational Product:	IkT-148009
Clinical Phase:	1
Sponsor:	Inhibikase Therapeutics 3350 Riverwood Pkwy SE Suite 1900 Atlanta, GA 30339 Telephone: 678 392 3419 Fax: 770 240 1401
Sponsor Study Physician:	Andrew McGarry, MD Medical Monitor Inhibikase Therapeutics and Clintrex Research Corporation
Date of Original Protocol:	Version 1.1; 09 September 2019
Date of Amendment 1:	Version 1.2; 07 October 2020
Date of Amendment 2:	Version 1.3; 18 March 2021
Date of Amendment 3:	Version 1.4; 01 June 2021
Date of Amendment 4:	Version 1.5; 29 July 2021
Date of Amendment 5:	Version 1.6; 19 October 2021
Date of Amendment 6:	Version 1.7; 24 January 2022

PROTOCOL SIGNATURE PAGE

Protocol Number:	IkT-148009-101
Product:	IkT-148009
IND No.:	138553
Study Phase:	1
Sponsor:	Inhibikase Therapeutics
Date of Original Protocol:	Version 1.1; 09 September 2019
Date of Amendment 1:	Version 1.2; 07 October 2020
Date of Amendment 2:	Version 1.3; 18 March 2021
Date of Amendment 3:	Version 1.4; 01 June 2021
Date of Amendment 4:	Version 1.5; 29 July 2021
Date of Amendment 5:	Version 1.6; 19 October 2021
Date of Amendment 6:	Version 1.7; 24 January 2022

Sponsor Approval

25-Jan-2022

Title: Chief Executive Officer
Inhibikase Therapeutics, Inc.

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for IkT-148009. I have read the IkT-148009-101 protocol and agree to conduct the study as outlined.

The signature of the Principal Investigator constitutes an agreement that this study will be conducted according to all stipulations, clinically and administratively, as stated in the protocol, including all statements as to confidentiality. It is agreed that the conduct and results of this study will be kept confidential and that the case report forms and other pertinent data will become the property of Inhibikase Therapeutics, Inc.

It is agreed that the protocol contains all necessary information required to conduct the study as outlined in the protocol, and that the study will not be initiated without the approval of an appropriate Institutional Review Board or Ethics Review Committee.

It is agreed that all participants in this study will provide written informed consent in accordance with ICH Guidelines for Good Clinical Practice and the requirements specified in the Code of Federal Regulations (21 CFR Parts 50, 56, 312) and/or the Declaration of Helsinki. All participants will also be informed that their medical records will be kept confidential except for review by authorized representatives of Inhibikase Therapeutics, Inc. and its associates, the U.S. Food and Drug Administration or other regulatory agencies.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
CRO Project Manager	Shannon Walaker Project Director Cognitive Research Corporation	200 Central Avenue Suite1230 Saint Petersburg, FL 33701 701-361-1021
Sponsor Physician	Andrew McGarry, MD Clintrex Research Corporation	2 North Tamiami Trail, Suite 308 Sarasota, FL 34236 732-330-8298
Principal Investigator (Part A and B only)	Howard Hassman, DO Hassman Research Institute	401 Route 73 North 30 Lake Center Executive Park, Suite 100 Marlton, NJ 08053 856-397-6666
SAE Reporting to CRO (Part A, B and C)	Dr. Larry Blob safety@cogres.com lblob@cogres.com Cognitive Research Corporation	200 Central Ave Suite 1230 St. Petersburg, FL 33701 410-262-1908
Medical Monitor	Dr. Larry Blob safety@cogres.com lblob@cogres.com Cognitive Research Corporation	200 Central Ave Suite 1230 St. Petersburg, FL 33701 410-262-1908

Table of Contents

1. SYNOPSIS

<table>
<tr><td>IND:</td><td>138553</td></tr>
<tr><td>Title:</td><td>A Phase I, randomized Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) study to determine the safety, tolerability and pharmacokinetics (PK) of IkT-148009 in Older Adult and Elderly Healthy Volunteers with Extension into Parkinson’s Patients</td></tr>
<tr><td>Protocol:</td><td>IkT-148009-101; Version 1.7</td></tr>
<tr><td>Investigational Medicinal Product and Dosage:</td><td>Part A (SAD):
IkT-148009 will be compounded at the clinical pharmacy from components supplied by the sponsor per the detailed instructions provided in the pharmacy instructions and given to the subjects as a gelatin capsule.
The maximum recommended starting dose for this part of the Phase I study is 25 mg. Doses will be prepared for each cohort based on the planned dose escalation scheme shown below:
<table>
<tr><th>Cohort</th><th>Maximum Escalation from Previous Cohort</th><th>IkT-148009 Maximum Dose (mg)</th></tr>
<tr><td>1</td><td>N/A</td><td>25</td></tr>
<tr><td>2</td><td>1/2X</td><td>12.5</td></tr>
<tr><td>3</td><td>3 X</td><td>37.5</td></tr>
<tr><td>4</td><td>2 X</td><td>75</td></tr>
<tr><td>5</td><td>1.33X</td><td>100</td></tr>
<tr><td>6</td><td>1.33 X</td><td>125[1]</td></tr>
<tr><td>7</td><td>1.4 X</td><td>175[1]</td></tr>
<tr><td>8</td><td>1.43 X</td><td>250[1]</td></tr>
<tr><td>9</td><td>1.3 X</td><td>325[1]</td></tr>
<tr><td>10</td><td>1.23 X</td><td>400[1]</td></tr>
<tr><td colspan="3">[1]Escalation to these doses or any fraction thereof subject to the determination by the Safety Review Committee</td></tr>
</table>
Part B (MAD):
Subjects who participate in Part A will not be eligible for enrolling in Part B.
The maximum recommended starting dose and doses for the dose escalation cohorts of the MAD will be selected by the Safety Review Committee (SRC) based on the pharmacokinetic and safety results from the SAD study. The SRC may add additional patients or re-run cohorts as appropriate.</td></tr>
</table>

If SAD clinical exposure and PK data through 2 or more cohorts raise no concerns to the SRC, the MAD may commence at the discretion of the SRC while the remaining SAD cohorts are completed.

Cohort	Maximum Escalation from Previous Cohort	IkT-148009 Maximum Dose (mg)
1	N/A	12.5
2	2 X	25
3	2 X	50[1]
4	2 X	100[1]
[1]Escalation to these doses or fraction thereof subject to the determination of the Safety Review Committee		

Part C: (MAD extension into Parkinson's Disease participants)

The doses for Part C cohorts will be selected by the Safety Review Committee (SRC) based on the pharmacokinetic and safety results from Parts A and B. The SRC may add additional participants or re-run cohorts as appropriate.

If Part B clinical experience and PK data through 2 or more cohorts raise no concerns to the SRC, the MAD extension into PD participants may commence at the discretion of the SRC while the remaining Part A and Part B cohorts are completed.

Cohort	Maximum Escalation from Previous Cohort	IkT-148009 MaximumDose (mg)
1	N/A	50
2	2 X	100[1]
3	2 X	200[1]
[1]Dose escalation to these doses or fraction thereof subject to the determination of the Safety Review Committee		

Comparator and Dosage:	Placebo capsule will be matched to study drug capsule at each dose cohort per the detailed instructions provided in the pharmacy instructions and given to the subjects as a gelatin capsule.
Duration of treatment:	Part A: Subjects participating in Part A of this study (all SAD cohorts) will be randomly assigned to either treatment with IkT-148009 or matching placebo according to a randomization schedule prepared by an independent statistician. Subjects in each of the SAD cohorts will receive a single dose of study drug, either IkT-148009 (6 subjects) or matching placebo (2 subjects) with food. Part B: Subjects participating in Part B of this study (all MAD cohorts) will be randomly assigned to either treatment with IkT-148009 or matching placebo according to a randomization schedule prepared by an independent statistician. Subjects in each of the MAD cohorts will receive a single daily dose of study drug, either IkT-148009 (6 subjects) or matching placebo (2 subjects) with food for a period of up to 7 days. The dose escalation pattern for IkT-148009 in Part A or Part B may be modified by the Safety Review Committee (SRC). Part C: Subjects participating in Part C of this study will be randomly assigned to either treatment with IkT-148009 or matching placebo according to a randomization schedule prepared by an independent statistician. Subjects in each of the Part C cohorts will receive a single daily dose of study drug, either IkT-148009 (6 subjects) or matching placebo (2 subjects) with food for a period of up to 7 days. The dose escalation pattern for IkT-148009 in Part C may be modified by the Safety Review Committee (SRC).

Methodology:	This is a randomized, Phase 1 study in older adult or elderly healthy volunteer subjects with subsequent extension into Parkinson patients to identify the safety, tolerability, maximum tolerated dose (MTD) and the pharmacokinetic (PK) profile of IkT-148009 capsules given as single or multiple capsules. In Part A (SAD) cohorts will consist of eight (8) subjects, six (6) of whom will receive treatment with IkT-148009 and two (2) with matching placebo. Sentinel dosing will be employed on the first day of each cohort, with one subject randomized to receive IkT-148009 and the other placebo. These two subjects in each cohort will be monitored for 48 hours after dosing before deciding to dose the remainder of the cohort. The other six subjects in the first cohort will be dosed approximately 48 hours later. Each cohort will be monitored for at least 48 hours before deciding whether to administer drug to the sentinel pair for the next cohort. Each cohort will be dosed at approximately weekly intervals to allow adequate time for collection and review of safety and PK data. A Safety Review Committee (SRC) will evaluate all available safety, tolerability, and PK data for each cohort. Escalation to a next dose will be undertaken only after these data have been reviewed by the SRC and agreement reached that it is safe to increase the dose. The SRC will not receive any unblinded PK data unless they agree to unblind a subject and/or cohort based on the completed safety review. If Part A clinical exposure and PK data through 2 or more cohorts raise no concerns to the SRC, Part B may commence at the discretion of the SRC while the remaining Part A cohorts are completed.

	In Part B (MAD) cohorts will consist of eight (8) subjects, six (6) of whom will receive treatment with IkT-148009 and two (2) with matching placebo daily for up to seven consecutive days. Subjects in each cohort will be observed for 48 hours after their last dose before deciding to initiate the next (higher dose) cohort. Each cohort will be dosed at approximately weekly intervals in order to allow adequate time for collection and review of safety and PK data. At the discretion of the SRC, MAD cohorts may be added consisting of eligible participants with Parkinson's Disease (Part C). In Part C, eligible PD participants will arrive the evening before initiation of study drug dosing. MDS-UPDRS, Part I and Part II will be assessed. No anti-parkinsonian medication will be given after midnight (V2). The following morning (Day 1/V3), they will be clinically assessed in the practically-defined OFF state using MDS-UPDRS Part III before administration of IkT-148009. MDS-UPDRS Part III will be administered at 1, 2, 3, 4, and 6 hours after dosing on Day 1. ON, ON with and without troublesome dyskinesias, and OFF will be documented every 30 minutes during waking hours on Day 1. If participants do not turn ON by 6 hours, usual PD medications will resume. If at any point before 6 hours participants and the Investigator feel PD medications are necessary, they may be given. PD medications will be given as usual on Days 2 through up to Day 11, with PD medications held after midnight on the day before the last IkT-148009 dose. On the morning of the last dose, participants will again be evaluated in the practically-defined OFF state before resuming usual PD medications that morning. After study activities, they will be discharged from clinic. Additional PD assessments will take place during the Follow-Up and End-Of Study Visits. Participants will not be required to arrive the evening before these visits for assessment in the practically-defined OFF state as done during the prior portion of the study. They will hold a dose of usual PD medication during the visit to allow for motor assessment in ON and OFF states at these visits.

	General Methodological Considerations Part A cohorts will consist of a total of up to 8 visits over a period of up to 28 days prior to dosing and 14 days after dosing. Part B cohorts will consist of up to 15 visits over a period of up to 49 days including up to 7 days of dosing and up to 14 days of follow up. Part C cohorts will consist of up to 15 visits over a period of up to 49 days including up to 7 days of dosing and 14 days of follow up. Subjects in each Part of the study will be admitted to an inpatient unit approximately 24 hours prior to the expected time of dosing. They will be confined to the unit for approximately 5 days in Part A of the study, and approximately 12 days in Part B and Part C. No subject may be discharged from the unit until the investigator is satisfied that they have no continuing and clinically significant adverse events that could be related to study drug. Optional lumbar puncture (LP) for PK measurements will be performed in MAD cohorts on the last dosing day. Participants with bleeding disorders, relevant blood dyscrasias, prior intolerance of LP, anatomical reasons preventing safe or successful collection of fluid (skin infection at site of puncture, relevant spine surgery, spinal deformity, etc.), known intracranial space-occupying lesions with mass effect, posterior fossa masses, or relevant brain malformations (Arnold-Chiari malformation, etc.), exam findings suggestive of increased intracranial pressure, or known allergy/sensitivity to lidocaine or its derivatives will not be eligible for LP. See the Schedule of Events (SOE) (Appendix 1 for the Part A cohorts and Appendix 2 for the Part B cohorts, and Appendix 3 for the Part C cohorts, respectively) for the full list of study assessments and timings.
Primary Objectives:	Parts A and B: 1. To assess the safety and tolerability of IkT-148009 given as a gelatin capsule; 2. To assess the PK profile of single doses and multiple doses (once daily for seven days) of IkT-148009 gelatin capsules in fed state; 3. To investigate plasma and urine concentrations of IkT-148009. Part C: To assess safety, tolerability, PK, biomarkers, and clinical effects inPD participants
Primary Endpoints:	The primary endpoints of this study in Parts A, B and C are:

	1. Safety (vital sign measurements, clinical laboratory data electrocardiogram [ECG] parameters and C-SSRS) 2. Tolerability (adverse event reporting) 3. Pharmacokinetic parameters: • Area under the concentration-time curve from time zero to 96 hours ($AUC_{0-\infty}$) • Maximum plasma concentration (C_{max}) • Area under the concentration-time curve from time zero to last time point (AUC_{0-last}) • Time to reach maximum concentration (T_{max}) • The distributional half-life and terminal half-life ($t_{1/2}$) • Maximum concentration at steady-state ($C_{max,ss}$) and area under the concentration-time curve at steady-state (AUC_{ss})
Exploratory Endpoints:	Part B: IkT-148009 drug concentration in the CSF at steady state if available. Part C: 1. Change from Baseline to Final visit in the MDS-UPDRS Motor Subscale (Part III) Score 2. Change from Baseline to Final Visit in the MDS-UPDRS Non-motor aspects of experiences of daily living (Part I) Score and in the MDS-UPDRS Motor aspects of experiences of daily living (Part II) Score. 3. Change in Clinical Global Impression of Improvement (CGI-I) Score and the Patient Global Impression of Change (PGI-C) Score 4. Change in Non-Motor Symptom Score (NMSS) 5. Change from Baseline to Final Visit in Parkinson's Disease Questionnaire 39 (PDQ-39). 6. Change from Baseline to Final Visit in the Patient Global Impression of Severity Score (PGI-S) 7. Change from Baseline to Final Visit in Complete Bowel Movement Score (CSBM).

	8. Change in Patient Assessment of Upper GI Disorders Severity Index (PAGI-SYM) 9. IkT-148009 drug concentration in the CSF at steady state if available 10. Biomarker analysis from CNS-derived exosomes if available.
Sample Size:	Part A: Up to 80 older adult and elderly healthy volunteers age 55-70 are planned to be recruited into the study, depending on the number of cohorts studied, anticipated to be 8 subjects per cohort and 8-10 cohorts. Part B: Up to 32 older adult and elderly healthy volunteers age 55-70, estimated to be 2-4 cohorts. Part C: Up to 24 participants with Parkinson's disease can be added at the discretion of the SRC based on the results of safety and tolerability studies of Parts A and B. Part C cohorts of 8 patients each may be added after a minimum of 2 cohorts in Part B have been completed. Up to three cohorts of Parkinson's patients may be added to the study. Subjects will be replaced only if they withdraw/are withdrawn prior to study drug dosing. Additional cohorts may be considered to accommodate dose repetition, slower dose escalation or escalation beyond currently planned doses.
Number of Sites:	Up to 5 clinical research units [CRU] specializing in Phase 1 studies.
Study Period:	The projected completion of this study is approximately 14 months from first patient dosed. Participation for subjects enrolled in Part A is projected to be up to 3 months and in Part B and Part C is up to 4 months.
Inclusion Criteria:	Parts A and B 1. Subject must have all questions about the study answered and must have signed the informed consent document before any study-specific procedures are performed. 2. Men or women aged 55 to 70 years (both inclusive) of any race. 3. Subjects must be otherwise healthy and ambulatory, with no history or evidence of clinically relevant medical disorders as determined by the Investigator in consultation with the Sponsor.

	4. Mini Mental State Examination (MMSE) ≥ 28 at Screening (V1) and Baseline (V2). 5. Physical examination, clinical laboratory values, vital signs (as defined in the CRU standard operating procedure [SOP]), and the electrocardiogram (ECGs) are clinically acceptable to the Investigator. Body weight ≥ 45 kg at screening and baseline visits. Body Mass Index (BMI) ≥ 18 and ≤33 kg/m^2 at screening. 6. Female subjects must be postmenopausal (12 months without menses and confirmed by follicle stimulating hormone [FSH] > 40 mIU/mL) or surgically sterile (hysterectomy or bilateral oophorectomy) or sterile for other medical reason (i.e., able to document premature low ovarian reserve, birth defect, other). Women who are several years postmenopausal may be considered for enrollment even with [FSH] below this threshold. 7. Male subjects must agree to practice an acceptable method of highly effective birth control from the Screening visit, while on study and for 7 days after receiving the last dose of study drug. Highly effective methods of birth control include sexual abstinence; vasectomy; or a condom with spermicide (men) in combination with their partner's highly effective method. 8. Males must be willing to abstain from sperm donation from the screening visit, while on study and through 30 days after receiving the last dose of study drug. Part C: Participants must be eligible as in Part A and B, with the following differences/additions: 9. MMSE ≥ 26 at screening (V1) and Baseline (V2) 10. Diagnosis of Parkinson`s Disease (consistent with the UK PD Society Brain Bank Criteria for the Diagnosis of PD), with bradykinesia and a clear motor response to levodopa. 11. Hoehn & Yahr staging of 3 or less in the ON state. 12. Good clinical response to levodopa as judged by participant and investigator. 13. Stable doses of all PD medications for at least 4 weeks prior to Screening.

	14. Approved by an Enrollment Authorization Committee (EAC).
Key Exclusion Criteria:	Parts A and B: 1. Clinically significant abnormal values for hematology, clinical chemistry or urinalysis at the screening and admission visits. Abnormalities considered to be non-clinically significant by the Investigator are acceptable. 2. Clinically significant abnormal findings on physical examination or 12-lead electrocardiogram (ECG) at the screening or admission visits. NOTE: QTcF interval of $\geq$ 450 msec in males or $\geq$ 470 msec in females will be the basis for exclusion from the study. Safety ECG may be repeated for confirmatory purposes if initial values obtained exceed the limits specified. 3. Significant history (within six months prior to receiving the study drug) and/or presence of clinically significant medical, surgical or psychiatric disorder. Subjects with co-morbid conditions that are stable and controlled may remain eligible (stable defined as no change in the dose or frequency of medications over the prior three months). 4. For optional lumbar puncture: participants with bleeding disorders, relevant lab abnormalities (Screening INR greater than 1.4, platelets less than 50), relevant blood dyscrasias, prior intolerance of LP, anatomical reasons preventing safe or successful collection of fluid (skin infection at site of puncture, relevant spine surgery, spinal deformity, etc.), known intracranialspace-occupying lesions with mass effect, posterior fossa masses, or relevant brain malformations (Arnold-Chiari malformation, etc.), exam findings suggestive of increased intracranial pressure, or known allergy/sensitivity to lidocaine or its derivatives will not be eligible. 5. eGFR < 60 mL/min 6. Creatinine, Amylase and/or Lipase > ULN 7. Any malignancy in the 5 years prior to screening excluding basal cell carcinoma or squamous cell carcinoma of the skin or cervical carcinoma in situ that have been successfully treated. 8. Any subject with a history, presence and/or current evidence of serologic positive result for hepatitis B surface antigen, hepatitis C antibodies, or HIV antibodies 1 or 2. Subjects considered to be cured for hepatitis C will be eligible.

	9. Recent history (within previous six months prior to screening) of alcohol or drug abuse (as judged by the investigator) or has consumed > 2 alcohol drinks/day during the last three months prior to screening (one glass is approximately equivalent to: beer [284 mL], wine [125 mL/4 ounces], or distilled spirits [25 mL/1 ounce]). Subjects that consume three glasses of alcoholic beverages per day but less than 14 glasses per week may be enrolled at the discretion of the Investigator. Positive screens for alcohol or controlled substances at the screening or admission visits will disqualify a subject from study participation. 10. Any subject with known hypersensitivity to IkT-148009. 11. Donation of blood or acute loss of blood within 60 days prior to screening visit. 12. Any subject who has received treatment with an investigational drug during the 30 days prior to screening. 13. Investigative site personnel or their immediate families (spouse, parent, child or sibling whether biological or legally adopted). 14. Any subject unwilling or unable to comply with study procedures. Part C: 15. For optional lumbar puncture: participants with bleeding disorders, relevant lab abnormalities (Screening INR greater than 1.4, platelets less than 50), prior intolerance of LP, anatomical reasons preventing safe or successful collection of fluid (skin infection at site of puncture, relevant spine surgery, spinal deformity, etc.), known intracranial space-occupying lesions with mass effect, posterior fossa masses, or relevant brain malformations (Arnold-Chiari malformation, etc.), exam findings suggestive of increased intracranial pressure, or known allergy/sensitivity to lidocaine or its derivatives will not be eligible. 16. Diagnosis of secondary or atypical parkinsonism 17. Prior neurosurgery for PD or treatment with DUODOPA or infused apomorphine

	18. Concurrent use of neuroleptic medications or other dopamine antagonists. 19. Severe or disabling fluctuations or dyskinesias that would, in the opinion of the investigator, interfere with completion of the study 20. Clinically significant hallucinations or delusions that, in the opinion of the investigator or EAC, may preclude completion of the study 21. Clinically significant orthostatic hypotension that, in the opinion of the investigator, may preclude completion of the study 22. Currently active major depression as determined by BDI-II score of >19 23. Previous surgical procedure for PD.
Dose Adjustment Criteria:	An SRC will be established, comprised of the Principal Investigator (PI), the Sponsor Study Physician and the Contract Research Organization (CRO) Drug Safety Physician. Designees may be utilized consistent with the SRC Charter. Optional attendees may participate as required. The roles and responsibilities of the SRC will be described in a SRC Charter which will be agreed and signed prior to the first dose of study drug being administered. The role of the SRC is to assess the safety, tolerability and pharmacokinetic information collected for each dose level and determine that the next cohort should: • advance to the next planned dose level; • advance to a dose lower than the next planned dose level; • repeat the previous or a lower dose level; • Discontinue the study In addition, the SRC may stop the study for safety reasons at any time. The committee may overrule these stopping criteria by being more conservative, i.e., next dose lower than planned, but may not rule that the next dose should be higher than planned. If Part A clinical exposure and PK data through 2 or more cohorts raise no concerns to the SRC, Part B may commence at the discretion of the SRC while the remaining Part A cohorts are completed. In this scenario, Part B may be paused or adapted based on subsequent Part A exposure or safety data.

Dose Escalation and Stopping Rules:	1. Serious Adverse Event: If any subject in a cohort experiences a serious adverse event (SAE) that is potentially life-threatening and is possibly study drug related, dose escalation will be halted. If any subject in a cohort has a serious adverse event (SAE) that is not potentially life-threatening but is possibly study drug related, the SRC may stop the study or may permit ongoing dosing at the prescribed or lower doses of IkT-148009 than that at which the event occurred, depending on the nature of the event. 2. Severe Adverse Event: If two (2) or more subjects in a cohort on active medication have a severe adverse event that the safety committee determines is related to IkT-148009, the safety committee may stop the study or may permit ongoing dosing at the same or lower doses of IkT-148009, depending on the nature of the event and the dose(s) at which the events occurred. 3. Clinically significant events observed in at least three (3) subjects exposed to IkT-148009 within a cohort: The SRC may not allow dose-escalation if at least two subjects on active medication report the same finding. However, if each subject reported a different finding, the SRC could allow dose escalation at lower doses than planned. In all circumstances, the SRC may allow dose-repetition or dose reduction: • Cytopenias (anemia, neutropenia and thrombocytopenia); • Fluid retention (pleural effusion, pericardial effusion, pulmonary edema and ascites) and edema (unexpected rapid weight gain); • Congestive heart failure, cardiogenic shock and left ventricular dysfunction; • Gastrointestinal irritation leading to nausea, vomiting, diarrhea, dyspepsia, abdominal pain, GI hemorrhage; • A sustained increase (>3X ULN) in alanine aminotransferase (ALT) or aspartate aminotransferase (AST), which must be confirmed elevated within 48 hours (Guideline of Liver Safety Assessment Best Practices Workshop 2014 [Avigan et al., 2014]); • Total bilirubin increase (>2X ULN) confirmed on repeat testing within 48 hours; • A sustained increase in alkaline phosphatase (>2X ULN) in association with an increase in ALT and AST confirmed on repeat testing within 48 hours; • QTc prolongation defined as QTcF increasing ≥60 msec and persisting for at least 10 minutes or QTcF >500 msec and persisting for at least 30 minutes;

	• A sustained increase in serum creatinine (> 1.3X ULN) confirmed on repeat testing within 48 hours. The SRC will carefully evaluate each safety and tolerability event and use clinical judgement to determine whether dosing should stop for a specific subject or for all subsequent study subjects.
Criteria for Evaluation:	**Safety and Tolerability:** Safety and tolerability of the study drug will be assessed by clinical laboratory assessments, physical examinations, vital sign measurements, Safety ECGs, Cardiodynamic ECGs, C-SSRS, concomitant medication usage and adverse event reporting. **Pharmacokinetics:** Plasma will be collected to assay for concentration of IkT-148009. The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC), C_{max}, T_{max}, C_{trough}, distributional half-life and terminal half-life (t1/2).
Statistical Considerations	The Safety Population is defined as all subjects who are administered study drug. The Pharmacokinetic (PK) Population is defined as all subjects who are administered IkT-148009 or placebo and have at least one bioanalysis result for the plasma concentration of the study drug. No formal sample size calculations have been undertaken for this safety, tolerability and PK study. The number of subjects in each cohort and at each dose level is thought to be sufficient to assess preliminary safety, tolerability and the PK profile of IkT-148009. No efficacy parameters are being collected or analyzed for this Phase I study. For categorical data, frequency counts and percentages will be presented. For continuous data, summary statistics will include the arithmetic mean, standard deviation (SD), median, minimum, maximum, and number; for log-normal data (e.g., the PK parameters of AUC, C_{max} and C_{trough}), the geometric mean and geometric coefficient of variation will also be presented. The In-transformed PK parameters will be compared using a generalized analysis of variance (ANOVA) model (Weerahandi 1994, Ogenstad 1998). For all safety analyses, AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) with the version used specified in the clinical study report. The overall incidence of adverse events will be displayed by MedDRA™ System Organ Class (SOC), preferred term, and dosing condition. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Data from vital signs,

	clinical laboratory measures and Safety ECG will be summarized by dosing condition. In addition, change from baseline values will be calculated at each time point and will be summarized using the same summary statistics. Out-of-range safety endpoints may be categorized as low or high, where applicable. PK parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentration (T_{max}) will be summarized using n, mean, standard deviation, median, minimum, and maximum. All other PK parameters will be summarized using n, geometric mean, coefficient of variation, median, minimum, and maximum. Dose proportionality will be analyzed using a generalized ANOVA model using the logarithm of PK parameter (AUC, C_{max} and C_{trough}) as the dependent variable and the logarithm of the dose as the independent variable (Weerahandi 1994, Ogenstad 1998). Point estimates and the corresponding generalized CIs will be estimated for both AUC, C_{max} and C_{trough}. For AUC, C_{max} and C_{trough}, the treatment ratio 'test/reference' will be calculated by taking the anti-logarithm of the difference between treatment means. Further details of the above analyses will be provided in the statistical analysis plan. Data from subjects who experience emesis will be deleted from statistical analyses if vomiting occurs at or before two times the median t_{max}. Statistical software for the analysis will be SAS version 9.4 (SAS Institute) or later and XPro (X-Techniques, Inc.).

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AD	Alzheimer's Disease
ADM	Absorption, Distribution and Metabolism
AIMP2	aminoacyl tRNA synthetase complex-interacting multifunctional
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANOVA	Analysis of variance
ATP	Adenosine tri phosphate
AST	Aspartate aminotransferase
AUC	Area under the time-concentration curve
BLQ	Below the limit of quantitation of assay
BMI	Body mass index
c-Abl	cellular Abelson tyrosine kinase
CBC	Complete blood count
CFR	Code of Federal Regulations
CK	Creatinine kinase
C_{max}	Maximum plasma concentration
CNS	Central Nervous System
CRO	Clinical Research Organization
CRU	Clinical Research Unit
CSF	Cerebro-spinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
C_{trough}	Concentration at trough
DA	Dopaminergic
ECG	Electrocardiogram

Abbreviation or Specialist Term	**Explanation**
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EAC	Enrollment Authorization Committee
ENS	Enteric Nervous System
FBP1	Far upstream element-binding protein 1
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good clinical practice
γ-GT or GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Good laboratory practice
GMP	Good manufacturing practice
HED	Human Equivalent Dose
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
INR	International normalized ratio of prothrombin time
IRB	Institutional Review Board
LBs	Lewy bodies
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MTD	Maximum tolerated dose
NOAEL	No observed adverse event limit
PARIS	PARkin Interacting Substrate

Abbreviation or Specialist Term	**Explanation**
PD	Parkinson's disease
PI	Principal Investigator
PK	Pharmacokinetics
PT	Prothrombin time
PT-INR	Prothrombin time – international normalized ratio
pY143-parkin	phosphorylates parkin on Tyr^{143}
QTcF	QT interval
RBC	Red blood cell count
SD	Standard deviation
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SNc	Substantia nigra pars compacta
SOC	System organ class
SOE	Schedule of events
SOP	Standard operating procedure
SRC	Safety Review Committee
T_{max}	Time at maximum plasma concentration
TEAE	Treatment emergent adverse event
$T_{1/2}$	Half-life
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
USP	United States Pharmacopeia
WBC	White blood cell count

3. INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder (Savitt et al, 2006), affecting approximately 1,000,000 persons in the United States, with 60,000 new cases and 38,000 deaths annually (Savitt et al, 2006; Dauer et al, 2003). PD is an inexorably progressive disorder that is characterized by bradykinesia, rigidity, rest tremor, and gait disturbances with postural instability (Savitt et al, 2006; Dauer et al, 2003). Pathologically, PD is characterized by degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc), coupled with the accumulation of protein aggregates in cell bodies and terminals known as Lewy bodies (LBs) and Lewy neurites, respectively, collectively known as Lewy pathology (Goedert, 2001; Goedert et al, 2013; Lee and Trojanowski, 2006). It is now appreciated that clinical and pathologic features are much more extensive than historically recognized. PD pathology affects serotonin, cholinergic, and norepinephrine neurons and nerve cells in the olfactory system, cerebral hemisphere, brain stem, spinal cord, and peripheral autonomic nervous system, in addition to SNc dopaminergic neurons (Jellinger, 2012). This non-dopaminergic pathology is associated with a variety of non-dopaminergic clinical features, none of which are adequately controlled with dopamine-replacement therapy (Schapira et al, 2014). These include falling, freezing, dysphagia, neuropsychiatric disorders, autonomic dysfunctions, sensory problems, and cognitive impairment with dementia (Schapira et al, 2014). Indeed, non-dopaminergic features, such as falling and dementia, represent the major source of disability for PD patients. Numerous symptomatic therapies based on a dopamine replacement strategy have been developed over the past half century that provide meaningful benefits, particularly for the classic motor features of the disease (Schapira et al, 2014).

Over the past 20 years, a number of studies have suggested that misfolding of alpha-synuclein plays a key role in the etiopathogenesis of PD and suggest that therapies directed at preventing or clearing pathologic alpha-synuclein might be neuroprotective (Winner et al, 2011; Olanow and Brundin, 2013; Polymeropoulos et al, 1997; Spillantini et al, 1997; Masliah et al, 2000; Kirik and Bjorklund, 2003; Jellinger, 2012). However, our understanding of the precise toxic form of alpha-synuclein has been lacking, confounding our ability to properly target toxic alpha-synuclein for a therapeutic purpose. Recent work by multiple laboratories and by ourselves has provided convincing evidence that a common pathway governs initiation and progression of the disease within the Central Nervous System (CNS) and in the periphery. At the core of this pathway is the cellular Abelson tyrosine kinase (c-Abl) which we believe acts as a checkpoint, playing a key role in the formation and accumulation of toxic alpha-synuclein to progressively cause disease. Toxic alpha-synuclein is the product of this biochemical pathway, arguing strongly that inhibition of c-Abl will be neuroprotective and such inhibitors are likely to blunt the rate or extent of alpha-synuclein toxicity in PD patients.

Alpha--synuclein in PD

A large body of evidence indicates that the accumulation and aggregation of alpha-synuclein into higher ordered oligomeric, protofibrillar and fibrillary pathologic species (collectively pathologic alpha-synuclein) is intimately linked to the neurodegenerative disease process of PD (Winner et

al, 2011; Olanow and Brundin, 2013; Polymeropoulos et al, 1997; Spillantini et al, 1997; Masliah et al, 2000; Kirik and Bjorklund, 2003; Jellinger, 2012). Point mutations (A30P, E46K, H50Q, G51D, A53E and A53T) are associated with rare, familial cases of PD and promote misfolding and hyperaggregation of alpha-synuclein (Polymeropoulos et al, 1997; Martin et al, 2011). Similarly, increased expression of alpha-synuclein associated with duplication or triplication of *SCNA*, the gene encoding alpha-synuclein, also cause a rare, heritable form of the disease with concomitant alpha-synuclein aggregation. Alpha-synuclein is also now recognized to be a major component of Lewy pathology (Spillantini et al, 1997), suggesting that alpha-synuclein plays a key role in sporadic PD as well in heritable forms.

Role of c-Abl in alpha-synuclein toxicity and neurodegeneration

c-Abl is a non-receptor tyrosine kinase that is an essential sensor of cellular stress, such as oxidation or nitrosation. C-Abl was first identified as the mammalian homolog of the oncogenic gene product of the Abelson murine leukemia virus. Since its discovery, the c-Abl family of tyrosine kinases (c- Abl, Abl or Abl1 and the Abl-related gene (Arg, Abl2)), has been shown to be highly conserved in amino-acid sequence across all species. C-Abl regulates many cellular processes, including the actin cytoskeleton, the cell cycle, and the apoptotic/cell cycle arrest response to stress.

c-Abl is also crucial for proper neuronal development, but is relatively quiescent in healthy, adult neurons, and there are few known functions of c-Abl in fully differentiated neurons. Inappropriate activation of c-Abl does occur in adult brain, usually in the context of human neurodegenerative disease (Imam et al, 2011; Ko et al, 2010; Jing et al, 2009; Tremblay et al, 2010), raising the possibility that inappropriate activation of c-Abl could contribute to the neurodegenerative disease process in PD. Indeed, activated c-Abl is robustly increased in brain samples derived from PD patients, as well as in animal models of alpha-synucleinopathies and in the acute neurotoxicity model using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Dawson et al, 2010).

There are several ways activated c-Abl might contribute to neurodegenerative disease. In neuroinflammation animal models, such as those used to mimic Alzheimer's Disease (AD), treating animals with c-Abl kinase inhibitors facilitates clearance of β-amyloid peptides, dissolves plaque, reduces astrocyte and dendritic cell numbers, modulates cytokine and chemokine profiles, and improves cognitive performance (Cancino et al, 2008; Hebron et al, 2013; Lonskaya et al, 2013). In these models, c-Abl inhibition promotes removal of deleterious proteins and suppresses neuro-inflammation. Since c-Abl inhibition results in removal of deleterious proteins in AD models, this raises the possibility that c-Abl is interfering with the clearance of misfolded proteins either by suppressing the ubiquitination/proteasome and/or otherwise disrupting the autophagy/lysosomal systems, both cellular mechanisms that promote removal of misfolded and aggregated proteins.

Using PD models, the effect of c-Abl activation on the clearance of misfolded or aggregated proteins via the ubiquitination/proteasome system was revealed, suggesting a direct role for c-Abl activation in the disease process (Dawson et al, 2017). Parkin is an E3-ubiquitin ligase that facilitates clearance of misfolded proteins through the proteasome and promotes mitophagy;

mutations in the Parkin gene lead to an autosomal recessive, young-onset form of PD. In response to oxidative stress, c-Abl is activated and directly phosphorylates parkin on Tyr^{143} (pY143-parkin), resulting in the loss of its E3-ligase activity (Imam et al, 2011; Ko et al, 2010), thereby shutting down the cell survival pathways dependent on parkin activity (Ko et al, 2010). Treatment with the c-Abl inhibitor imatinib decreases parkin phosphorylation and promotes neuroprotection in PD animal models (Gaki and Papavassiliou, 2014; Brahmachari et al, 2017). Studies suggest that suppression of parkin inactivation by c-Abl inhibition should reduce the toxicity of pathologic alpha-synuclein. That alpha-synuclein is a substrate for c-Abl is also supported by structural studies of recombinant alpha-synuclein and from the analysis of rat brain tissues showing that c-Abl was upregulated when alpha-synuclein was artificially overexpressed.

In vivo studies have also explored whether the formation of pY39-alpha-syn is c-Abl dependent. In transgenic mice expressing the familial PD mutant, A53T-alpha-synuclein (hA53T-7-syn), there is a progressive build-up in the brain of activated c-Abl and pY39-alpha-syn over 6 months (Brahmachari et al, 2016). In these studies, pY39-alpha-syn is found in a highly insoluble fraction, indicating that alpha-synuclein is in a hyperaggregated or in a high molecular weight/oligomeric state. Prompted by this observation, preserved tissue from post-mortem brains of PD patients were examined and found to contain increased levels of pY39-alpha-synuclein (Brahmachari et al, 2016).

In view of the above, a very different picture of how neurodegeneration might develop in the PD brain emerges. Accumulation of alpha-synuclein within cells could be generated by misfolding of intracellular alpha-synuclein due to genetic factors, impaired clearance, toxic cytokines, or by internalization of extracellular pathologic alpha-synuclein that may have spread from other previously affected cells. While genetic mutations and/or environmental stresses can lead to the accumulation of alpha-synuclein, *this is not, in and of itself the sole driving force of neurodegeneration*. Rather, accumulating alpha-synuclein serves as a substrate that is acted on by c-Abl intracellularly to form pY39-alpha-syn, and it is pY39-alpha-syn within neurons that contributes to and accelerates the progressive disease process. Emerging evidence demonstrates that there is a sequential process wherein misfolded or accumulating species of alpha-synuclein are recognized by an intracellular 'sensor' that leads to activation of c-Abl. Activated c-Abl, shuts down a cell survival pathway through parkin phosphorylation and inactivation, and also phosphorylates alpha-synuclein at Tyr^{39} to create a more toxic form of pathologic alpha-synuclein. Figure 1 summarizes this sequence of events. This includes accumulation of toxic substrates such as PARIS (PARkin Interacting Substrate), aminoacyl tRNA synthetase complex-interacting multifunctional protein 2 (AIMP2) and far upstream element-binding protein 1 (FBP1). PARIS and AIMP2, for example, may be important pathogenic parkin substrates, since they accumulate in familial PD with parkin mutations, sporadic PD, adult conditional parkin knockout mice and in MPTP-intoxicated mice. Under pathogenic conditions, where parkin is inactivated, PARIS levels increase, which subsequently leads to mitochondrial dysfunction through down-regulation of PGC-1a and loss of dopamine neurons in a PARIS-dependent manner. Overexpression of AIMP2, on the other hand, leads to an age-dependent, selective neurodegeneration of dopamine neurons through activation of poly (ADP-ribose) polymerase 1 (PARP1), driving PARP1-mediated parthanatos. This suggests that AIMP2 is an important contributor to the loss of DA neurons following parkin inactivation.

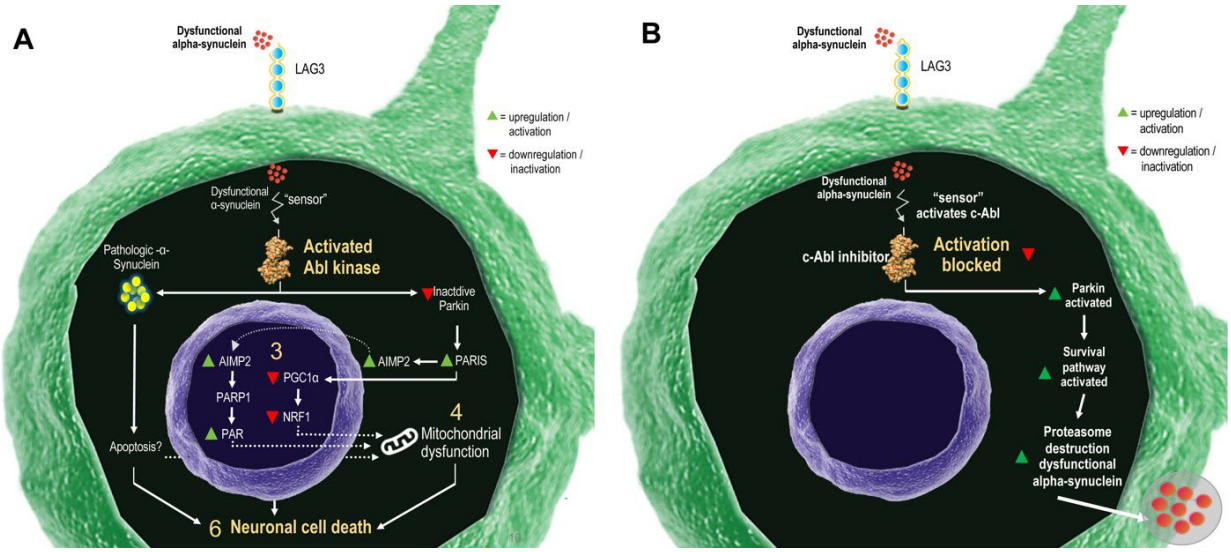


Fig. 1: The pathways driving neurodegeneration and the role of c-Abl as a checkpoint in neurodegenerative disease. A. The process of neurodegeneration. Dysfunctional α-synuclein can arise from a variety of cellular stressors, leading to the misfolding and/or aggregation of alpha-synuclein. Dysfunctional alpha-synuclein gets into a neuron through a variety of potential mechanisms, which includes the immunologic receptor Lag3. Once internalized, dysfunctional alpha-synuclein is 'sensed' and c-Abl activated, driving the formation of pathologic α-synuclein by chemical modification and inactivating parkin to suppress the ubiquitin/proteasome survival pathway. Formation of pathologic alpha-synuclein drives cell death, possibly through mitochondrial dysfunction and/or apoptosis. Suppression of the survival pathway induces parthanatos through PARP (*36*). **B.** The consequence of a c-Abl inhibitor on the disease process. In the presence of a c-Abl inhibitor, the presence of dysfunctional synuclein fails to activate c-Abl, but stimulates the survival pathway through parkin and the ubiquitin/proteasome pathway, resulting in the removal of dysfunctional alpha-synuclein in a vesicle following proteasome degradation.

IkT-148009: A novel, c-Abl inhibitor that is neuroprotective in Central and Enteric Nervous Systems

IkT-148009 is a novel chemical derivative of the anti-cancer agent imatinib (marketed as Gleevec®). In contrast to Gleevec®, IkT-148009 is 18-fold more potent inhibitor of the wild type c-Abl enzyme with an IC_{50} for c-Abl of 47 nM (Table 3).

Table 3: Small molecule inhibitors of the Abelson Tyrosine Kinase

Drug	IC_{50} c-Abl1	IC_{50} c-Abl2/Arg
IkT-148009	33 nM	14 nM
Imatinib	828 nM	1000 nM

Oral gavage of IkT-148009 in C57Bl/6 mice demonstrated that IkT-148009 readily penetrates the brain, accumulates to > 1 μM total brain concentration over 7 days and completely blocks c-Abl activation in the acute neurotoxicity model using MPTP (Fig. 2).

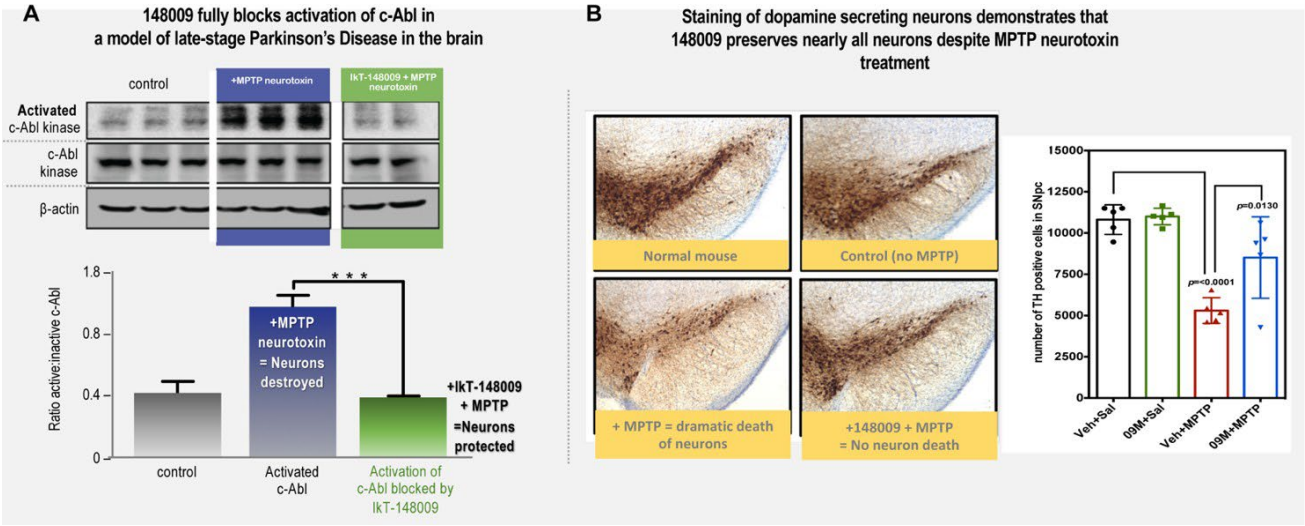


Fig. 2: IkT-148009 blocks activation of c-Abl by the acute neurotoxin MPTP. A) Orally delivered IkT-148009 at 50 or 100 mg/kg/day during a 14 day experiment blocks activation of c-Abl by MPTP in mouse brain. On the top is a Western Blot that enables quantification of the amount of inactive and activated c-Abl in mouse brain. On the bottom, the quantitation of the Western Blots for activated c-Abl demonstrates that IkT-148009 maintains the level of activated c-Abl at baseline levels. The asterisks refer to the statistical analysis of the blots across three animals, with three asterisks representing a $P < 0.001$ in a Student's T-test. **B)** Four images of mouse brain from the substania nigra pars compacta, the brain region where dopamine secreting neurons are located. These neurons are the ones that degenerate in the Parkinson's Disease patient brain. The images represent brain slices and the dopamine secreting neurons are stained brown. Going clockwise from the top left is 1) a normal mouse brain; 2) a normal mouse brain that has had daily dosing of IkT-148009 for 14 days at 100 mg/kg/day; 3) consequences in a mouse brain given MPTP in the presence of IkT-148009 show nearly normal density of dopamine secreting neurons; we interpret this as indicative of nearly complete protection from neurodegeneration in this context. This image is nearly the same as the normal mouse in the upper left quadrant; and 4) the impact on neural density following administration of the acute neurotoxin MPTP to a mouse in the absence of IkT-148009. The neural density in the absence of IkT-148009 is significantly reduced following 4 intraperitoneal injections of MPTP at 20 mg/kg in these mice, representing the substantial degradation of dopamine secreting neurons in the test animal. The histogram to the right quantifies these images, illustrating that statistically significant protection against neurodegeneration in this model is achieved with IkT-148009. In this histogram, 'Veh' refers to the vehicle in which IkT-148009 was dissolved, '09M' refers to IkT-148009 as a mesylate salt, and 'Sal' refers to saline solution that replaces the drug solution in the indicated columns.

Four progressive disease models are currently being analyzed to demonstrate the breadth of potential efficacy of IkT-148009 against familial and sporadic PD. Figure 3 demonstrates that treatment of A53T-alpha-synuclein transgenics with IkT-148009 at 50 mg/kg/day is sufficient to completely protect these mice from neurodegeneration in the gut. The drug-treated mice display a WGTT essentially identical to wildtype alpha-synuclein expressing mice. In a separate group of mice, treatment at 150 mg/kg/day showed similar results. This experiment will continue out to 6 months, at which time the CNS defects will be quantified with rotarod and open field tests relative to wildtype alpha-synuclein controls. The outcome of this experiment provides convincing proof that pharmaceutical inhibition of c-Abl in the CNS and Enteric Nervous System (ENS) is likely to be highly neuroprotective and that the pathway described in Fig. 1 likely governs the disease process. c-Abl inhibition, therefore, is likely to be a highly effective, disease-modifying therapy

for alpha-synuclein-related diseases, including PD. CNS models of pathologic alpha-synuclein-related disease that mimics sporadic PD are currently being evaluated.

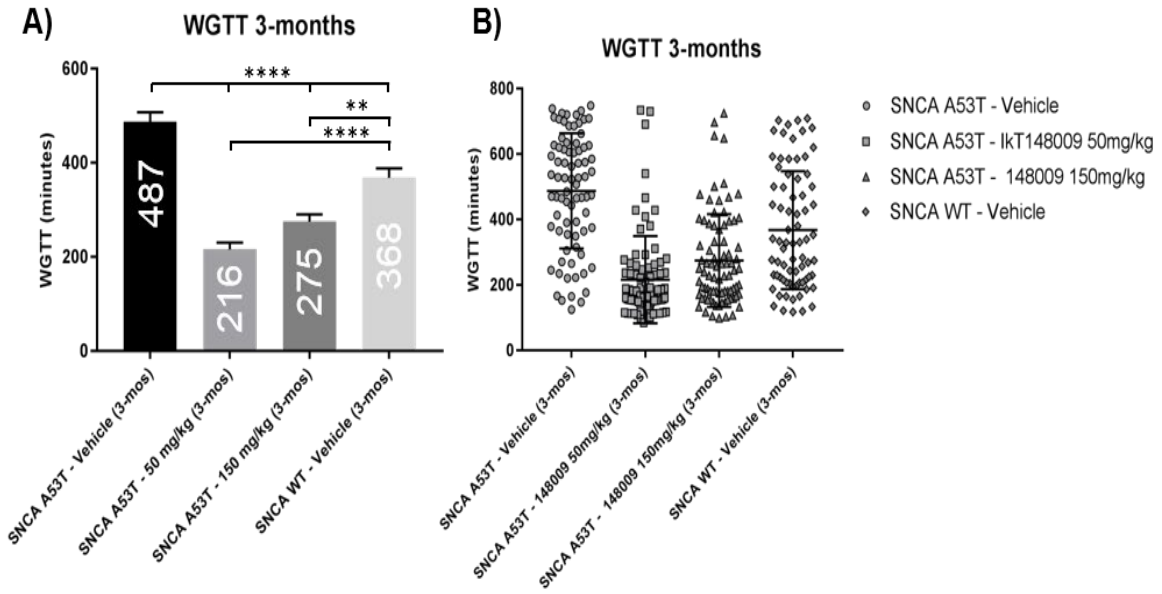


Figure 3: IkT-148009 reduces WGTT deficit in SNCA A53T animals at 3-months of age. A) Average WGTT at 3 months of age for vehicle-treated SNCA WT animals (n=23) along with vehicle -treated (n=25) IkT148009 50mg/kg (n=24) and 150mg/kg (n=24) treated SNCA A53T animals (error bars= SEM, **** p<.0001, **p<.0021) . B) Scatter plot of individual WGTT measures for M1-M4 of the 3-month WGTT assay. Bars and error bars are mean and standard deviation.

3.1. Unmet Medical Need

Despite the success of anti-parkinsonian therapies, no satisfactory intervention has been discovered for the non-dopamine features of the illness, and no therapy is capable of slowing or stopping disease progression. These remain major unmet medical needs.

3.2. Scientific Rationale

IkT-148009 is a novel chemical derivative of the anti-cancer agent imatinib (marketed as Gleevec®) wherein a methyl-isooxazole ring has been attached to the 4-pyridyl ring of imatinib on the end of the molecule that engages the ATP binding site of Abelson tyrosine kinases. IkT- 148009 is a highly potent inhibitor of wildtype Abelson tyrosine kinase, c-Abl (a.k.a. c-Abl1, Abl1) and c-Abl2 (a.k.a. Arg) and is at least **18-fold more potent against the wildtype enzyme relative to imatinib with similar pharmacokinetic, metabolic and toxicological characteristics**. IkT-148009 readily penetrates the brain, accumulates to > 1 μM total brain concentration over 7 days and completely blocks c-Abl activation in the acute neurotoxicity model.

Over the past 20 years, a number of studies have suggested that misfolding of α-synuclein plays a key role in the etiopathogenesis of PD, and suggest that therapies directed at preventing or clearing pathologic alpha-synuclein might be neuroprotective (Dauer and Przedborski, 2003; Goedert, 2001; Goedert et al, 2013; Lee and Trojanowski, 2006; Jellinger, 2012; Schapira et al, 2014;

Winner et al, 2011). c-Abl is a non-receptor tyrosine kinase that is an essential sensor of cellular stress, such as oxidation or nitrosation. c-Abl regulates many cellular processes, including the actin cytoskeleton, the cell cycle, and the apoptotic/cell cycle arrest response to stress. c-Abl is also crucial for proper neuronal development, but is relatively quiescent in healthy, adult neurons,and there are few known functions of c-Abl in fully differentiated neurons. The role of c-Abl in PD might extend well beyond parkin phosphorylation. In vitro and in vivo biochemical analyses have established a direct link between c-Abl activation and the formation of toxic forms of alpha-synuclein and suggests that c-Abl phosphorylation of alpha-synuclein may drive alpha-synuclein misfolding and aggregation. c-Abl inhibition is likely to be a highly effective, disease-modifying therapy for alpha-synuclein related diseases, including PD.

IkT-148009 is a well-characterized drug with extensive pre-clinical data whose Absorption, Distribution and Metabolism (ADM) closely parallels the active ingredient in the anti-cancer drug Gleevec® and is intended to be used as a therapy in PD. The design of IkT-148009 was intended to mimic in most respects the ADME of imatinib while improving the potency of imatinib by approximately 18-fold (Table 4).

Table 4: Small molecule inhibitors of the Abelson Tyrosine Kinase

Drug	**IC_{50} c-Abl1**	**IC_{50} c-Abl2/Arg**
IkT-148009	33 nM	14 nM
Imatinib	828 nM	1000 nM

IkT-148009 is at least 18-fold more potent against the wildtype enzyme relative to imatinib. A kinase inhibitory profile was measured at 500 nM (Table 5), illustrating that IkT-148009 may have off-target kinase inhibition potential, but none that are associated with known toxicity pathways.

Table 5: Kinase inhibitory profile of IkT-148009 relative to imatinib at 500 nM[1]

Kinase	**IkT-148009M % Residual Activity**	**Imatinib % Residual Activity**
Abl1(h)	-2	44.3
Abl2/Arg(h)	5	55.9
Blk(h)	31	89
cKit(h)	87	49.6
cSrc(h)	95	86.5
DDR2(h)	13	27.1
EphA2(h)	49	87.1
EphA8(h)	52	94.7
EphB1(h)	43	101.8
FAK(h)	17	94.9
Fes(h)	10	101
Fgr(h)	44	80.1
Fms(h)	5	15.3
Hck(h)	4	84.9
Lck(h)	3	30.9
Lck(h) activated	16	N/A

Lyn(h)	3	59.6
MELK(h)	47	89.2
PDGFRa	69	5.9
PDGFRP	76	39.1
PTK5(h)	36	93.8
Pyk2(h)	37	100.6
Yes(h)	47	N/A

[1](h) refers to the human enzyme. N/A = not available

While Lck is an important enzyme related to T-cell recruitment, toxicity of Lck inhibition is usually occurring in the context of cSrc and/or YES co-inhibition. Up to a 120-day dosing in C57Bl/6 mice at 150 mg/kg/day has not resulted in any overt toxicity.

The metabolites of IkT-148009 and imatinib are essentially chemically identical with the exception that the added methyl-isooxazole ring of IkT-148009 is present in each of the metabolic species but does not lead to the formation of new metabolites**.** These metabolites are in comparable proportions from rat, monkey and human liver microsomes, which argues that the safety profile of IkT-148009 and imatinib will be comparable to one another. This has been validated from the comparative toxicology studies. At higher doses, IkT-148009 was close to the dose-limiting toxicity similar to reported data with imatinib. The similarity in metabolic profiles argues strongly that both Gleevec® and IkT-148009 will share toxicology profiles and other properties that could be predictive of human safety with IkT-148009.

The doses selected for the SAD and the MAD parts of this study are based on the non-clinical data and the FDA approved dose of imatinib (Gleevec®) 400 or 600 mg, once a day, in addition to clinical dose proportionality for IkT-148009 observed in SAD subjects in the ongoing Part A of this study. In order to identify the maximum tolerated dose in the SAD and the MAD study, study drug will be administered orally as 25 mg in the first cohort and the dose will then be escalated if needed in subsequent cohorts per the dose escalation schema and the stopping rules specified in this protocol.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. Monitoring will be conducted according to the applicable International Committee on Harmonisation (ICH) and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

3.3. Benefit-Risk Evaluation of the Present Study

This is a first-in-human study for IkT-148009, thus there is no expected benefit for older adult and elderly healthy volunteers in this study. Because of the microscopic findings observed in the reproductive organs in the GLP rodent study and lack of these observations in the non-GLP rodent and the GLP non-human primate studies, the sponsor has chosen not to enroll healthy adult volunteers (18 -54 years old), and furthermore exclude subjects of child bearing potential from this first-in-human study. Clinical trial subjects will go through an extensive screening process throughout the duration of this study, thereby mitigating or eliminating the possibility of being at risk given the known side effects of imatinib.

This study will be conducted at a specialized Phase 1 CRU where all subjects will be institutionalized way beyond receiving their last dose of the study drug and will be under constant medical supervision. SRC will operate under a clearly defined charter and pre-defined stopping rules prohibiting a dose escalation. SRC will review available data from each cohort and determine the dose selection for the subsequent cohort, not to exceed the maximum proposed dose for each cohort. In addition to selection of a proposed starting dose with an anticipated 29-fold safety margin (HED from the non-human primate GLP toxicology study NOAEL), all cohorts in the single ascending dose portion of this study will utilize sentinel dosing in which one subject will be administered IkT-148009 and one subject will be administered placebo to provide additional assurance that the starting dose and the subsequent dose escalations are appropriate. These subjects will be followed for a minimum of 48 hours before deciding to dose the remainder of thecohort. Each SAD cohort will be completed and monitored for at least 48 hours before deciding whether to start the sentinel pair in the next (higher dose) cohort. In the multiple ascending dose part of the protocol, dosing will be completed in the initial (or prior) cohort and subjects will be observed for a minimum of 48 hours after the last dose before deciding to initiate the next (higherdose) cohort. The protocol also includes clear stopping rules with regard to clinically significant medical events of interest, as well as seriousness and severity of adverse events. A placebo controlhas been added within each cohort to get an objective evaluation of the IkT-148009 profile. Finally, subjects participating in a cohort will not be allowed to enroll in subsequent cohorts.

The ability to monitor for potential adverse effects, the sentinel dosing approach, the low proposed starting dose, the cautious dose escalation plan, the careful consideration of safety data before increasing the dose for the next cohort, the exclusion of subjects of child bearing potential, the careful selection of subjects otherwise deemed healthy, and the pre-specified escalation and stopping rules mitigate the risk of the-reported effects observed in animal studies occurring in this first-in-human study of IkT-148009.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objective

Parts A and B

1. To assess the safety and tolerability of IkT-148009 given as gelatin capsule;
2. To assess the PK profile of single doses and multiple doses (once daily for seven days) of IkT-148009 gelatin capsules in fed state;
3. To investigate plasma and urine concentrations of IkT-148009.

Part C

4. To assess safety, tolerability, PK, biomarkers, and clinical effects in PD participants

4.2. Endpoints

4.2.1. Primary Endpoints

Parts A, B, and C are:

1. Safety (vital sign measurements, clinical laboratory data, electrocardiogram [ECG] parameters and C-SSRS); and
2. Tolerability (adverse event reporting); and
3. Assess the pharmacokinetics (PK) of IkT-148009 by determining the:
    - Area under the concentration-time curve from time zero to 96 hours ($AUC_{0-\infty}$);
    - Maximum plasma concentration (C_{max});
    - Area under the concentration-time curve from time zero to last time point (AUC_{0-last});
    - Time to reach maximum concentration (T_{max});
    - The distributional half-life and terminal half-life ($t_{1/2}$); and
    - Maximum concentration at steady-state ($C_{max,ss}$) and area under the concentration-time curve at steady-state (AUC_{ss})

4.2.2. Exploratory Endpoints

Part B

1. IkT-148009 drug concentration in the CSF at steady state if available.

Part C

1. Change from Baseline to Final visit in the MDS-UPDRS Motor Subscale (Part III) Score
2. Change from Baseline to Final Visit in the MDS-UPDRS Non-motor aspects of experiences of daily living (Part I) Score and in the MDS-UPDRS Motor aspects of experiences of daily living (Part II) Score.
3. Change in Clinical Global Impression of Improvement (CGI-I) Score and the Patient Global Impression of Change (PGI-C) Score
4. Change in Non-Motor Symptom Score (NMSS)
5. Change from Baseline to Final Visit in Parkinson's Disease Questionnaire 39 (PDQ-39).
6. Change from Baseline to Final Visit in the Patient Global Impression of Severity Score (PGI-S)
7. Change from Baseline to Final Visit in Complete Bowel Movement Score (CSBM).
8. Change in Patient Assessment of Upper GI Disorders Severity Index (PAGI-SYM)
9. IkT-148009 drug concentration in the CSF at steady state if available.
10. Biomarker analysis from CNS-derived exosomes if available.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

This is a randomized, Phase I, Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) study to determine the safety, tolerability and pharmacokinetics (PK) of IkT-148009 gelatin capsules in Older and Elderly Healthy Adults with extension into Parkinson's Disease. Escalation to the next dose will be undertaken only after safety, tolerability and PK data have been reviewed by the SRC and agreement reached that it is safe to increase the dose. The SRC will not receive any unblinded PK data unless it is agreed upon by the SRC to unblind a subject and/or cohort based on the completed safety review.

5.1.1. Part A (Single Ascending Dose [SAD] Cohorts)

Cohorts will consist of eight (8) subjects; six (6) of whom will receive treatment with IkT-148009 and two (2) with matching placebo. The maximum recommended starting dose for this part of the Phase 1 study is 25 mg.

Cohort	Maximum Escalation from Previous Cohort	IkT-148009 Maximum Dose (mg)
1	N/A	25
2	1/2X	12.5
3	3 X	37.5
4	2 X	75
5	1.33 X	100
6	1.33 X	125[1]
7	1.4 X	175[1]
8	1.43 X	250[1]
9	1.3 X	325[1]
10	1.23X	400[1]
[1]Escalation to these doses or any fraction thereof subject to the determination of the Safety Review Committee		

Subjects in each cohort of the study will be admitted to the unit approximately 24 hours prior to the expected time of dosing and will be confined to the unit for approximately 5 days in Part A of the study. The SAD cohorts will consist of up to 8 visits over a period of up to 28 days prior to dosing and 14 days after dosing.

Sentinel dosing will be employed for each cohort in the SAD part of this study, with one subject randomized to receive IkT-148009 and the other placebo on the first day. These two subjects in each cohort will be monitored for 48 hours after dosing before deciding to dose the remainder of the cohort. As such, the other six subjects in the first cohort will be dosed approximately 48 hours later. Each cohort will be monitored for at least 48 hours before deciding to initiate the next (higher dose) cohort. Each cohort will be dosed at approximately weekly intervals in order to allow adequate time for collection and review of safety and PK data.

If SAD clinical exposure and PK data through 2 or more cohorts raise no concerns to the SRC, the MAD may commence at the discretion of the SRC while the remaining SAD cohorts arecompleted.

5.1.2. Part B (Multiple Ascending Dose [MAD] Cohorts)

Cohorts will consist of eight (8) subjects; six (6) of whom will receive treatment with IkT-148009 and two (2) with matching placebo. The maximum recommended starting dose and the doses for the dose escalation cohorts for this portion of the Phase I study will be selected based on the available nonclinical data, and the pharmacokinetic and safety results from the SAD study.

Cohort	Maximum Escalation from Previous Cohort	IkT-148009 Maximum Dose (mg)
1	N/A	12.5
2	2 X	25
3	2 X	50[1]
4	2 X	100[1]
[1]Escalation to these doses or fraction thereof subject to the determination of the Safety Review Committee		

MAD cohorts will consist of up to 15 visits over a period of 49 days including 7 days of dosing.

Subjects in each cohort of Part B of the study will be admitted to the unit approximately 24 hours prior to the expected time of dosing and will be confined to the unit for approximately 12 days in Part B. No subject may be discharged from the unit until the investigator is satisfied that they have no continuing adverse events that could be related to study drug.

If SAD clinical exposure and PK data through 2 or more cohorts raise no concerns to the SRC, the MAD may commence at the discretion of the SRC while the remaining SAD cohorts are completed. The MAD may be paused or adapted based on subsequent SAD exposure or safety data.

In the Part B MAD cohorts, optional cerebrospinal fluid (CSF) collection will be offered to eligible participants. To be eligible, participants must have INR values at screening less than or equal to 1.4 and platelets greater than 50. After consent, approximately 4cc of CSF (2 cc in each of 2 tubes) will be collected using standard sterile technique. CSF will be used for PK analysis and banked for future exploratory analysis.

See the SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively) for the full list of study assessments and timings.

5.1.3. Part C (Multiple Ascending Dose [MAD] extension into PD patients)

If Part B clinical experience and PK data through 2 or more cohorts raise no concerns to the SRC, the MAD extension into PD participants may commence at the discretion of the SRC while the remaining Part A and Part B cohorts are completed.

Cohorts will consist of eight (8) subjects; six (6) of whom will receive treatment with IkT-148009 and two (2) with matching placebo. The starting dose and the subsequent doses for this portion of

the Phase I study will be selected based on available nonclinical data and the pharmacokinetic and safety results from Parts A and B.

Cohort	Maximum Escalation from Previous Cohort	IkT-148009 MaximumDose (mg)
1	N/A	50
2	2 X	100[1]
3	2 X	200[1]
[1]Dose escalation to these doses or fraction thereof subject to the determination of the Safety Review Committee		

Subjects in each cohort of Part C of the study will be admitted to the unit approximately 24 hours prior to the expected time of dosing and will be confined to the unit for up to 12 days in Part C. No subject may be discharged from the unit until the investigator is satisfied that they have no continuing adverse events that could be related to study drug.

In the Part C MAD cohorts, optional cerebrospinal fluid (CSF) collection will be offered to eligible participants. To be eligible, participants must have INR values at screening less than or equal to 1.4 and platelets greater than 50. After consent, approximately 4cc of CSF (2 cc in each of 2 tubes) will be collected using standard sterile technique. CSF will be used for PK analysis and banked for future exploratory analysis.

See the SOE in Appendix 3 for the full list of study assessments and timings for this part of the study.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

6.1. Subject Inclusion Criteria

The following inclusion criteria must be met for subjects to be eligible for the trial in Parts A and B:

1. Subject must have all questions about the study answered and must have signed the informed consent document before any study-specific procedures are performed.
2. Men or women aged 55 to 70 years (both inclusive) of any race.
3. Subjects must be otherwise healthy and ambulatory, with no history or evidence of clinically relevant medical disorders as determined by the Investigator in consultation with the Sponsor.
4. Mini Mental State Examination (MMSE) ≥ 28 at Screening (V1) and Baseline (V2).
5. Physical examination, clinical laboratory values, vital signs (as defined in the CRU standard operating procedure [SOP]), and the electrocardiogram (ECGs) are clinically acceptable to the Investigator. Body weight ≥ 45 kg at screening and baseline visits. Body Mass Index (BMI) ≥ 18 and ≤33 kg/m^2 at screening.
6. Female subjects must be postmenopausal (12 months without menses and confirmed by follicle stimulating hormone [FSH] > 40 mIU/mL) or surgically sterile (hysterectomy or bilateral oophorectomy) or sterile for other medical reason (i.e., able to document premature low ovarian reserve, birth defect, other). Women who are several years postmenopausal may be considered for enrollment even with [FSH] below this threshold.
7. Male subjects must agree to practice an acceptable method of highly effective birth control from the Screening visit, while on study and for 7 days after receiving the last dose of study drug. Highly effective methods of birth control include sexual abstinence; vasectomy; or a condom with spermicide (men) in combination with their partner's highly effective method.
8. Males must be willing to abstain from sperm donation from the screening visit, while on study and through 30 days after receiving the last dose of study drug.

For Part C, participants must be eligible as in Part A and B, with the following differences/additions:

9. MMSE ≥ 26 at screening (V1) and Baseline (V2)
10. Diagnosis of Parkinson`s Disease (consistent with the UK PD Society Brain Bank Criteria for the Diagnosis of PD), with bradykinesia and clear motor response to levodopa.

11. Hoehn & Yahr staging of 3 or less in the ON state.

12. Good clinical response to levodopa as judged by participant and investigator.

13. Stable doses of all PD medications for at least 4 weeks prior to Screening.

14. Approved by an Enrollment Authorization Committee (EAC).

6.2. Subject Exclusion Criteria

Parts A and B

1. Clinically significant abnormal values for hematology, clinical chemistry or urinalysis at the screening and admission visits. Abnormalities considered to be non-clinically significant by the Investigator are acceptable.
2. Clinically significant abnormal findings on physical examination or 12-lead electrocardiogram (ECG) at the screening or admission visits. NOTE: QTcF interval of $\geq$ 450 msec in males or $\geq$ 470 msec in females will be the basis for exclusion from the study. Safety ECG may be repeated for confirmatory purposes if initial values obtained exceed the limits specified.
3. Significant history (within six months prior to receiving the study drug) and/or presence of clinically significant medical, surgical or psychiatric disorder. Subjects with co-morbid conditions that are stable and controlled may remain eligible (stable defined as no change in the dose or frequency of medications over the past three months).
4. For optional lumbar puncture: participants with bleeding disorders, relevant lab abnormalities (Screening INR greater than 1.4, platelets less than 50), relevant blood dyscrasias, prior intolerance of LP, anatomical reasons preventing safe or successful collection of fluid (skin infection at site of puncture, relevant spine surgery, spinal deformity, etc.), known intracranial space-occupying lesions with mass effect, posteriorfossa masses, or relevant brain malformations (Arnold-Chiari malformation, etc.), examfindings suggestive of increased intracranial pressure, or known allergy/sensitivity to lidocaine or its derivatives will not be eligible.
5. eGFR < 60 mg/mL
6. Creatinine, Amylase and/or Lipase > ULN
7. Any malignancy in the 5 years prior to screening excluding basal cell carcinoma or squamous cell carcinoma of the skin or cervical carcinoma in situ that have been successfully treated.
8. Any subject with a history, presence and/or current evidence of serologic positive result for hepatitis B surface antigen, hepatitis C antibodies, or HIV antibodies 1 or 2. Subjects considered to be cured for hepatitis C will be eligible.

9. Recent history (within previous six months prior to screening) of alcohol or drug abuse (as judged by the investigator) or has consumed > 2 alcohol drinks/day during the last three months prior to screening (one glass is approximately equivalent to: beer [284 mL], wine [125 mL/4 ounces], or distilled spirits [25 mL/1 ounce]). Subjects that consume three glasses of alcoholic beverages per day but less than 14 glasses per week may be enrolled at the discretion of the Investigator. Positive screens for alcohol or controlled substances at the screening or admission visits will disqualify a subject from study participation.

10. Any subject with known hypersensitivity to IkT-148009.

11. Donation of blood or acute loss of blood within 60 days prior to screening visit.

12. Any subject who has received treatment with an investigational drug during the 30 days prior to screening.

13. Investigative site personnel or their immediate families (spouse, parent, child or sibling whether biological or legally adopted).

14. Any subject unwilling or unable to comply with study procedures.

Part C:

15. For optional lumbar puncture: participants with bleeding disorders, relevant lab abnormalities (Screening INR greater than 1.4, platelets less than 50), prior intolerance of LP, anatomical reasons preventing safe or successful collection of fluid (skin infection at site of puncture, relevant spine surgery, spinal deformity, etc.), known intracranial space-occupying lesions with mass effect, posterior fossa masses, or relevant brain malformations (Arnold-Chiari malformation, etc.), exam findings suggestive of increased intracranial pressure, or known allergy/sensitivity to lidocaine or its derivatives will not be eligible.

16. Diagnosis of secondary or atypical parkinsonism

17. Prior neurosurgery for PD or treatment with DUODOPA or infused apomorphine

18. Concurrent use of neuroleptic medications or other dopamine antagonists.

19. Severe or disabling fluctuations or dyskinesias that would, in the opinion of the investigator, interfere with completion of the study

20. Clinically significant hallucinations or delusions that, in the opinion of the investigator or EAC, may preclude completion of the study

21. Clinically significant orthostatic hypotension that, in the opinion of the investigator, may preclude completion of the study

22. Currently active major depression as determined by BDI-II score of >19
23. Previous surgical procedure for PD

6.3. Subject Withdrawal Criteria

If there is an adverse event or medical reason for the withdrawal, the subject should be followed medically until the condition has either resolved itself or is stable. Details of the reason for withdrawal should be recorded in the subject's electronic Case Report Form (eCRF).

Subjects who withdraw should, if possible, have a follow-up examination, including a physical examination, the appropriate investigations, vital signs, Safety ECG, Cardiodynamic ECGs and clinical laboratory tests. All details of this follow-up examination should be recorded in the subject's medical source documents.

6.3.1.1. Study Drug Withdrawal and Withdrawal from the Study

Participation in the study is strictly voluntary. Subjects are free to discontinue the study at any time without giving their reason(s).

A subject must be withdrawn from the study treatment in the event of any of the following:

- withdrawal of the subject's consent;
- new onset of a condition which would have met exclusion criterion, is clinically relevant and affects the subject's safety, and discontinuation is considered necessary by the Investigators and/or Sponsor;
- occurrence of intolerable AEs;
- intake of non-permitted concomitant medication;
- lack of subject compliance;
- significant protocol deviation determined in consultation with the sponsor Medical Monitor.

If a subject fails to attend scheduled assessments during the course of the study, the Investigator must determine the reasons and the circumstances as completely and accurately as possible and document this in the subject's source documents.

Subjects may be withdrawn from the study if there is concern for the subject's safety or it is determined that the subject is no longer a qualified participant. Any subject who is withdrawn from the study for any reason is to have the final visit assessments performed applicable to that cohort.

Subjects who withdraw or are withdrawn from the study prior to study drug dosing will be replaced. The sponsor may choose to replace subjects who withdraw or are withdrawn from the study after study drug dosing.

7. TREATMENT OF SUBJECTS

7.1. Number of Subjects

Up to 80 older adult and elderly subjects, 55 – 70 years old, otherwise considered healthy are planned to be recruited in Part A of this study, depending on the number of cohorts studied, up to 32 subjects are planned to be recruited in Part B and up to 24 patients in Part C, again depending on the number of cohorts studied. Subjects who withdraw or are withdrawn from the study prior to dosing will be replaced and subjects who withdraw or are withdrawn from the study after study drug dosing may be replaced at the discretion of the sponsor. Additional cohorts may be considered to accommodate dose repetition, slower dose escalation or escalation beyond currentlyplanned doses.

7.2. Treatment Assignment

Subjects in Parts A, B and C will be randomly assigned to either IkT-148009 or a matching placebo according to a randomization schedule prepared by an independent statistician.

7.3. IkT-148009 Single Ascending Dosing Regimen

IkT-148009 or matching placebo will be administered once with a meal. The starting dose will be 25 mg (Cohort 1). The doses for the subsequent cohorts will be determined based on the results from the previous cohorts until the MTD has been determined. Please refer to Section 5.1.1 for the planned dose escalation schema.

7.4. IkT-148009 Part B Multiple Ascending Dosing Regimen

The SRC will determine overall safety and characterize the PK of SAD dose cohorts through two or more cohorts. If at this point the SRC finds these data to be reassuring, Part B of this study (MAD) may begin. IkT-148009 or matching placebo will be administered once with a meal daily for up to 7 days in Part B. The maximum recommended starting dose and the doses for the dose escalation cohorts for this portion of the Phase I study will be selected based on the available nonclinical data, and the pharmacokinetic and safety results from the SAD study. Please refer to Section 5.1.2 for the planned dose escalation schema.

If the MAD Part B begins before the SAD is completed, the MAD studies may be paused or adapted based on SAD exposure or safety data subsequent to two or more SAD cohorts.

7.5. IkT-148009 Part C Multiple Ascending Dosing Regimen

If Part B clinical exposure and PK data through 2 or more cohorts raise no concerns to the SRC, Part C may commence at the discretion of the SRC while the remaining Part A and Part B cohorts are completed.

IkT-148009 or matching placebo will be administered once with a meal daily for up to 7 days. The starting dose and subsequent doses for this portion of the Phase I study will be selected based on

available nonclinical data and the pharmacokinetic and safety results from Parts A and B. Please refer to Section 5.1.23 for the planned dose escalation schema.

7.6. Dose Adjustment Criteria

7.6.1. Safety Review Committee

A SRC will be established comprised of the PI, the Sponsor Study Physician and the CRO Drug Safety Physician. Designees may be utilized consistent with the SRC Charter. Optional attendees may participate as required. The roles and responsibilities of the SRC will be described in the SRC Charter which will be agreed and signed prior to the first dose of study drug beingadministered. The role of the SRC is to assess the safety, tolerability and pharmacokinetic information collected for each dose level and determine that the next cohort should:

- advance to the next planned dose level;
- advance to a dose lower than the next planned dose level; or
- repeat the previous dose level.

In addition, the SRC may stop the study for safety reasons at any time. The committee may overrule these stopping criteria by being more conservative, i.e., next dose lower than planned, butmay not rule that the next dose should be higher than planned.

7.6.2. Dose Escalation and Stopping Rules

1. Serious Adverse Event: If any subject in a cohort experiences a serious adverse event (SAE) that is potentially life-threatening and is possibly study drug related, dose escalation will be halted. If any subject in a cohort has a serious adverse event (SAE) that is not potentially life-threatening but is possibly study drug related, the SRC may stop the study or may permit ongoing dosing at lower doses of IkT-148009 than that at which the event occurred, depending on the nature of the event.

2. Severe (or multiple moderate AEs in the same subject) Adverse Event: If two (2) or more subjects in a cohort have a severe adverse event that the safety committee determines is related to IkT-148009, the safety committee may stop the SAD phase of the study or may permit ongoing dosing at the same or lower doses of IkT-148009, depending on the nature of the event and the dose(s) at which the events occurred.

3. Clinically significant events observed at least three (3) subjects exposed to IkT-148009 within a cohort: The SRC may not allow dose-escalation if at least two subjects report the same finding. However, if each subject reported a different finding, the SRC could allow dose escalation at lower doses than planned. In all circumstances, the SRC may allow dose-repetition or dose reduction:

- Cytopenias (anemia, neutropenia and thrombocytopenia);
- Fluid retention (pleural effusion, pericardial effusion, pulmonary edema and ascites) and edema (unexpected rapid weight gain);

- Congestive heart failure, cardiogenic shock and left ventricular dysfunction;
- Gastrointestinal irritation leading to nausea, vomiting, diarrhea, dyspepsia, abdominal pain, GI hemorrhage;
- A sustained increase (>3X ULN) in alanine aminotransferase (ALT) or aspartate aminotransferase (AST), which must be confirmed elevated within 48 hours (Guideline of Liver Safety Assessment Best Practices Workshop 2014 [Avigan et al., 2014]);
- Total bilirubin (>2X ULN) increase confirmed on repeat testing within 48 hours;
- A sustained increase (> 2X ULN) in alkaline phosphatase (ALP) in association with increased ALT and AST confirmed on repeat testing within 48 hours;
- QTc prolongation defined as QTcF increasing ≥60 msec and persisting for at least 10 minutes or QTcF >500 msec and persisting for at least 30 minutes;
- A sustained increase (> 1.3X ULN) in serum creatinine confirmed on repeat testing within 48 hours.

7.6.3. Pharmacokinetic Criteria for Adjustment or Stopping Doses

The SRC will review the plasma concentration information (e.g., AUC and C_{max}) from previous cohorts to determine whether to adjust the dose for the next cohort (dose reduction, dose repetition, or reduced dose escalation).

7.7. Concomitant Medications

Record the name, start date (if known), indication for use and whether ongoing or stopped of medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study. Concomitant medications used for prophylaxis are allowed as is acetaminophen for minor pain (up to 2 grams in 24 hours).

The charts of all study participants will be reviewed for new concomitant medications. Chart reviews will include examination of nursing and physician progress notes, vital signs and medication records in order to identify AEs that may be associated with new concomitant medications. New concomitant medications, ongoing concomitant medications with a change in dose and medical procedures ordered, e.g., laboratory assessments and radiological assessments, will be reviewed to determine if they are associated with an AE not previously identified.

7.8. Treatment Compliance

The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for non-compliance will also be documented, including:

- missed visits;
- interruptions in the schedule of administration;
- non-permitted medications.

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. As this is a Phase I study, it is critical that study activities be carried out per the protocol schedule.

7.9. Randomization and Blinding

In Part A (SAD), subjects will be randomly assigned to study drug (IkT-148009 or placebo) based on the randomization scheme on Day 1. Sentinel dosing will be employed for each cohort, and randomization will be 1:1 for the first two subjects with one subject randomized to receive IkT-148009 and the other placebo on the first day, and then 5:1 for the remaining 6 in each SAD cohort resulting in an overall randomization ratio of 6:2 for each cohort of 8 subjects. In Parts B (MAD) or C (PD) there will be no sentinel dosing, subjects will be randomized 3:1 for each cohort of 8 subjects. However, dosing will be completed in the initial (or prior) cohort and subjects will be observed for a minimum of 48 hours after the administration of the last dose before deciding to initiate the next (higher dose) cohort.

The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the database hard lock has occurred.

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1. Study Drug

IkT-148009 will be compounded at the pharmacy of the CRU per their SOP from components supplied by the sponsor per the detailed instructions provided in the pharmacy instructions and given to the subjects as a gelatin capsule for Parts A and B. Part C will have capsules centrally prepared and distributed to sites on an as needed basis. Placebo capsules will be matched to IkT-148009 capsules in Parts A, B or C.

8.2. Study Drug Packaging and Labeling

The composition and pharmaceutical quality of the investigational product will be maintained according to the current Good Manufacturing Practice (GMP) and GCP guidelines and available for review in the study medication documentation.

8.3. Study Drug Storage

Upon receipt of the medication, the Investigator or designee will inspect the medication and complete and return the acknowledgment of receipt form enclosed with the parcel. A copy of the signed receipt will be kept in the study files.

The study medication must be carefully stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. It should be protected from moisture. Direct contact of the active pharmaceutical ingredient (API) with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references.

The study medication may not be used for any purpose other than the present study. After the study is completed, all unused study medication must be retained, returned as directed or destroyedon site per the Sponsor's instructions.

The Investigator or designee will be responsible for ensuring appropriate storage, compounding, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory must be available for inspection by the designated representatives of the Sponsor or the Sponsor's representatives on request, and must include the information below:

- the identification of the subject to whom the drug was dispensed;
- the date(s) and quantity of the drug dispensed to the subject;

A copy of the inventory record and a record of any clinical supplies that have been destroyed must be documented as directed. This documentation must include at least the information below or as agreed with the Sponsor:

- the number of unused units;
- the number of units destroyed at the end of the study;
- the date, method and location of destruction.

8.4. Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator or designee must keep a record of all study drug received, used and discarded. It must be clear from the records which subject received which dose of treatment.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. Under no circumstances is the Investigator allowed to release study drug supplies to any other physician not named in the FDA Form 1572 or to administer these supplies to a patient not enrolled in this study.

8.5. Study Drug Handling and Disposal

At the end of the study, any unused study drug will be retained or returned to the Sponsor for destruction or destroyed locally per the Sponsor's directions; disposition of study drug will be documented.

9. PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic blood samples will be taken and processed for analysis for concentrations of IkT-148009 at the time points described in the SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively). Residual plasma samples will be used to investigate and identify IkT-148009 metabolites present by LC-MS/MS analysis and perform a semi-quantitative estimate of their abundance; urine samples may also be tested for this purpose. This metabolite identification and semi-quantification work will be performed under a separate protocol and the study report included as an appendix to this clinical study report.

The following PK parameters will be calculated (Table 6), using a non-compartmental approach from the individual plasma concentration-time profiles of study drug. Actual PK sample collection times relative to dosing will be used to calculate the PK parameters.

Table 6: Pharmacokinetic Parameters of IkT-148009

PK Parameter	Definition
AUC_{0-24} (ng h/mL)	Area under the plasma drug concentration-time curve from time zero to 24 hours post dose.
$AUC_{0-\infty}$(ng h/mL)	Area under the plasma drug concentration-time curve from time zero to infinity hours post dose.
C_{max} (ng/mL)	Maximum observed plasma concentration.
T_{max} (h)	Time to peak plasma concentration.
C_{trough}(ng/mL)	Plasma concentration observed at trough
$T_{1/2}$ (h)	Terminal half-life

For the purpose of PK parameter calculations, concentration values below the limit of quantification (BLQ) will be set to missing. Pharmacokinetic parameters of the study drug will be computed using a fully validated version of NONMEM. Additional information will be provided in the SAP.

9.1. Blood Sample Collection

Plasma samples for PK analysis will be collected according to the sampling collection times specified in the SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively). The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. The Investigator or designee will arrange to have the plasma samples processed, stored and transported as directed for bioanalysis.

Selected samples will also be analyzed by LC-MS/MS to investigate and identify metabolites of IkT-148009 that are present and a semi-quantitative estimate of their abundance performed. This work will be conducted under a separate protocol and the study report included as an appendix to this clinical study report.

An additional PK sample may be collected at any time if clinically indicated and at the discretion of the Investigator (e.g., for unusual or severe AEs).

Each sample will be marked with unique identifiers such as the study number, subject number, and the nominal sample time. The date and actual time that the blood sample was taken will be recorded on the case report form or electronically with a bar code or other method.

9.2. Urine Sample Collection

Urine samples will be collected as per the SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively) and processed for analysis of IkT-148009 concentrations. Urine samples may also be analyzed for IkT-148009 metabolite identification and semi-quantification purposes under a separate protocol. The pre-dose urine sample is to be collected within approximately 60 minutes prior to dosing.

9.3. Storage and Shipment of Pharmacokinetic and Urine Samples

The plasma and urine samples should be kept frozen at approximately -70°C to -80°C until analyzed. They should be packed as directed to avoid breakage during transit and with sufficient dry ice to prevent thawing for at least 72 hours. A specimen-identification form must be completed and sent to the laboratory with each set of samples. The clinical site will arrange to have the plasma and urine samples transported as directed for bioanalysis as detailed in the PK instructions.

9.4. Lumbar Puncture CSF Collection

When applicable, approximately 4 cc (2 cc in each of 2 tubes) of CSF will be collected from eligible participants via a single lumbar puncture and processed for analysis of IkT-148009 concentrations.

9.5. Sample Analysis

Bioanalysis of plasma samples for the determination of IkT-148009 will be performed utilizing a validated method; and bioanalysis of urine samples for the determination of IkT-148009 will also be performed utilizing a validated method.

10. EXPLORATORY ENDPOINTS

10.1 Part B

10.1.1 IkT-148009 drug concentration in the CSF at steady state (if available).

10.2 Part C

10.2.1 MDS-UPDRS Parts I, II, III

The Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is a well-established tool for characterizing the signs and symptoms of PD (Goetz et al, 2008). The three parts used in this study are: Part I (Non-Motor Aspect of Experiences of Daily Living), Part II (Motor Aspects of Experiences of Daily Living), and Part III (Motor Examination). Items in each domain are rated from 0-4, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

10.2.2 Clinical Global Impression of Improvement (CGI-I) Score

The CGI-I is a 7-point scale used to indicate how the clinician views whether a participant has changed since baseline (Guy, 1976). The range includes 1 ("very much improved"), 2 ("much improved"), 3 ("minimally improved") , 4 ("no change"), 5 ("minimally worse"), 6 ("much worse"), and 7 ("very much worse").

10.2.3 Patient Global Impression of Change (PGI-C)

The PGI-C is used to characterize a participant's sense of change compared to baseline. The range includes 1 ("very much improved"), 2 ("much improved"), 3 ("minimally improved") , 4 ("no change"), 5 ("minimally worse"), 6 ("much worse"), and 7 ("very much worse").

10.2.4 Patient Global Impression of Severity Score (PGI-S)

The PGI-S is a single-item tool used to determine how severe a person feels their symptoms are at the time of questioning. It is based on a 4-point scale (1=normal, 2=mild, 3=moderate, 4=severe).

10.2.5 Non-Motor Symptom Score (NMSS)

The NMSS is a 30-item scale divided into 9 domains (cardiovascular, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function, miscellaneous) (Chaudhuri et al 2007). Each item is rated for frequency (rarely/often/frequent/very frequent) and severity (none/mild/moderate/severe) of symptoms.

10.2.6 Parkinson's Disease Questionnaire 39 (PDQ-39)

The PDQ-39 is a self-administered questionnaire that assesses how often people affected by PD experience difficulties across 8 dimensions of daily living, including relationships, social situations, and communication (Peto et al 1995). It also assesses the impact of PD on specific dimensions of functioning and well-being. The PDQ-39 is scored on a scale of 0 to 100, with lower scores indicating better health and higher scores more severe symptoms.

10.2.7 Complete Satisfaction with Bowel Movement Scale (CSBM)

The Complete Satisfaction with Bowel Movement (CSBM) is defined as a bowel movement occurring in the absence of a laxative, enema or suppository use during the previous 24 hour period with the bowel movement accompanied by the patient self-reporting a feeling of complete evacuation. This endpoint is designed with the intent of better identifying a patient experiencing clinically meaningful improvement in symptoms (Lacy et al., 2012).

10.2.8 Patient Assessment of Upper GI Disorders Severity Index (PAGI-SYM)

PAGI-SYM is a clinical assessment composed of a series of questions evaluating the severity of upper GI symptoms and is composed of six subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain. The 20-item questionnaire assesses symptoms of gastroparesis, dyspepsia, and gastroesophageal reflux disease; it includes the 9 symptoms of gastroparesis cardinal symptom index (GCSI). Total GCSI score equals the mean of the nausea/vomiting subscore, postprandial fullness/early satiety subscore, and bloating subscore where nausea/vomiting subscore = mean of scores for nausea, retching, and vomiting; postprandial fullness/early satiety subscore = mean of scores for stomach fullness, inability to finish meal, excessive fullness, and loss of appetite; and bloating subscore = mean of scores for bloating and large stomach. Upper abdominal pain subscore was the average of upper abdominal pain and upper abdominal discomfort. Patients are asked to assess the severity of their symptoms during the previous 2 weeks using a 0 to 5 scale where no symptoms = 0, very mild = 1, mild = 2, moderate = 3, severe = 4, and very severe = 5 (Rentz *et al*., 2004).

10.2.9 Biomarker screen in CNS-derived exosomes (if available)

Antibody selection for CNS-derived exosomes isolated by FACS from up to 100 ml peripheral blood for examination of biomarkers of c-Abl activity in Parkinson's disease participants.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

The safety and tolerability of IkT-148009 will be assessed via treatment emergent adverse event reporting, serious adverse event reporting, vital sign measurement, physical and neurological examination, laboratory data, Safety ECG and Cardiodynamic ECG parameters and C-SSRS.

Physical and neurological examinations, vital signs, daily weights, tracking of fluid intake and urine output volumes, laboratory assessments, Safety and Cardiodynamic ECG evaluations and observations by experienced personnel will be undertaken throughout the study based on the following sections and SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively). All study assessments may be performed by suitably trained personnel, but the results must be reviewed and signed off by medical personnel.

11.1.1. Demographics

Age, gender, race, and ethnic origin will be recorded at Screening.

11.1.2. Medical History

A full medical history including medication history will be recorded at Screening.

11.1.3. Physical Examination including a neurological exam

A physical examination of all major body systems (general appearance, skin, head, eyes, ears, nose, neck, throat, lungs, heart, abdomen, back, lymph nodes and extremities) will be undertaken and recorded at Screening. Additional exams may be performed if any changes from the screening assessment or symptom driven. This will include body weight and height at the Screening visits. Additional physical examinations will be undertaken and recorded per the SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively). Height will be measured on study day 1 only.

Significant findings that are present prior to the first dose of study drug must be included in the Medical History/Current Medical Conditions page of the eCRF. Significant findings made after the first dose of study drug through the End of Study Visit which meet the definition of an AE must be recorded in the Adverse Event CRF summary page.

11.1.4. Screening and Safety Laboratory Tests (Clinical chemistry and CBC)

Clinical chemistry tests will include albumin, alkaline phosphatase, total bilirubin, calcium, cholesterol, creatinine, creatinine clearance, creatinine kinase (CK), gamma-glutamyltransferase (γ-GT), glucose, lactate dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, potassium, magnesium, total protein, aspartate transaminase (AST), alanine transaminase (ALT), sodium, triglycerides, urea and uric acid, bicarbonate and chloride. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated. TSH levels will also be monitored.

CBC assessments will include hemoglobin, hematocrit, red blood cell (RBC) count, reticulocyte count, white blood cells (WBC) count with differential, platelet count and PT-INR. PT-INR should be reported in both prothrombin time (second) and international normalized ratio (no unit).

Men and women will undergo additional laboratory tests for reproductive organ function to include leutenizing hormone (LH), follicle stimulating hormone (FSH), testosterone and inhibin B in both genders.

Safety laboratory samples will be collected per the SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively). Clinical chemistry or complete blood count (CBC) may be collected at any time during the study if clinically indicated.

11.1.5. Chest X-ray and Echocardiogram

Baseline chest x-ray and echocardiogram will be performed prior to dosing on subjects in Parts A and B who have completed all other screening events and continue to meet eligibility criterion. In Part C, only a chest x-ray will be performed prior to dosing on patients who have completed all other screening events and continue to meet eligibility criteria.

11.2. Vital Signs

Vital signs (VS) for blood pressure and pulse are to be measured after subjects remain supine for 5 min and after 2 min standing. Baseline VS will be measured 3 times at baseline over the course of an hour. Respiratory rate, pulse oximetry and temperature will also be collected. Vital signs measurements outside of the normal range (as per the CRU SOP) should be repeated. All time points are relative to the time of dosing.

VS will be obtained per the SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively).

11.3. 12-Lead Electrocardiogram (ECG)

ECGs will be classified as either Safety ECGs, which will be collected for real time safety review or Cardiodynamic ECGs (SAD cohorts only) which will be extracted from the Holter recordings for later analysis. Global Instrumentation M12A Enterprise Holter application and compatible ECG/Holter devices will be used for the collection, interpretation, and review of safety 12-lead ECG and Holter data. A subject will be withdrawn from the study by the PI or designee if, in their medical judgment, ECG findings are present which make continued study participation not in the subject's best interest.

The SRC will employ a consulting cardiologist for Parts B and C of the study. This person will review the Baseline ECG tracings of individual subject cases sent for review within 48 hours of receipt and render a clinical judgment as to whether the subject is eligible to participate in the study. They will review any other ECGs sent during the course of a subject's participation that demonstrate a change from baseline and provide a clinical assessment of the ECG within 48 hoursof receipt. At the

completion of each Part C cohort, they will participate in the SRC meeting having reviewed any ECG findings of the cohort in advance of the call and render a clinical opinion as towhether it is safe to proceed to the next cohort in the open session.

11.3.1. **Safety ECGs**

The 12-lead Safety ECG assessments (after at least 10 minutes of rest) will be performed and the standard intervals recorded as well as any abnormalities. These Safety ECGs will be obtained per the SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively) and should be collected at any time if clinically indicated based on vital signs or symptoms at the discretion of the Investigator. ECGs will be performed with subjects resting in a supine position for at least 10 min. All ECG tracings will be reviewed by the PI or designee. ECGs will be interpreted and signed and dated by the PI or designee. The ECGs will be classified as normal, having a non-clinically significant abnormality, or having a clinically significant abnormality. In addition, ECG parameters of ventricular rate, RR or PR interval, QRS complex, and QTcF interval (corrected and uncorrected) will be noted on the CRF. All clinically significant abnormality findings will be recorded as AEs.

When scheduled post-dose, ECGs will be performed within approximately 20 min of the scheduled time point. When scheduled during the continued Holter monitoring period, safety ECGs will be extracted from the Holter Monitor using Bluetooth transmission. When scheduled at any other time, a standard ECG machine will be used.

11.3.2. Cardiodynamic ECGs (SAD only)

Holter monitors will be used to collect continuous 12-lead ECG data on Day 1 for the purpose of collecting cardiodynamic ECGs. Recording will be started and stopped at logistically optimal times to ensure that all scheduled time points are collected. EPQT, 12-lead ECG recordings will be extracted from the Holter monitor data within a 5-min time window around the scheduled time points outlined in Appendix 1. Timing and recording technique for ECGs will be standardized for all subjects. Subjects will be required to lie quietly in a supine position with minimal movement and minimal exposure to noise and other environmental stimuli for at least 10 min prior to and 5 min during the ECG extraction window to allow for quality ECG extraction. If targeted ECG time points are artifactual and/or of poor quality, analyzable 10-sec ECGs will be extracted as close as possible to the targeted time points. Nominal time of the ECG recording will be used for the cardiodynamic analysis. Subjects must be awakened at least 1 hour prior to the start of the cardiodynamic ECGs on Day 1 and before the cardiodynamic ECG recording scheduled at the 24-hour (Day 2) post-dose time point.

Cardiodynamic analysis will be performed in the ECG core laboratory, employing a limited number of qualified readers, will be used. A single reader will be used for the review of ECGs from a particular subject. The ECG recordings will be measured and classified by software from AMPS, LLC. All ECG recordings not meeting specific quality criteria thresholds and all

waveforms identified for review by the automated algorithm will be assigned to a board certified cardiologist for review. The cardiologist will be blinded to subject, time, and treatment. All ECG recordings reviewed by the cardiologist will be analyzed using a superimposed representative complex method, which will be used consistently throughout the study, where automatic calculation of a representative beat comprise all the raw beats considered as normal from each lead is generated and the representative complexes are superimposed for all Baseline and on treatment ECGs. The algorithm positions the cursor determining P wave onset, QRS onset, QRS offset, and end of T wave with the position confirmed or adjusted by the cardiologist. T wave morphology and presence of U waves will be assessed for all ECGs reviewed by the cardiologist.

11.4. Blood Sample Collection for Pharmacokinetic Assessments

Plasma samples for analysis of IkT-148009 concentrations will be collected at the time points as shown in the SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively).

The time of study drug administration is time zero and all post-dosing sampling times are relative to dosing time. The investigator will arrange to have the plasma samples processed and transported for bioanalysis as directed by the Sponsor. In the highest dose group of the MAD phase (Cohort 4), an additional volume of blood will be taken at the same PK sampling time points, plasma harvested and the samples stored frozen. Aliquots of the urine samples collected in that Cohort will also be taken and stored frozen. Those plasma samples will be used to investigate and identify IkT-148009 metabolites present by LC-MS/MS analysis and perform a semi-quantitative estimate of their abundance.

An additional plasma sample for analysis of IkT-148009 concentrations may be collected at any time if clinically indicated and at the discretion of the investigator (e.g., for unusual or severe AEs).

Residual plasma samples from (high dose) MAD phase together with pre-dose samples from each volunteer (at that dose level), will be used for metabolite investigation and identification following bioanalysis.

Each sample will be marked with unique identifiers as determined by the sponsor or its designee.

11.5. Urine Sample Collection for Pharmacokinetic Assessments

A urine sample will be collected as per the SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively) and processed for analysis of IkT-148009. In the highest dose group of the MAD phase (Cohort 4), an additional volume of urine will be collected in that Cohort and stored frozen. The additional urine samples will be used to investigate and identify IkT-148009 metabolites present by LC-MS/MS analysis and perform a semi-quantitative estimate of their abundance. An additional urine sample for analysis of IkT-148009 concentrations may be collected at any time if clinically indicated and at the discretion of the investigator (e.g., for unusual or severe AEs).

A “Window Allowance” outlining acceptable windows for intervals between nominal times and actual times for PK sampling times has been included in the SOE (Appendix 1 for the SAD cohorts

and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively). This will allow flexibility when multiple procedures are scheduled for the same time point.

11.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the study using the C-SSRS. This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicidal ideation and behavior, and a post-baseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes 'yes' or 'no' responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

The "Baseline/Screening" C-SSRS form will be completed at screening (lifetime history and past 24 months). The "Since Last Visit" C-SSRS form will be completed at all subsequent time points outlined in the SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively).

11.7. Mini Mental State Exam

The Mini Mental State Examination (MMSE) is a brief test assessing general cognitive function (Folstein et al., 1975) used in the current study to ensure the study participants have no cognitive impairment before being administered IKT-148009 and to evaluate the subject's cognition after receiving the study drug at subsequent visits per the SOE (Appendix 1 for the SAD cohorts and Appendix 2 for the MAD cohorts and Appendix 3 for PD cohorts, respectively). The MMSE consists of five cognitive components: 1) orientation to time and place; 2) registration of three words; 3) attention and calculation (the investigator can choose in this study whether to administer the "WORLD Backwards" or "Calculation" sub-component); 4) recall of three words; and 5) language. The scores from each of the five components are summed to obtain an overall MMSE score. The score can range from 0-30, with lower scores indicating greater impairment in cognitive functioning. Part A and B participants will only be permitted to Screen and Baseline if they score ≥ 28 (representing normal cognition; Larner, 2013) on the MMSE at each of these respective visits. For Part C (PD participants), the minimum acceptable value will be 26. The MMSE takes about 5-10 minutes to administer and is conducted by an investigator with experience conducting this scale as delegated by the Primary Investigator.

11.8. Adverse and Serious Adverse Events

11.8.1. Definition of Adverse Events

11.8.1.1. Treatment Emergent Adverse Event (TEAE)

A TEAE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

All TEAEs that occur after any subject has been enrolled, during treatment or within 14 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by Inhibikase Therapeutics or designee. AEs occurring more than once will be

reported as a single AE with maximum severity with the onset date recorded as the occurrence of the first event.

Examples of TEAEs are as follows:

- Changes in the general condition of the subject
- Subjective symptoms offered by or elicited from the subject
- Objective signs observed by the PI or other study personnel
- All diseases that occur after the first dose of study drug
- All clinically significant abnormalities in laboratory values or clinically significant physical findings that occur after the first dose of study drug

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Suspected adverse reactions are any AEs for which there is a reasonable possibility that the drug caused the AE.

11.8.1.2. Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening (see Section 10.8.1.2.1)
- It requires in-subject hospitalization or prolongation of existing hospitalization
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

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

All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or within 14 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by Inhibikase Therapeutics or designee.

11.8.1.2.1. Life-threatening

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

11.8.1.3. Unexpected

An AE or suspected adverse reaction is considered "unexpected":

- If it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

In the clinical trial setting, the term "expected" would not mean "anticipated" for the condition being treated or population being studied since "expected" would indicate being "listed in the Investigator's Brochure." For example, some AEs can be anticipated to occur as a result of a disease or condition or in a certain population (e.g., cancer-related deaths in a cancer trial, strokes or acute myocardial infarctions in an older population).

However, for reporting purposes, these anticipated events are not considered "expected" if they are not listed in the Investigator's Brochure (i.e., the investigational drug is not suspected or known to cause them).

11.8.2. Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

11.8.2.1. Pregnancy

Pregnancy in itself is not regarded as an AE. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.
Any pregnancy from female partner occurring during this study will be reported within 24 hours of notification of the Investigator. The Investigator will promptly notify the Medical Monitor and

withdraw the subject from the study. The Investigator should request permission to contact the subject, the subject's spouse/partner (if the subject is male and his spouse/partner becomes pregnant) or the obstetrician for information about the outcome of the pregnancy, and in the case of a live birth, about any congenital abnormalities.

11.9. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

Guidelines for Assigning Relationship of the AE to the Study Drug

Not Related:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possibly Related:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probably Related:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

11.10. Action Taken with Investigational Drug

Action taken with regard to administration of study drug will be recorded.

11.11. Assessment of Outcome

Assessment of outcome of AEs will be categorized as one of the following:

- Recovered/Resolved: The event has improved or recuperated
- Recovering/Resolving: The event is improving
- Not Recovered/Not Resolved: The event has not improved or recuperated
- Recovered/Resolved with Sequelae: The subject recuperated but retained pathological conditions resulting from the prior disease or injury
- Fatal: The termination of life as a result of an adverse event
- Unknown: Not known, not observed, not recorded, or refused.

11.12. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs unless they prompt corrective medical action by the Investigator, constitute an SAE or lead to discontinuation of administration of study drug.

Information about AEs will be collected from the signing of the consent form until the final visit of the study for that subject. Adverse events that occur after the first administration of study drug will be denoted Treatment Emergent Adverse Events. All AEs will be followed until they are resolved or have reached a clinical plateau with no expectation of future change.

The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution or clinical plateau (date and time), intensity, causality, action taken, outcome, and whether or not it caused the subjectto discontinue the study.

Severity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 10.8.1.2. An AE of severe intensity may not necessarily be considered serious.

11.13. Reporting Adverse Events

All SAEs (regardless of causality) will be recorded from the signing of the consent form until 14 days following the last dose of study drug. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to Inhibikase Therapeutics or Inhibikase's designee within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy to Inhibikase Therapeutics or designee.

Additional follow-up information, if required or available, should all be sent (fax, e-mail, etc.) to Inhibikase Therapeutics or designee within 24 hours of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

Inhibikase Therapeutics or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the PI's responsibility to notify the IRB of all SAEs that occur at his or her site if applicable per the IRB's requirements. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB of these additional SAEs.

Reporting to FDA

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32[c][1][i]). Before submitting an IND safety report, the Sponsor will ensure the event meets all 3 of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all 3 of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the AE and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence of serious suspected adverse reactions over that listed in the protocol or Investigator's Brochure.

12. STATISTICS

12.1. General Principles

The below mentioned general principles will be followed throughout the study:

- A detailed description of the analysis methods to be performed in the study will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized andapproved prior to the database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the clinical study report.
- All summaries (safety, tolerability and PK) will be presented by the groups subjects are randomized to and on each schedule time point.
- For vital signs, the baseline value is defined as the last value observed prior to first administration of study medication on Day 1. For other safety variables the baseline value is defined as the value observed on Day -1. If for a subject the Day -1 value is missing, then Screening value will be considered as baseline.
- The change from baseline is defined as the post-baseline value minus the baseline value.
- Missing data will not be imputed but will be analyzed as missing.
- Descriptive statistics will include number of non-missing patients (n), mean, standard deviation (SD), median, minimum, and maximum values for continuous variables, and for categorical variables the frequencies and percentages of patients will be presented.
- For continuous safety data, mean and median will be rounded to 1 additional decimal place, SD will be rounded to 2 additional decimal places compared to the original data and minimum and maximum will be displayed with the same accuracy as the original data, except the baseline and demographic characteristic.
- For continuous baseline and demographic characteristic data, mean and median will be rounded to 1 decimal place, SD will be rounded to 2 decimal places and minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- In addition, for PK data, arithmetic mean, geometric mean, SD and coefficient of variation (CV%) will be rounded to 3 significant figures.
- For the PK analysis, plasma and urine concentrations that are reported as below the limit of quantification of the assay (BLQ) will be treated as zero if they occur before T_{max} and will be treated as missing thereafter.
- The number of BLQ values i.e., the n below lower limit of quantification (LLOQ) will be reported for each time point.
- All study data will be included in study data listings. In general, all data will be listed by time point within subject. All summary tables will present descriptive statistics for the parameters being analyzed.
- No adjustment will be done for multiple comparisons in this study as this is exploratory study.
- SAS® version 9.4 or higher will be used for all analyses.

12.2. Populations

The Pharmacokinetic (PK) Population is defined as all subjects who are administered IkT-148009 and have at least one bioanalysis result for the plasma concentration of IkT-148009.

The Safety Population is defined as all subjects who are administered study drug.

12.3. Sample Size Calculation

No formal sample size calculations have been undertaken for this pharmacokinetic, safety and tolerability study. The number of subjects in each cohort and at each dose level is thought to be sufficient to assess preliminary pharmacokinetic profile of IkT-148009 in addition to safety and tolerability following single or multiple doses of IkT-148009. No efficacy parameters are being collected or analyzed for this Phase I study.

This study is not powered for direct inferential statistical analyses.

12.4. Safety Analysis

Safety assessments will include TEAEs tabulated by cohort; descriptive statistics for continuous variables and frequency counts for discrete variables. No inferential statistical analysis is planned for safety data.

The number and percentage of subjects reporting TEAEs will be tabulated for the safety analyses set by MedDRA preferred term and system organ class with a breakdown by treatment, and further by relationship to study drug, as well as by maximum severity. Listings of deaths, SAEs, and TEAEs that lead to discontinuation of a subject will be presented.

For laboratory data, a treatment-emergent abnormal value is an abnormality that was not present before dosing, but was present after dosing, or one that represents an exacerbation of a pre-existing abnormal value.

All clinical laboratory data will be listed by subject for the safety analysis set, with abnormal lab results presented by subject in another listing. Descriptive statistics will be provided for baseline, end of study and for other times during the study if appropriate.

Vital signs will be listed at each time point for all subjects in the safety analysis set. Clinically significant findings on Safety and Cardiodynamic ECG will be recorded as TEAEs, coded, listed and tabulated. Physical examination findings including neurological examination findings will be listed for all subjects in the safety analysis set. Clinically significant findings will be included as TEAEs.

No imputation of values for missing data will be performed. Standard clinical monitoring and data management practices will be used to ensure the integrity of data.

For all safety analyses, the placebo dose group will be pooled across cohorts. AEs will be coded using MedDRA™ with the version used specified in the clinical study report. The overall incidence of AEs will be displayed by System Organ Class (SOC), preferred term, and dose group.Incidence of AEs will also be presented by maximum severity and relationship to study drug. Datafrom vital signs, clinical laboratory measures, Safety and Cardiodynamic ECGs will be summarized using descriptive statistics by dose group and time point, where applicable. Continuous endpoints will be summarized with n, mean, standard deviation, median, minimum and maximum. In addition, change from baseline values will be calculated at each time point andwill be summarized using descriptive statistics. Out-of-range safety endpoints may be categorizedas low or high, where applicable. For all categorical endpoints, summaries will include counts andpercentages.

12.5. Pharmacokinetic Analysis

PK parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentration (T_{max}) will be summarized using n, mean, standard deviation, median, minimum, and maximum. All other PK parameters will be summarized using n, geometric mean, coefficient of variation, median, minimum, and maximum.

Dose proportionality will be analyzed using a generalized ANOVA model using the logarithm of PK parameter (AUC, C_{max} and C_{trough}) as the dependent variable and the logarithm of the dose as the independent variable (Weerahandi, 1994; Ogenstad, 1998). Point estimates and the corresponding generalized CIs will be estimated for AUC, C_{max} and C_{trough}. For AUC, C_{max} and C_{trough}, the treatment ratio 'test/reference' will be calculated by taking the anti-logarithm of the difference between treatment means. A 90% confidence interval will be constructed for the geometric mean test-to-reference ratio for AUC, C_{max} and C_{trough}. Apparent clearance and apparent volume of distribution will be estimated by using the population pharmacokinetic (PPK) approach. Further details of the above analyses will be provided in the SAP.

Data from subjects who experience emesis will be deleted from statistical analyses if vomiting occurs at or before two times the median T_{max}.

Statistical software for the analysis will be SAS version 9.4 (SAS Institute) or later and XPro (X-Techniques, Inc.).

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Inhibikase Therapeutics or designee will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to the protocol adherence, and the responsibilities of Inhibikase Therapeutics or designee or its representatives. This will be documented in a Clinical Study Agreement between Inhibikase Therapeutics and the Investigator.

During the study, a monitor from Inhibikase Therapeutics or designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Inhibikase Therapeutics or designee.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Inhibikase Therapeutics or designee and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

13.2. Audits and Inspections

Authorized representatives of Inhibikase Therapeutics, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an Inhibikase Therapeutics or designee audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH), and any applicable

regulatory requirements. The Investigator should contact Inhibikase Therapeutics immediately if contacted by a regulatory agency about an inspection.

13.3. Institutional Review Board (IRB)

The PI must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator and institution will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Inhibikase Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

15. ETHICS

15.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form (ICF), must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Inhibikase Therapeutics or designee before he or she can enroll any subject/subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Inhibikase Therapeutics or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

15.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Appendix 8) and are consistent with ICH/Good Clinical Practice and other applicable regulatory requirements.

15.3. Written Informed Consent

The PI will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The PI must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

Inhibikase Therapeutics or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

16.2. Retention of Records

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Inhibikase Therapeutics or designee or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

16.3. Confidentiality

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Inhibikase Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

17. PUBLICATION POLICY

All information concerning IkT-148009 is considered confidential and shall remain the sole property of Inhibikase Therapeutics.

Inhibikase and the Investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Inhibikase and the Investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the Investigators or their personnel and associates resulting from or relating to this study must be submitted to Inhibikase for review and approval before submission for publication or presentation. If the proposed publication or presentation contains patentable subject matter, which, at Inhibikase' sole discretion, warrants intellectual property protection, Inhibikase may delay any publication or presentation for up to 30 days after approval for the purpose of pursuing such protection.

18. LIST OF REFERENCES

S. Brahmachari, P. Ge, S. H. Lee, D. Kim, S. S. Karuppagounder, M. Kumar, X. Mao, J. H. Shin, Y. Lee, O. Pletnikova, J. C. Troncoso, V. L. Dawson, T. M. Dawson, H. S. Ko, Activation of tyrosine kinase c-Abl contributes to α-synuclein-induced neurodegeneration. J Clin Invest. 126, 2970-88 (2016).

S. Brahmachari, S. S. Karuppagounder, P. Ge, S. Lee, V. L. Dawson, T. M. Dawson, H. S. Ko, c-Abl and Parkinson's Disease: Mechanisms and Therapeutic Potential. J Parkinsons Dis. 7, 589-601 (2017).

G. I. Cancino, E. M. Toledo, N. R. Leal, D. E. Hernandez, L. F. Yévenes, N. C. Inestrosa, A. R., STI571 prevents apoptosis, tau phosphorylation and behavioural impairments induced by Alzheimer's beta-amyloid deposits of article. Brain 131, 2425–2442 (2008).

W. Dauer, S. Przedborski, Parkinson’s disease: mechanisms and models. Neuron. 39, 889–909 (2003).

T. M. Dawson, V. L. Dawson, J. Fan, Cell Death Mechanisms of Neurodegeneration. Adv Neurobiol. 15, 403-425 (2017).

T. M. Dawson, H. S. Ko, V. L. Dawson, Genetic animal models of Parkinson’s disease. Neuron. 66, 646–661 (2010).

G. S. Gaki, A. G. Papavassiliou, Oxidative stress-induced signaling pathways implicated in the pathogenesis of Parkinson's disease. Neuromolecular Med. 16, 217-30 (2014).

M. Goedert, α-Synuclein and neurodegenerative diseases. Nat Rev Neurosci. 2, 492–501 (2001).

M. Goedert, M. G. Spillantini, K. Del Tredici, H. Braak, 100 years of Lewy pathology. Nat Rev Neurol. 9, 13–24 (2013).

M. L. Hebron, I. Lonskaya, C. E. Moussa, Nilotinib reverses loss of dopamine neurons and improves motor behavior via autophagic degradation of α-synuclein in Parkinson's disease models. Hum Mol Genet. 22, 3315-28 (2013).

S. Z. Imam, W. Trickler, S. Kimura, Z. K. Binienda, M. G. Paule, W. Slikker Jr, S. Li, R. A. Clark, S. F. Ali, Neuroprotective efficacy of a new brain-penetrating C-Abl inhibitor in a murine Parkinson’s disease model. *PLoS One*. **8**, e65129 (2013).

S. Z. Imam, Q. Zhou, A. Yamamoto, A. J. Valente, S. F. Ali, M. Bains, J. L. Roberts, P. J. Kahle, R. A. Clark, S. Li, Novel regulation of parkin function through c-Abl-mediated tyrosine phosphorylation: implications for Parkinson’s disease. J Neurosci. 31,157–163 (2011).

K. A. Jellinger, Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. Mov Disord 27, 8–30 (2012).

Z. Jing, J. Caltagarone, R. Bowser Altered subcellular distribution of c-Abl in Alzheimer's disease of article. J Alzheimers Dis. 17,409–422 (2009).

S. S. Karuppagounder, S. Brahmachari, Y. Lee, V. L. Dawson, T. M. Dawson, H. S. Ko,The c-Abl inhibitor, nilotinib, protects dopaminergic neurons in a preclinical animal model of Parkinson's disease. Sci Rep. 4,4874 (2014).35. Weerahandi, S. (1994) Exact Statistical Methods for Data Analysis, New York: Springer-Verlag.

D. Kirik, A. Bjorklund, Modeling CNS neurodegeneration by overexpression of disease-causing proteins using viral vectors. Trends Neurosci 26,386–392 (2003).

H. S. Ko, Y,. Lee, J. H. Shin, S. S. Karuppagounder, B. S. Gadad, A. J. Koleske, O. Pletnikova, J. C. Troncoso, V. L. Dawson, T. M. Dawson, Phosphorylation by the c-Abl protein tyrosine kinase inhibits parkin's ubiquitination and protective function. Proc Natl Acad Sci U S A. 107,16691–16696 (2010).

Kuo YM, Li Z, Jiao Y, Gaborit N, Pani AK, Orrison BM, Bruneau BG, Giasson BI, Smeyne RJ, Gershon MD, Nussbaum RL. Extensive enteric nervous system abnormalities in mice transgenic for artificial chromosomes containing Parkinson disease-associated alpha-synuclein gene mutations precede central nervous system changes. Hum Mol Genet. 19, 1633-50 (2010).

Lacy BE, Levenick JM, Crowell M. Chronic constipation: new diagnostic and treatment approaches. Ther Adv Gastoenterol 5:233-247 (2012).

V. M. Lee, J. Q. Trojanowski, Mechanisms of Parkinson's disease linked to pathological alpha-synuclein: new targets for drug discovery. Neuron. 52, 33–38 (2006).

I. Lonskaya, M. L. Hebron, S. T. Selby, R. S. Turner, C. E. Moussa, Nilotinib and bosutinib modulate pre-plaque alterations of blood immune markers and neuro-inflammation in Alzheimer's disease models. Neuroscience 304, 316-27 (2015).

I. Lonskaya, M. L. Hebron, N. M. Desforges, A. Franjie, C. E. Moussa, Tyrosine kinase inhibition increases functional parkin-Beclin-1 interaction and enhances amyloid clearance and cognitive performance. EMBO Mol Med. 5, 1247-62 (2013).

K. C. Luk, V. Kehm, J. Carroll, B. Zhang, P. O'Brien, J. Q. Trojanowski, V. M. Lee, Pathological α-synuclein transmission initiates Parkinson-like neurode- generation in nontransgenic mice. Science. 338, 949–953 (2012).

X. Mao, M. T. Ou, S. S. Karuppagounder, T. I. Kam, X. Yin, Y. Xiong, P. Ge, G. E. Umanah, S. Brahmachari, J. H. Shin, H. C. Kang, J. Zhang, J. Xu, R. Chen, H. Park, S. A. Andrabi, S. U. Kang, R. A. Gonçalves, Y. Liang, S. Zhang, C. Qi, S. Lam, J. A. Keiler, J. Tyson, D. Kim, N. Panicker,

S. P. Yun, C. J. Workman, D. A. Vignali, V. L. Dawson, H. S. Ko, T. M. Dawson, Pathological α-synuclein transmission initiated by binding lymphocyte-activation gene 3. Science 353, (2016).

E. Masliah, E. Rockenstein, I. Veinbergs, M. Mallory, M. Hashimoto, A. Takeda, Y. Sagara, A. Sisk, L. Mucke, Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders. Science 287,1265– 1269 (2000).

I. Martin, V. L. Dawson, T. M. Dawson, Recent advances in the genetics of Parkinson's disease. Annu Rev Genomics Hum Genet. 12, 301–325 (2011).

Ogenstad, S. The Use of Generalized Tests in Medical Research. Journal of Biopharmaceutical Statistics, 8(4), 497-508, 1998.

C. W. Olanow, P. Brundin, Parkinson's disease and alpha synuclein: is Parkinson's disease a prion-like disorder? Mov Disord. 28, 31-40 (2013)

C. W. Olanow, S. B. Prusiner, Is Parkinson's disease a prion disorder. Proc Natl Acad Sci U. S. A. 106,12571–12572 (2009).

M. H. Polymeropoulos, C. Lavedan, E. Leroy, S. E. Ide, A. Dehejia, A. Dutra, B. Pike, H. Root, J. Rubenstein, R. Boyer, E. S. Stenroos, S. Chandrasekharappa, A. Athanassiadou, T. Papapetropoulos, W. G. Johnson, A. M. Lazzarini, R. C. Duvoisin, G. Di Iorio, L. I. Golbe, R. L. Nussbaum, Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276, 2045–2047 (1997).

Rentz AM, Kahrilas P, Stanghellini V, *et al*. Development and psychometric evaluation of the patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM) in patients with upper gastrointestinal disorders. Qual Life Res. 2004;13:1737‑1749.

J.M. Savitt, V. L. Dawson, T. M. Dawson, Diagnosis and treatment of Parkinson disease: molecules to medicine. J Clin Invest. 116, 1744–1754 (2006).

A. H. V. Schapira, C. W. Olanow, J. T. Greenamyre, E. Bezard, Slowing of neurodegeneration in Parkinson's disease and Huntington's disease: future therapeutic perspectives. Lancet 384, 545-555 (2014).

M. G. Spillantini, M. L. Schmidt, V. M. Lee, J. Q. Trojanowski, R. Jakes, M. Goedert M, Alpha-synuclein in Lewy bodies. Nature 388, 839–840 (1997).

M. A. Tremblay, C. M. Acker, P. Davies, Tau phosphorylated at tyrosine 394 is found in Alzheimer's disease tangles and can be a product of the Abl-related kinase, Arg. J Alzheimers Dis. 19, 721–733 (2010).

Weerahandi, S. Exact Statistical Methods for Data Analysis, New York: Springer-Verlag. 1994.

B. Winner, R. Jappelli, S. K. Maji SK, P. A. Desplats , L. Boyer, S. Aigner , C. Hetzer, T. Loher, M. Vilar, S. Campioni S, C. Tzitzilonis , A. Soragni, S. Jessberger, H. Mira, A. Consiglio, E. Pham, E. Masliah, F. H. Gage, R. Riek, In vivo demonstration that alpha-synuclein oligomers are toxic. Proc Natl Acad Sci USA 108: 4194–4199 (2011).

X-Techniques, Inc: XPro: Exact Procedures for Parametric Inference, X-Techniques, Inc., Millington, NJ, 1994.

Folstein, M., Folstein, S. E., & McHugh, P. R., Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12, 189-198 (1975).

Larner, A. J. (Ed.) Cognitive screening instruments: A practical approach. NY: Springer. (2013).

Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N; Movement Disorder Society UPDRS Revision Task Force. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008 Nov 15;23(15):2129-70. doi: 10.1002/mds.22340. PMID: 19025984.

Guy, W. "Clinical Global Impressions". *ECDEU Assessment Manual for Psychopharmacology—Revised*. Rockville, MD: U.S. Department of Health, Education, and Welfare; Public Health Service, Alcohol; Drug Abuse, and Mental Health Administration; National Institute of Mental Health; Psychopharmacology Research Branch; Division of Extramural Research Programs. 1976, pp. 218-222. OCLC 2344751. DHEW Publ No ADM 76–338 – via Internet Archive.

Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, Ondo W, Abe K, Macphee G, Macmahon D, Barone P, Rabey M, Forbes A, Breen K, Tluk S, Naidu Y, Olanow W, Williams AJ, Thomas S, Rye D, Tsuboi Y, Hand A, Schapira AH. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. Mov Disord. 2007 Oct 15;22(13):1901-11. doi: 10.1002/mds.21596. PMID: 17674410.

Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Qual Life Res. 1995 Jun;4(3):241-8. doi: 10.1007/BF02260863. PMID: 7613534.

19. APPENDICES

APPENDIX 1. SCHEDULE OF EVENTS FOR PART A (SAD COHORTS)

Appendix 1. Schedule of Events for Part A (SAD Cohorts)

Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Visit Window	**D-28 to D-1**	**D-1**	**0 to +24h**	**+24h to +48h**	**+48h to +72h**	**+72h to +96h**	**V2+7d (±1d)**	**V2+14d (±1d)**
Visit Days	**Screen**		**D1**	**D2**	**D3**	**D4**	**Follow Up**	**End of Study**
Informed Consent	X							
Inclusion/Exclusion	X							
Demographics	X							
Medical History	X							
Physical Examination / Neurological Exam	X						X	X
MMSE[10]	X	X				X		
Body Weight/Height/Fluid intake/Urine output[9]	X	X	X	X	X	X	X	X
CBC/Serum Chemistry[1]	X	X	X	X		X	X	X
FSH/LH/testosterone/inhibin B[2]	X	X		X			X	X
Urinalysis[1]	X	X		X	X		X	
Drug/Alcohol Screen[3]	X	X						
Hepatitis & HIV Screen	X							
Vital Signs[4]	X		X	X	X	X	X	X
Pulse oximetry	X		X	X	X	X	X	X
12-Lead Safety ECG[5]	X	X	X	X	X	X	X	X
Cardiodynamic[6]			X					

Chest x-ray and Echocardiogram		X						
Plasma PK Samples[7]			X	X	X	X	X	X
Urine PK Samples[7]			X	X	X			
Confined to Unit			X	X	X	X		
C-SSRS	X		X			X	X	X
Administer Study Drug			X					
Adverse Events[9]	X	X	X	X	X	X	X	X
Concomitant Meds[9]	X	X	X	X	X	X	X	X
Study Completion								X

[1]Screening and Safety Laboratory Tests: V1 (Screening and Day -1 [Admission]); V3 pre-dose; V4 24h post-dose; V6 72h post-dose; V7 and V8. To be performed prior to dosing, but after the last baseline cardiodynamic EPQT 12-lead Safety ECG reading. Urinalysis will be performed at Screening and Day -1, 24 hours and 72 hours post dose, and follow-up V7.

[2]At screening, baseline, 24 hr post-dose, follow-up and end of study. FSH/LH/Inhibin B/Testosterone to be tested in both genders.

[3]Urine drug screen and alcohol breathalyzer will be conducted at Visit 1 during Screening and Day -1 (Admission).

[4]Vital Signs: V1 (Screening and Day -1 ([Admission]), V3 pre-dose and post-dose 15, 30 and 60 minutes, and 2, 4, 6, 8, 12, 18 and 24 hours; V4 - 28, 32, 36, and 48 hours after dosing; V5 - 60 and 72 hours after dosing; V6; V7 and V8.

[5]12-Lead Safety ECG: V1 Screening and Day -1 (Admission), V3 pre-dose and post-dose 1, 2, 4, 8, 12 and 24 hours; V4: 36 and 48 hours after dosing; and V5 - 72 hours after dosing; V7 and V8. Standardized meal or snack must be completed at least 60 min before any Holter recording extractions and/or safety 12-lead ECG tracings.

[6]Holter monitors will be used to collect continuous cardiodynamic samples on Day 1 over approximately 24 hours. Three pre-dose timepoints will be collected at 45 min, 30 min, and 15 min prior to dosing. EPQT, 12-lead Safety ECG recordings will be extracted from the Holter monitor data within a 5-min time window prior to the PK blood samples collected as close to the exact time point as possible. Standardized meal or snack must be completed at least 60 min before any Holter recording extractions and/or safety 12-lead ECG tracings. Cardiodynamic measurements are to be taken post safety ECG, but prior to PK blood samples.

[7]Plasma PK samples; V3: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), 12 (+/- 30 min), 16 (+/-1hr) and 24 hours (+/-1hr); V4: 48 hours post dose (+/-2 hr); V5: 72 hours post dose (+/-2h r); V6: 96 hours post dose (+/- 2hr); V7 and V8. To be performed prior to dosing, but after the last baseline cardiodynamic or EPQT 12-lead Safety ECG reading. Urine PK samples will collect 24-hour pooled urines on the indicated days.

[8]Adverse Events and concomitant medications (new or changed) will be collected during Visit 1 at both Screening and Day -1 (Admission) in addition to the other time points noted in the Schedule of Events.

[9] Height is measured only at screening. Weight is collected daily. Fluid intake/Urinary output volumes collected from 0 hour to 72 hour.

[10]The MMSE is administered at screening and repeated pre-dose at V2 to ensure the MMSE inclusion criteria is met. The MMSE is repeated at approximately the same time of day (+/-1 hour) on V6 as it was administered at V2. The MMSE is administered again at V8 only if the MMSE score at V6 was considered clinically and meaningfully different then baseline, per investigator's clinical judgment, than it was at the V2 administration.

APPENDIX 2. SCHEDULE OF EVENTS FOR PART B (MAD COHORTS)

Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Visit Window	**D-28 to D-1**	**D-1**	**0 to +24h**	**+24h to +48h**	**+48h to +72h**	**+72h to +96h**	**+96 to +120h**	**+120 to +144h**	**+144 to +168h**	**+168 to +192h**	**+192 to 216h**			**D14 (±1d) Follow -up**	**D21 (±1d) End of Study**
Visit Days	**Screen**		**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**Follow Up**	**End of Study**
Informed Consent	X														
Inclusion/Exclusion	X														
Demographics	X														
Medical History	X														
MMSE[11]	X	X							X						X
Physical Examination / Neurological Examination	X					X					X				X
Body Weight/Height/Fluid intake/Urine output[10]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
CBC/Serum Chemistry[1]	X	X	X	X	X	X	X	X		X	X			X	X
FSH/LH/testosterone/inhibin B[2]	X	X		X						X				X	X
Urinalysis[1]	X	X		X						X					X
Drug/Alcohol Screen[3]	X	X													
Hepatitis & HIV Screen	X														
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pulse oximetry	X	X	X	X	X	X	X	X	X	X	X	X		X	X

12-Lead Safety ECG[5]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Chest x-ray and Echocardiogram		X													
Plasma PK Samples[6]			X	X		X		X	X	X	X	X	X		
CSF collection[8]									X						
Biomarker screen[7]		X								X					
Urine PK Samples[6]			X						X						
Confined to Unit			X	X	X	X	X	X	X	X	X	X	X		
C-SSRS	X		X			X			X					X	X
Administer Study Drug			X	X	X	X	X	X	X						
Adverse Events[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion															X

[1]Screening and Safety Laboratory Tests: V1; V2; V3: pre-dose; V4: pre-dose; V5: pre-dose; V6: pre-dose; V7: pre-dose; V8: pre-dose; V10: 24 hr post-V9 dose; V11: 48 hr post-V9 dose; V14 and V15. Urinalysis will be performed at V1, V2, V4: pre-dose; V10: 24 hr post-V9 dose, and V15.

[2]At screening, baseline, 24 hours after D1 dosing but before dosing on D2, 24 hours after last dose, follow-up and end of study. FSH/LH/Inhibin B/Testosterone to be tested in both genders.

[3]Urine drug screen and alcohol breathalyzer will be conducted at Visit 1 during Screening and Day -1 (Admission).

[4]Vital Signs: V1, V2, V3: pre-dose and post-dose at: 1hr, 2 hr, 4 hr, 8 hr, 12 hr, 18 hr; V4: pre-dose and post-dose at 4 hr, 8 hr, 12 hr; V5: pre-dose and post-dose 12 hr; V6: pre-dose and post-dose 12 hr; V7: pre-dose and post-dose 12 hr; V8: pre-dose and post-dose 12 hr; V9: pre-dose and post-dose 12 hr; V10: 24 hr post-V9 dose; V11: 48 hr post-V9 dose; V12: 72 hours post-V9 dose; V14 and V15.

[5]12-Lead Safety ECG: V1; V2; V3 pre-dose and post-dose at 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, V4: pre-dose and 12 hr post-dose; V5: pre-dose and 12 hr post-dose; V6: pre-dose and 12 hr post-dose; V7: pre-dose and 12 hr post-dose; V8: pre-dose and 12 hr post-dose; V9: pre-dose and 12 hr post-dose; V10: 24 hr post-V9 dose; V11: 48 hr post-V9 dose; V12: 72 hr post-V9 dose; V14 and V15.

[6]Plasma PK samples; V3: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), 12 (+/- 30 min), 16 (+/-1hr); V4: pre-dose (-15 min), 2 hr (+/- 30 min), 5 hr (+/- 30 min), 8 hr (+/- 30 min); V6: pre-dose (-15 min), 2 hr (+/- 30 min), 5 hr (+/- 30 min), 8 hr (+/- 30 min); V8: pre-dose (- 15 min); V9: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), and 16 (+/-1hr); V10: 24 hr post-V9 dose +/- 1 hr; and V11: 48 hr post-V9 dose +/- 1 hr; V12: 72 hr post-V9 dose +/- 2 hr; V13: 96 hr post-V9 dose +/- 2 hr . Urine PK samples will collect 24-hour pooled urines on the indicated days. The 24-hour collection on Day 1 starts at dosing and collected for 24 hours prior to next day's dose. The 24-hour collection on Day 7 starts at dosing and collected for 24 hours prior to the next day's dose.

[7]Biomarker screen for CNS derived exosomes: Day -1 (Admission) pre-dose and V10.
[8]CSF collection V9 **prior** to dose on last dosing day.
[9]Adverse Events and concomitant medications (new or changed) will be collected during Visit 1 at both Screening and Day -1 (Admission) in addition to the other time points noted in the Schedule of Events.
[10]Height is measured only at screening. Weight is collected daily. Fluid intake/Urinary output volumes collected from 0 hour to 192 hour.
[11]The MMSE is administered at screening and repeated pre-dose at V2 to ensure the MMSE inclusion criteria is met. The MMSE is repeated at approximately the same time of day (+/-1 hour) on V9 as it was administered at V2. The MMSE is administered again at V15 (End of Study) only if the MMSE score at V9 was significantly different, per investigator clinical judgment, than it was at the V2 administration or upon early termination of the subject.

APPENDIX 3. SCHEDULE OF EVENTS FOR PART C (PD MAD COHORTS)

Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Visit Days	**Screen**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D14 (±1d) Follow -up**	**D21 (±1d) End of Study**
Informed Consent	X														
Inclusion/Exclusion	X														
Demographics	X														
Medical History	X														
MMSE[11]	X	X							X						X
MDS-UPDRS III[12]		X	X						X					X	X
ON/OFF Diary[12] assessment			X						X						
MDS-UPDRS I + II[12]		X							X					X	X
CGI-I and PGIC										X				X	X
PDQ-39[12]		X								X				X	X
PGI-S[12]		X								X				X	X
CSBM, PAGI-SYM[12]		X								X				X	X
NMSS[13]		X							X					X	X
BDI-II	X	X													
Physical Examination / Neurological Examination	X					X					X				X

Body Weight/Height/Fluid intake/Urine output[10]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
FSH/LH/testosterone/inhibin B[2]	X	X		X						X				X	X
CBC/Serum Chemistry[1]	X	X	X	X	X	X	X	X		X	X			X	X
Urinalysis[1]	X	X		X						X					X
Drug/Alcohol Screen[3]	X	X													
Hepatitis & HIV Screen	X														
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pulse oximetry	X	X	X	X	X	X	X	X	X	X	X	X		X	X
12-Lead Safety ECG[5]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Chest x-ray		X													
Plasma PK Samples[6]			X	X		X		X	X	X	X	X	X		
CSF collection[8]									X						
Biomarker screen[7]		X								X					
Urine PK Samples[6]			X						X						
Confined to Unit			X	X	X	X	X	X	X	X	X	X	X		
C-SSRS	X		X			X			X					X	X
Administer Study Drug			X	X	X	X	X	X	X						
Adverse Events[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Completion															X

[1]Screening and Safety Laboratory Tests: V1; V2; V3: pre-dose; V4: pre-dose; V5: pre-dose; V6: pre-dose; V7: pre-dose; V8: pre-dose; V10: 24 hr post-V9 dose; V11: 48 hr post-V9 dose; V14 and V15. Urinalysis will be performed at V1, V2, V4: pre-dose; V10: 24 hr post-V9 dose, and V15.

[2]At screening, baseline, 24 hours after D1 dosing but before dosing on D2, 24 hours after last dose, follow-up and end of study. FSH/LH/Inhibin B/Testosterone to be tested in both genders.

[3]Urine drug screen and alcohol breathalyzer will be conducted at Visit 1 during Screening and Day -1 (Admission).

[4]Vital Signs: V1, V2, V3: pre-dose and post-dose at: 1hr (+/-15 min), 2 hr (+/-15 min), 4 hr (+/-15 min), 8 hr (+/-15 min), 12 hr (+/-15 min), 18 hr (+/-15 min); V4: pre-dose and post-dose at 4 hr (+/-15 min), 8 hr (+/-15 min), 12 hr (+/-15 min); V5: pre-dose and post- dose 12 hr (+/-15 min); V6: pre-dose and post-dose 12 hr (+/-15 min); V7: pre-dose and post-dose 12 hr (+/-15 min); V8: pre-dose and post-dose 12 hr (+/-15 min); V9: pre-dose and post-dose 12 hr (+/-15 min); V10: 24hr post-V9 dose (+/-15 min); V11: 48 hr post-V9 dose (+/-15 min); V12: 72 hours post-V9 dose (+/-15 min); V14 and V15.

[5]12-Lead Safety ECG: V1; V2; V3 pre-dose and post-dose at 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, V4: pre-dose and 12 hr post-dose; V5: pre-dose and 12 hr post-dose; V6: pre-dose and 12 hr post-dose; V7: pre-dose and 12 hr post-dose; V8: pre-dose and 12 hr post-dose; V9: pre-dose and 12 hr post-dose; V10: 24 hr post-V9 dose; V11: 48 hr post-V9 dose; V12: 72 hr post-V9 dose; V14 and V15.

[6]Plasma PK samples; V3: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), 12 (+/- 30 min), 16 (+/-1hr); V4: pre-dose (-15 min), 2 hr (+/- 30 min), 5 hr (+/- 30 min), 8 hr (+/- 30 min); V6: pre-dose (-15 min), 2 hr (+/- 30 min), 5 hr (+/- 30 min), 8 hr (+/- 30 min); V8: pre-dose (- 15 min); V9: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), and 16 (+/-1hr); V10: 24 hr post-V9 dose +/- 1 hr; and V11: 48 hr post-V9 dose +/- 1 hr; V12: 72 hr post-V9 dose +/- 2 hr; V13: 96 hr post-V9 dose +/- 2 hr . Urine PK samples will collect 24-hour pooled urines on the indicated days. The 24-hour collection on Day 1 starts at dosing and collected for 24 hours prior to next day's dose. The 24-hour collection on Day 7 starts at dosing and collected for 24 hours prior to the next day's dose.

[7]Biomarker screen for CNS derived exosomes: Day -1 (Admission) pre-dose and V10.

[8]CSF collection V9 **prior** to dose on last dosing day.

[9]Adverse Events and concomitant medications (new or changed) will be collected during Visit 1 at both Screening and Day -1 (Admission) in addition to the other time points noted in the Schedule of Events.

[10]Height is measured only at screening. Weight is collected daily. Fluid intake/Urinary output volumes collected from 0 hour to 192 hour. (Visit 3 through Visit 11).

[11]The MMSE is administered at screening and repeated pre-dose at V2 to ensure the MMSE inclusion criteria is met. The MMSE is repeated at approximately the same time of day (+/-1 hour) on V9 as it was administered at V2. The MMSE is administered again at V15 (End of Study) only if the MMSE score at V9 was significantly different, per investigator clinical judgment, than it was at the V2 administration or upon early termination of the subject.

[12] In Part C, eligible PD participants will arrive the evening before initiation of study drug dosing. MDS-UPDRS, Part I and Part II will be assessed. No anti-parkinsonian medication will be given after midnight (V2). The following morning (Day 1/V3), they will be clinically assessed in the practically-defined OFF state using MDS-UPDRS Part III before administration of IkT-148009. MDS-UPDRS Part III will be administered at 1 (+/-15 min), 2 (+/-15 min), 3 (+/-15 min), 4 (+/-15 min), and 6 hours (+/-15 min) after dosing on Day 1. ON, ON with and without troublesome dyskinesias, and OFF will be documented every 30 minutes during waking hours on Day 1. If participants do not turn ON by 6 hours, usual PD medications will resume. If at any point before 6 hours participants and the Investigator feel PD medications are necessary, they may begiven. PD medications will be given as usual on Days 2 through up to Day 11, with PD medications held after midnight on the day before the last IkT-148009 dose. On the morning of the last dose, participants will again be evaluated in the practically-defined OFF state before resuming usual PD medications that morning. After study activities, they will be discharged from clinic. PD assessments will be conducted at Follow-Up (V14), and the End-Of Study Visit (V15). These will not involve practically-defined OFF motor evaluations as done previously, but participants will hold a dose of usual PD medication during the visit to allow for motor assessment in ON and OFF states.

[13] NMSS to be performed at baseline, prior to last dose on Day 7, follow-up and end of study.

APPENDIX 4. COLUMBIA – SUICIDE SEVERITY RATING SCALE (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit - Clinical

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes No** ☐ ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes No** ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes No** ☐ ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes No** ☐ ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____

Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of preparatory acts _____

Suicide: Death by suicide occurred since last assessment.	**Yes** **No** ☐ ☐
	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 5. PATIENT ASSESSMENT OF UPPER GI DISORDERS SEVERITY INDEX (PAGI-SYM)

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

Please rate the severity of the following symptoms during the past 2 weeks.

		None	Very Mild	Mild	Moderate	Severe	Very Severe
1)	nausea (feeling sick to your stomach as if you were going to vomit or throw up)	○	○	○	○	○	○
2)	retching (heaving as if to vomit, but nothing comes up)	○	○	○	○	○	○
3)	vomiting	○	○	○	○	○	○
4)	stomach fullness	○	○	○	○	○	○
5)	not able to finish a normal-sized meal	○	○	○	○	○	○
6)	feeling excessively full after meals	○	○	○	○	○	○
7)	loss of appetite	○	○	○	○	○	○
8)	bloating (feeling like you need to loosen your clothes)	○	○	○	○	○	○
9)	stomach or belly visibly larger	○	○	○	○	○	○
10)	upper abdominal (above the navel) pain	○	○	○	○	○	○
11)	upper abdominal (above the navel) discomfort	○	○	○	○	○	○
12)	lower abdominal (below the navel) pain	○	○	○	○	○	○
13)	lower abdominal (below the navel) discomfort	○	○	○	○	○	○
14)	heartburn (burning pain rising in your chest or throat) during the day	○	○	○	○	○	○
15)	heartburn (burning pain rising in your chest or throat) when lying down	○	○	○	○	○	○
16)	feeling of discomfort inside your chest during the day	○	○	○	○	○	○
17)	feeling of discomfort inside your chest at night (during sleep time)	○	○	○	○	○	○
18)	regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) during the day	○	○	○	○	○	○
19)	regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) when lying down	○	○	○	○	○	○
20)	bitter, acid or sour taste in your mouth	○	○	○	○	○	○

APPENDIX 6. COMPLETE BOWEL MOVEMENT SCORE (CSBM)

Please read each question and select the best answer choice.	
Approximately how many complete, spontaneous bowel movements have you had over the last week?	 *(Place a mark on the scale above)*
Which stool type best characterizes the typical consistency of your stool over the last week?	◯ Type 1: Separate hard lumps, like nuts ◯ Type 2: Sausage-shaped but lumpy ◯ Type 3: Like a sausage or snake but with cracks on its surface ◯ Type 4: Like a sausage or snake, smooth and soft ◯ Type 5: Soft blobs with clear-cut edges ◯ Type 6: Fluffy pieces with ragged edges, a mushy stool ◯ Type 7: Watery, no solid pieces

APPENDIX 7. MINI MENTAL STATE EXAM (MMSE)

MINI MENTAL STATE EXAMINATION (MMSE)

Patient's name:

Hospital number:

ONE POINT FOR EACH ANSWER	DATE			
ORIENTATION				
Year Month Day Date Time	____/5	____/5	____/5	____/5
Country Town District Hospital Ward	____/5	____/5	____/5	____/5
REGISTRATION				
Examiner names 3 objects (eg apple, table, penny) Patient asked to repeat (1 point for each correct). THEN patient to learn the 3 names repeating until correct.	____/3	____/3	____/3	____/3
ATTENTION AND CALCULATION				
Subtract 7 from 100, then repeat from result. Continue 5 times: 100 93 86 79 65 Alternative: spell "WORLD" backwards - dlrow.	____/5	____/5	____/5	____/5
RECALL				
Ask for names of 3 objects learned earlier.	____/3	____/3	____/3	____/3
LANGUAGE				
Name a pencil and watch.	____/2	____/2	____/2	____/2
Repeat "No ifs, ands, or buts".	____/1	____/1	____/1	____/1
Give a 3 stage command. Score 1 for each stage. Eg. "Place index finger of right hand on your nose and then on your left ear".	____/3	____/3	____/3	____/3
Ask patient to read and obey a written command on a piece of paper stating "Close your eyes".	____/1	____/1	____/1	____/1
Ask the patient to write a sentence. Score if it is sensible and has a subject and a verb.	____/1	____/1	____/1	____/1
COPYING				
Ask the patient to copy a pair of intersecting pentagons: 	____/1	____/1	____/1	____/1
TOTAL	____/30	____/30	____/30	____/30

APPENDIX 8. DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964

and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human patients, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human patients to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human patients.

6. The primary purpose of medical research involving human patients is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be

evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is patient to ethical standards that promote and ensure respect for all human patients and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research patients.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients. The responsibility for the protection of research patients must always rest with the physician or other health care professionals and never with the research patients, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human patients in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human patients must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.

15. Appropriate compensation and treatment for patients who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human patients may only be conducted if the importance of the objective outweighs the risks and burdens to the research patients.

17. All medical research involving human patients must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human patients unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human patients must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human patients must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for patients and information regarding provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study’s findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human patients capable of giving informed consent, each potential patient must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential patient must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information.

After ensuring that the potential patient has understood the information, the physician or another appropriately qualified individual must then seek the potential patient's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research patients should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential patient is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research patient who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential patient, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research patient who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential patient's dissent should be respected.

30. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the

study may proceed without informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the patient or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable;

or

where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention;

and

the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be patient to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human patients must be registered in a publicly accessible database before recruitment of the first patient.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human patients and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or

otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Inhibikase Therapeutics

PROTOCOL NUMBER: IkT-148009-102

A Phase I, 7-Day Dosing Study of 200 mg IkT-148009 to determine the safety, tolerability and pharmacokinetics (PK) of IkT-148009 in OlderAdult and Elderly Healthy Volunteers

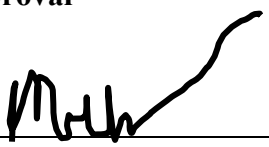
IND NUMBER: 138553

Investigational Product:	IkT-148009
Clinical Phase:	1
Sponsor:	Inhibikase Therapeutics 3350 Riverwood Pkwy SE Suite 1900 Atlanta, GA 30339 Telephone: 678 392 3419 Fax: 770 240 1401
Sponsor Study Physician:	Andrew McGarry, MD Medical Monitor Clintrex ResearchCorporation
Date of Original Protocol:	Version 1.4; 3 February 2023

PROTOCOL SIGNATURE PAGE

Protocol Number:	IkT-148009-102
Product:	IkT-148009
IND No.:	138553
Study Phase:	1
Sponsor:	Inhibikase Therapeutics
Date of Original Protocol:	Version 1.4; 3 February 2023

Sponsor Approval



2/3/2023

Title: Chief Executive Officer
Inhibikase Therapeutics, Inc.

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for IkT-148009. I have read the IkT-148009-102 protocol and agree to conduct the study as outlined.

The signature of the Principal Investigator constitutes an agreement that this study will be conducted according to all stipulations, clinically and administratively, as stated in the protocol, including all statements as to confidentiality. It is agreed that the conduct and results of this study will be kept confidential and that the case report forms and other pertinent data will become the property of Inhibikase Therapeutics, Inc.

It is agreed that the protocol contains all necessary information required to conduct the study as outlined in the protocol, and that the study will not be initiated without the approval of an appropriate Institutional Review Board or Ethics Review Committee.

It is agreed that all participants in this study will provide written informed consent in accordance with ICH Guidelines for Good Clinical Practice and the requirements specified in the Code of Federal Regulations (21 CFR Parts 50, 56, 312) and/or the Declaration of Helsinki. All participants will also be informed that their medical records will be kept confidential except for review by authorized representatives of Inhibikase Therapeutics, Inc. and its associates, the U.S. Food and Drug Administration or other regulatory agencies.

Tiffany Nguyen

Printed Name of Investigator

DocuSigned by:
Tiffany Nguyen
Signer Name: Tiffany Nguyen
Signing Reason: I approve this document
Signing Time: 03-Feb-2023 | 19:53:37 GMT
0B21948F980A470CB994E96431B1E781

Signature of Investigator

03-Feb-2023 | 19:53:42 GMT

Date

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
CRO Project Manager	Leslie Engelman, MPH Global Project Manager	Celerion Inc. 621 Rose Street Lincoln, NE 68502 1-402-580-5436
Sponsor Physician and Medical Monitor	Andrew McGarry, MD	Clintrex Research Corporation 2 North Tamiami Trail Suite 308 Sarasota, FL 34236 1-732-330-8298
Principal Investigator	Tiffany Nguyen, MD	Celerion Inc. 621 Rose Street Lincoln, NE 68502

Table of Contents

1. SYNOPSIS

<table>
<tr><td>IND:</td><td>138553</td></tr>
<tr><td>Title:</td><td>A Phase I, 7-Day Dosing Study of 200 mg IkT-148009 to determine the safety, tolerability and pharmacokinetics (PK) of IkT-148009 in Older Adult and Elderly Healthy Volunteers</td></tr>
<tr><td>Protocol:</td><td>IkT-148009-102; Version 1.0</td></tr>
<tr><td>Investigational Medicinal Product and Dosage:</td><td>IkT-148009 will be administered as 4x50mg gelatin capsules per the detailed instructions provided in the pharmacy instructions and given to the subjects as a gelatin capsule.<table><tr><th>Cohort</th><th>IkT-148009 MaximumDose (mg)</th></tr><tr><td>1</td><td>200</td></tr></table></td></tr>
<tr><td>Comparator and Dosage:</td><td>No comparator will be used in this study.</td></tr>
<tr><td>Duration of treatment:</td><td>Subjects in this study will be assigned to treatment with IkT-148009 only. Subjects will receive a single daily dose of study drug with a meal for a period of up to 7 days. A full breakfast must be given no more than 60 mins prior to dosing. The meal must be a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal. The meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. The caloric breakdown of the meal must be provided in the study report. The single dose of IkT-148009 is to be taken after the meal with a large glass of water (240 ml or 8 oz) each day.</td></tr>
<tr><td>Methodology:</td><td>This is a Phase 1 study in older adult or elderly healthy volunteer subjects to measure the safety, tolerability and pharmacokinetic (PK) profile of IkT-148009 capsules given as multiple capsules.

A Safety Review Committee (SRC) will evaluate all available safety, tolerability, and PK data.</td></tr>
</table>

	General Methodological Considerations The study will consist of a total of up to 15 visits over a period of up to 29 days prior to dosing, 7 days of dosing and 14 days of follow up. Subjects in the study will be admitted to an inpatient unit approximately 24 hours prior to the expected time of dosing. Subjects will be confined to the unit for approximately 12 days. No subject may be dischargedfrom the unit until the investigator is satisfied that they have no continuing and clinically significant adverse events that could be related to study drug. See the Schedule of Events (SOE) (Appendix 1) for the full list of study assessments and timings.
Primary Objectives:	1. To assess the safety and tolerability of IkT-148009 given as a gelatin capsule; 2. To assess the PK profile of IkT-148009 4 x 50 mg gelatin capsules administered once daily in the fed state; 3. To investigate plasma and urine concentrations of IkT-148009.
Primary Endpoints:	The primary endpoints of this study are: 1. Safety (adverse event reporting, vital sign measurements, clinical laboratory data, electrocardiogram [ECG] parameters and C-SSRS) 2. Tolerability (percent completers) 3. Pharmacokinetic parameters: • Area under the concentration-time curve from time zero to 96 hours ($AUC_{0-\infty}$) • Maximum plasma concentration (C_{max}) • Area under the concentration-time curve from time zero to last time point (AUC_{0-last}) • Time to reach maximum concentration (T_{max}) • The distributional half-life and terminal half-life ($t_{1/2}$) • Maximum concentration at steady-state ($C_{max,ss}$) and area under the concentration-time curve at steady-state (AUC_{ss})
Sample Size:	Up to 6 older adult and elderly healthy volunteers age 45-70.
Number of Sites:	Up to 2 clinical research units [CRU] specializing in Phase 1 studies.

Study Period:	The projected completion of this study is approximately 2 months from first patient dosed.
Key Inclusion Criteria:	1. Subject must have all questions about the study answered and must have signed the informed consent document before any study-specific procedures are performed. 2. Men or women aged 45 to 70 years at screening (both inclusive) of any race. 3. Subjects must be otherwise healthy and ambulatory, with no history or evidence of clinically relevant medical disorders as determined by the Investigator in consultation with the Sponsor. 4. Mini Mental State Examination (MMSE) ≥ 28 at Screening (V1) and Baseline (V2). 5. Physical examination, clinical laboratory values, vital signs (as defined in the CRU standard operating procedure [SOP]), and the electrocardiogram (ECGs) are clinically acceptable to the Investigator. Body weight ≥ 45 kg at screening and baseline visits. Body Mass Index (BMI) ≥ 18 and ≤33 kg/m^2 at screening. 6. Female subjects must be postmenopausal (12 months without menses and confirmed by follicle stimulating hormone [FSH] > 40 mIU/mL) or surgically sterile (hysterectomy or bilateral oophorectomy) or sterile for other medical reason (i.e., able to document premature low ovarian reserve, birth defect, other). Women who are several years postmenopausal may be considered for enrollment even with [FSH] below this threshold. 7. Male subjects must agree to practice an acceptable method of highly effective birth control from the Screening visit, while on study and for 7 days after receiving the last dose of study drug. Highly effective methods of birth control include sexual abstinence; vasectomy; or a condom with spermicide (men) in combination with their partner's highly effective method. 8. Males must be willing to abstain from sperm donation from the screening visit, while on study and through 30 days after receiving the last dose of study drug.

Key Exclusion Criteria:	1. Clinically significant abnormal values for hematology, clinical chemistry or urinalysis at the screening and admission visits. Minimal abnormalities considered to be non-clinically significant by the Investigator are acceptable. 2. Clinically significant abnormal findings on physical examination or 12-lead electrocardiogram (ECG) at the screening or admission visits. NOTE: QTcF interval of $\geq$ 450 msec in males or $\geq$ 470 msec in females will be the basis for exclusion from the study. Safety ECG may be repeated for confirmatory purposes if initial values obtained exceed the limits specified. 3. Significant history (within six months prior to receiving the study drug) and/or presence of clinically significant medical, surgical or psychiatric disorder in the judgement of the Investigator. Subjects with co-morbid conditions that are stable and controlled may remain eligible(stable defined as no change in the dose or frequency of medications over the prior three months). 4. Clinically significant problems in the retina 5. eGFR < 60 mL/min 6. Creatinine, Amylase and/or Lipase > ULN 7. Any malignancy in the 5 years prior to screening excluding basal cell carcinoma or squamous cell carcinoma of the skin or cervical carcinoma in situ that have been successfully treated. 8. Any subject with a history, presence and/or current evidence of serologic positive result for hepatitis B surface antigen, hepatitis C antibodies, or HIV antibodies 1 or 2. Subjects considered to be cured for hepatitis C will be eligible. 9. Recent history (within previous six months prior to screening) of alcohol or drug abuse (as judged by the investigator) or has consumed > 2 alcohol drinks/day during the last three months prior to screening (one glass is approximately equivalent to: beer [284 mL], wine [125 mL/4 ounces], or distilled spirits [25 mL/1 ounce]). Subjects that consume three glasses of alcoholic beverages per day but less than 14 glasses per week may be enrolled at the discretion of the Investigator. Positive screens for alcohol or controlled substances at the screening or admission visits will disqualify a subject from study participation. 10. Any subject with known hypersensitivity to IkT-148009. 11. Donation of blood or acute loss of blood within 60 days prior to screening visit.

	12. Use of tobacco or nicotine-containing products during the 60 days prior to screening and for the duration of the study. 13. Any subject who has received treatment with an investigational drug during the 30 days prior to screening. 14. Investigative site personnel or their immediate families (spouse, parent, child or sibling whether biological or legally adopted). 15. Any subject unwilling or unable to comply with study procedures.
Dose Adjustment Criteria:	An SRC will be established, comprised of the Sponsor Study Physician and an outside Drug Safety Physician. The roles and responsibilities of the SRC will be described in the SRC Charter which will be agreed to and signed prior to the first dose of study drug being administered. The role of the SRC is to assess any safety and tolerability concerns that may arise during dosing that may require dosing adjustment and/or termination.
Dose Stopping Rules:	1. Serious Adverse Event: If any subject has a serious adverse event (SAE) that is not potentially life-threatening but is possibly study drug related, the SRC may stop the study. 2. Severe Adverse Event: If two (2) or more subjects have a severe adverse event that the safety committee determines is related to IkT-148009, the safety committee must meet to consider if they should stop the study. 3. Clinically significant events observed in at least two (2) subjects exposed to IkT-148009: The SRC may not allow dose continuation if at least two subjects report the same finding. However, if each subject reported a different finding, the SRC could allow dose continuation. In all circumstances, the SRC may allow dose-repetition or dose reduction if: • Cytopenias (anemia, neutropenia and thrombocytopenia); • Fluid retention (pleural effusion, pericardial effusion, pulmonary edema and ascites) and edema (unexpected rapid weight gain); • Congestive heart failure, cardiogenic shock and left ventricular dysfunction; • Gastrointestinal irritation leading to nausea, vomiting, diarrhea, dyspepsia, abdominal pain, GI hemorrhage; • A sustained increase (>3X ULN) in alanine aminotransferase (ALT) or aspartate aminotransferase (AST), which must be confirmed elevated within 48 hours (Guideline of Liver Safety Assessment Best Practices Workshop 2014 [Avigan et al., 2014]);

	• Total bilirubin increase (>2X ULN) confirmed on repeat testing within 48 hours; • A sustained increase in alkaline phosphatase (>2X ULN) in association with an increase in ALT and AST confirmed on repeat testing within 48 hours; • QTc prolongation defined as QTcF increasing ≥60 msec and persisting for at least 10 minutes or QTcF >500 msec and persisting for at least 30 minutes; • A sustained increase in serum creatinine (> 1.3X ULN) confirmed on repeat testing within 48 hours. The SRC will carefully evaluate each safety and tolerability event and use clinical judgement to determine whether dosing should stop for a specific subject or for all study subjects.
Criteria for Evaluation:	**Safety and Tolerability:** Safety and tolerability of the study drug will be assessed by adverse event reporting, clinical laboratory assessments, physical examinations, vital sign measurements,Safety ECGs, C-SSRS, percent completers, concomitant medication usage and adverse event reporting. **Pharmacokinetics:** Plasma will be collected to assay for concentration of IkT-148009. The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC), C_{max}, T_{max}, C_{trough}, distributional half-life and terminal half-life (t1/2).
Statistical Considerations	The Safety Population is defined as all subjects who are administered study drug. The Pharmacokinetic (PK) Population is defined as all subjects who are administered IkT-148009 and have at least one bioanalysis resultfor the plasma concentration of the study drug. No formal sample size calculations have been undertaken for this safety, tolerability and PK study. The number of subjects is thought to be sufficient to assess preliminary safety, tolerability and the PK profile of IkT-148009. No efficacy parameters arebeing collected or analyzed for this Phase I study. For categorical data, frequency counts and percentages will be presented. For continuous data, summary statistics will include the arithmetic mean, standard deviation (SD), median, minimum, maximum, and number; for log-normal data (e.g., the PK parameters of AUC, C_{max} and C_{trough}), the geometric

	mean and geometric coefficient of variation will also be presented. The In-transformed PK parameters will be compared using a generalized analysis of variance (ANOVA) model (Weerahandi 1994, Ogenstad 1998). Safety data will be reported descriptively. For all safety analyses, AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) with the version used specified in the clinical study report. The overall incidence of adverse events will be displayed by MedDRA™ System Organ Class (SOC), preferred term, and dosing condition. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Data from vital signs, clinical laboratory measures and Safety ECG will be summarized by dosing condition. In addition, change from baseline values will be calculated at eachtime point and will be summarized using the same summary statistics. Out- of-range safety endpoints may be categorized as low or high, where applicable. PK parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentration (T_{max}) will be summarized using n, mean, standard deviation, median, minimum, and maximum. All other PK parameters will be summarized using n, geometric mean, coefficient of variation, median, minimum, and maximum. Dose proportionality will be analyzed using a generalized ANOVA model using the logarithm of PK parameter (AUC, C_{max} and C_{trough}) as the dependent variable and the logarithm of the dose as the independent variable (Weerahandi 1994, Ogenstad 1998). Point estimates and the corresponding generalized CIs will be estimated for both AUC, C_{max} and C_{trough}. For AUC, C_{max} and C_{trough}, the treatment ratio 'test/reference' will be calculated by taking the anti-logarithm of the difference between treatment means. Further details of the above analyses will be provided in the statistical analysis plan. Data from subjects who experience emesis will be deleted from statistical analyses if vomiting occurs at or before two times the median t_{max}. Statistical software for the analysis will be SAS version 9.4 (SAS Institute) or later and XPro (X-Techniques, Inc.).

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AD	Alzheimer's Disease
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the time-concentration curve
BLQ	Below the limit of quantitation of assay
BMI	Body mass index
c-Abl	cellular Abelson tyrosine kinase
CBC	Complete blood count
CFR	Code of Federal Regulations
CK	Creatinine kinase
Cmax	Maximum plasma concentration
CNS	Central Nervous System
CRO	Clinical Research Organization
CRU	Clinical Research Unit
C-SSRS	Columbia Suicide Severity Rating Scale
Ctrough	Concentration at trough
DA	Dopaminergic
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good clinical practice

Abbreviation or Specialist Term	**Explanation**
GI	Gastrointestinal
GMP	Good manufacturing practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
INR	International normalized ratio of prothrombin time
IRB	Institutional Review Board
LBs	Lewy bodies
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
PD	Parkinson's disease
PI	Principal Investigator
PK	Pharmacokinetics
PT	Prothrombin time
PT-INR	Prothrombin time – international normalized ratio
QTcF	QT interval
RBC	Red blood cell count
SD	Standard deviation
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SNc	Substantia nigra pars compacta
SOC	System organ class
SOE	Schedule of events
SOP	Standard operating procedure
SRC	Safety Review Committee

Abbreviation or Specialist Term	**Explanation**
Tmax	Time at maximum plasma concentration
TEAE	Treatment emergent adverse event
$T_{1/2}$	Half-life
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
USP	United States Pharmacopeia
WBC	White blood cell count

3. INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder (Savitt et al, 2006), affecting approximately 1,000,000 persons in the United States, with 60,000 new cases and 38,000 deaths annually (Savitt et al, 2006; Dauer et al, 2003). PD is an inexorably progressive disorder that is characterized by bradykinesia, rigidity, rest tremor, and gait disturbances with postural instability (Savitt et al, 2006; Dauer et al, 2003). Pathologically, PD is characterized by degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc), coupled with the accumulation of protein aggregates in cell bodies and terminals known as Lewy bodies (LBs) and Lewy neurites, respectively, collectively known as Lewy pathology (Goedert, 2001; Goedert et al, 2013; Lee and Trojanowski, 2006). It is now appreciated that clinical and pathologic features are much more extensive than historically recognized. PD pathology affects serotonin, cholinergic, and norepinephrine neurons and nerve cells in the olfactory system, cerebral hemisphere, brain stem, spinal cord, and peripheral autonomic nervous system, in addition to SNc dopaminergic neurons (Jellinger, 2012). This non-dopaminergic pathology is associated with a variety of non-dopaminergic clinical features, none of which are adequately controlled with dopamine-replacement therapy (Schapira et al, 2014). These include falling, freezing, dysphagia, neuropsychiatric disorders, autonomic dysfunctions, sensory problems, and cognitive impairment with dementia (Schapira et al, 2014). Indeed, non-dopaminergic features, such as falling and dementia, represent the major source of disability for PD patients. Numerous symptomatic therapies based on a dopamine replacement strategy have been developed over the past half century that provide meaningful benefits, particularly for the classic motor features of the disease (Schapira et al, 2014).

Over the past 20 years, a number of studies have suggested that misfolding of alpha-synuclein plays a key role in the etiopathogenesis of PD and suggest that therapies directed at preventing or clearing pathologic alpha-synuclein might be neuroprotective (Winner et al, 2011; Olanow and Brundin, 2013; Polymeropoulos et al, 1997; Spillantini et al, 1997; Masliah et al, 2000; Kirik and Bjorklund, 2003; Jellinger, 2012). However, our understanding of the precise toxic form of alpha-synuclein has been lacking, confounding our ability to properly target toxic alpha-synuclein for a therapeutic purpose. Recent work by multiple laboratories and Inhibikase has providedconvincing evidence that a common pathway governs initiation and progression of the disease within the Central Nervous System (CNS) and in the periphery. At the core of this pathway is thecellular Abelson tyrosine kinase (c-Abl) which we believe acts as a checkpoint, playing a key rolein the formation and accumulation of toxic alpha-synuclein to progressively cause disease. Toxicalpha-synuclein is the product of this biochemical pathway, arguing strongly that inhibition of c- Abl will be neuroprotective and such inhibitors are likely to blunt the rate or extent of alpha- synuclein toxicity in PD patients.

IkT-148009: A novel, c-Abl inhibitor that is neuroprotective in Central and Enteric Nervous Systems

IkT-148009 is a novel chemical derivative of the anti-cancer agent imatinib (marketed as Gleevec®). In contrast to Gleevec®, IkT-148009 is 25-fold more potent inhibitor of the wild type

c-Abl enzyme with an IC_{50} for c-Abl of 33 nM (Table 3).

Table 3: Small molecule inhibitors of the Abelson Tyrosine Kinase

Drug	IC_{50} c-Abl1	IC_{50} c-Abl2/Arg
IkT-148009	33 nM	14 nM
Imatinib	828 nM	1000 nM

Oral gavage of IkT-148009 in C57Bl/6 mice demonstrated that IkT-148009 readily penetrates the brain, accumulates to > 1 µM total brain concentration over 7 days and completely blocks c-Abl activation in several different models of Parkinson's disease (Karruppagounder et al., 2022)

3.1. Unmet Medical Need

Despite the success of anti-parkinsonian therapies, no satisfactory intervention has been discovered for the non-dopamine features of the illness, and no therapy is capable of slowing or stopping disease progression. These remain major unmet medical needs.

3.2. Scientific Rationale

IkT-148009 is a novel, selective inhibitor of the non-receptor Abelson tyrosine kinases. IkT-148009 is a highly potent inhibitor of wildtype Abelson tyrosine kinase, c-Abl (a.k.a. c-Abl1, Abl1) and c-Abl2 (a.k.a. Arg) with similar pharmacokinetic and metabolic characteristics of other drugs in this class. IkT-148009 readily penetrates the brain, accumulates to > 1 µM total brain concentration over 7 days and completely blocks c-Abl activation in the acute neurotoxicity model.

Over the past 20 years, a number of studies have suggested that misfolding of α-synuclein plays a key role in the etiopathogenesis of PD, and suggest that therapies directed at preventing or clearing pathologic alpha-synuclein might be neuroprotective (Dauer and Przedborski, 2003; Goedert, 2001; Goedert et al, 2013; Lee and Trojanowski, 2006; Jellinger, 2012; Schapira et al, 2014; Winner et al, 2011). c-Abl is a non-receptor tyrosine kinase that is an essential sensor of cellular stress, such as oxidation or nitrosation. c-Abl regulates many cellular processes, including the actin cytoskeleton, the cell cycle, and the apoptotic/cell cycle arrest response to stress. c-Abl is also crucial for proper neuronal development, but is relatively quiescent in healthy, adult neurons,and there are few known functions of c-Abl in fully differentiated neurons. The role of c-Abl in PD might extend well beyond parkin phosphorylation. In vitro and in vivo biochemical analyses have established a direct link between c-Abl activation and the formation of toxic forms of alpha-synuclein and suggests that c-Abl phosphorylation of alpha-synuclein may drive alpha-synuclein misfolding and aggregation. c-Abl inhibition is likely to be a highly effective, disease-modifying therapy for alpha-synuclein related diseases, including PD.

IkT-148009 has completed chronic toxicology studies in rats and monkeys for 6 and 9 months, respectively, and been dosed across 113 clinical trial participants in single and multiple doses up to 200 mg for up to 11 weeks in healthy subjects and Parkinson's patients. However, a steady-state PK profile has not been measured clinically at 200 mg given once daily. Dose escalation trials that suggested exposures at 200 mg may be necessary to achieve sufficient coverage of c-Abl in the Central Nervous System (CNS).

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. Monitoring will be conducted according to the applicable International Committee on Harmonisation (ICH) and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

3.3. Benefit-Risk Evaluation of the Present Study

This is a healthy subject study to characterize the steady-state pharmacokinetics for IkT-148009 dosed once daily for 7 days, thus there is no expected benefit for older adult and elderly healthy volunteers in this study. Drugs in this class are known to cause reproductive abnormalities and could be lethal to a developing embryo and lead to birth defects or even death of a fetus or newborn, thus the sponsor has chosen not to enroll healthy adult volunteers between ages 18 - 44 years of age, and furthermore excludes subjects of child-bearing potential from this study. Drugs in this class have been known to have an effect on vision. Clinical trial subjects will go through an extensive screening process throughout the duration of this study, thereby mitigating or eliminating the possibility of being at risk given the known side effects of IkT-148009.

This study will be conducted at a specialized Phase 1 CRU where all subjects will be institutionalized and under constantmedical supervision. A Safety Review Committee will operate under a clearly defined charter and pre-defined stopping rules. The protocol also includes clear stopping rules with regard to clinically significant medical events of interest, as well as seriousness and severity of adverse events.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objective

1. To assess the safety and tolerability of IkT-148009 given as gelatin capsule;
2. To assess the PK profile of 200mg (once daily for seven days) of IkT-148009 delivered as 4 x 50 mg gelatin capsules in the fed state;
3. To investigate plasma and urine concentrations of IkT-148009.

4.2. Endpoints

4.2.1. Primary Endpoints

1. Safety (adverse event reporting, vital sign measurements, clinical laboratory data, electrocardiogram [ECG] parameters and C-SSRS); and
2. Tolerability (percent completers); and
3. Assess the pharmacokinetics (PK) of IkT-148009 by determining the:
    - Area under the concentration-time curve from time zero to 96 hours ($AUC_{0-\infty}$);
    - Maximum plasma concentration (C_{max});
    - Area under the concentration-time curve from time zero to last time point (AUC_{0-last});
    - Time to reach maximum concentration (T_{max});
    - The distributional half-life and terminal half-life ($t_{1/2}$); and
    - Maximum concentration at steady-state ($C_{max,ss}$) and area under the concentration-time curve at steady-state (AUC_{ss})

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

This is a Phase I, Single Dose Study to determine the safety, tolerability and pharmacokinetics (PK) of IkT-148009 gelatin capsules in Older and Elderly Healthy Adults at 200 mg IkT-148009.

5.1.1. Cohort

The cohort will consist of six (6) subjects.

Cohort	IkT-148009 (mg)
1	200

The cohort will consist of up to 15 visits over a period of 29 days including 7 days of dosing and 14 days of follow-up after the last dose.

Subjects in the cohort will be admitted to the unit approximately 24 hours prior to the expected time of dosing and will be confined to the unit for approximately 12 days. No subject may be discharged from the unit until the investigator is satisfied that they have no continuing adverse events that could be related to study drug.

See the SOE (Appendix 1) for the full list of study assessments and timings.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

6.1. Subject Inclusion Criteria

The following inclusion criteria must be met for subjects to be eligible for the trial:

1. Subject must have all questions about the study answered and must have signed the informed consent document before any study-specific procedures are performed.
2. Men or women aged 45 to 70 years at screening (both inclusive) of any race.
3. Subjects must be otherwise healthy and ambulatory, with no history or evidence of clinically relevant medical disorders as determined by the Investigator in consultation with the Sponsor.
4. Mini Mental State Examination (MMSE) ≥ 28 at Screening (V1) and Baseline (V2).
5. Physical examination, clinical laboratory values, vital signs (as defined in the CRU standard operating procedure [SOP]), and the electrocardiogram (ECGs) are clinically acceptable to the Investigator. Body weight ≥ 45 kg at screening and baseline visits. Body Mass Index (BMI) ≥ 18 and ≤33 kg/m^2 at screening.
6. Female subjects must be postmenopausal (12 months without menses and confirmed by

follicle stimulating hormone [FSH] > 40 mIU/mL) or surgically sterile (hysterectomy or bilateral oophorectomy) or sterile for other medical reason (i.e., able to document premature low ovarian reserve, birth defect, other). Women who are several years postmenopausal may be considered for enrollment even with [FSH] below this threshold.

7. Male subjects must agree to practice an acceptable method of highly effective birth control from the Screening visit, while on study and for 7 days after receiving the last dose of study drug. Highly effective methods of birth control include sexual abstinence; vasectomy; or a condom with spermicide (men) in combination with their partner's highly effective method.
8. Males must be willing to abstain from sperm donation from the screening visit, while on study and through 30 days after receiving the last dose of study drug.

6.2. Subject Exclusion Criteria

1. Clinically significant abnormal values for hematology, clinical chemistry or urinalysis at the screening and admission visits. Minimal abnormalities considered to be non-clinically significant by the Investigator are acceptable.
2. Clinically significant abnormal findings on physical examination or 12-lead electrocardiogram (ECG) at the screening or admission visits. NOTE: QTcF interval of $\geq$ 450 msec in males or $\geq$ 470 msec in females will be the basis for exclusion from the study. Safety ECG may be repeated for confirmatory purposes if initial values obtained exceed the limits specified.
3. Significant history (within six months prior to receiving the study drug) and/or presence of clinically significant medical, surgical or psychiatric disorder in the judgement of the investigator. Subjects with co-morbidconditions that are stable and controlled may remain eligible (stable defined as no changein the dose or frequency of medications over the past three months).
4. History of clinically significant problems in the retina as reported by a subject
5. eGFR < 60 mg/mL
6. Creatinine, Amylase and/or Lipase > ULN
7. Any malignancy in the 5 years prior to screening excluding basal cell carcinoma or squamous cell carcinoma of the skin or cervical carcinoma in situ that have been successfully treated.
8. Any subject with a history, presence and/or current evidence of serologic positive result for hepatitis B surface antigen, hepatitis C antibodies, or HIV antibodies 1 or 2. Subjects considered to be cured for hepatitis C will be eligible.
9. Recent history (within previous six months prior to screening) of alcohol or drug abuse (as judged by the investigator) or has consumed > 2 alcohol drinks/day during the last three months prior to screening (one glass is approximately equivalent to: beer [284 mL], wine [125 mL/4 ounces], or distilled spirits [25

mL/1 ounce]). Subjects that consume three glasses of alcoholic beverages per day but less than 14 glasses per week may be enrolled at the discretion of the Investigator. Positive screens for alcohol or controlled substances at the screening or admission visits will disqualify a subject from study participation.

10. Any subject with known hypersensitivity to IkT-148009.
11. Donation of blood, plasma, or acute loss of blood within 60 days prior to screening visit.
12. Use of tobacco or nicotine-containing products during the 60 days prior to screening and for the duration of the study.
13. Any subject who has received treatment with an investigational drug during the 30 days prior to screening.
14. Investigative site personnel or their immediate families (spouse, parent, child or sibling whether biological or legally adopted).
15. Any subject unwilling or unable to comply with study procedures.

6.3. Subject Withdrawal Criteria

If there is an adverse event or medical reason for the withdrawal, the subject should be followed medically until the condition has either resolved itself or is stable. Details of the reason for withdrawal should be recorded in the subject's electronic Case Report Form (eCRF).

Subjects who withdraw should, if possible, have a follow-up examination, including a physical examination, the appropriate investigations, vital signs, Safety ECG and clinical laboratory tests. All details of this follow-up examination should be recorded in the subject's medical source documents.

6.3.1.1. Study Drug Withdrawal and Withdrawal from the Study

Participation in the study is strictly voluntary. Subjects are free to discontinue the study at any time without giving their reason(s).

A subject must be withdrawn from the study treatment in the event of any of the following:

- withdrawal of the subject's consent;
- new onset of a condition which would have met exclusion criterion, is clinically relevant and affects the subject's safety, and discontinuation is considered necessary by the Investigators and/or Sponsor;
- occurrence of intolerable AEs;
- intake of non-permitted concomitant medication;
- lack of subject compliance;
- significant protocol deviation determined in consultation with the sponsor Medical Monitor.

If a subject fails to attend scheduled assessments during the course of the study, the Investigator must determine the reasons and the circumstances as completely and accurately as possible and document this in the subject's source documents.

Subjects may be withdrawn from the study if there is concern for the subject's safety or it is determined that the subject is no longer a qualified participant. Any subject who is withdrawn from the study for any reason is to have the final visit assessments performed applicable to that cohort.

Subjects who withdraw or are withdrawn from the study prior to study drug dosing will be replaced. The sponsor may choose to replace subjects who withdraw or are withdrawn from the study after study drug dosing.

7. TREATMENT OF SUBJECTS

7.1. Number of Subjects

Up to 6 older adult and elderly subjects, 45 – 70 years old, otherwise considered healthy are planned to be recruited. Subjects who withdraw or are withdrawn from the study prior to dosing will be replaced and subjects who withdraw or are withdrawn from the study after study drug dosing may be replaced at the discretion of the sponsor. Additional cohorts may be considered to accommodate dose repetition, slower dose escalation or escalation beyond currently planned doses.

7.2. IkT-148009 Dosing Regimen

IkT-148009 will be administered once with a meal daily for 7 days as 4 x 50 mg gelatin capsules. A full breakfast must be given no more than 60 mins prior to dosing. The meal must be a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal. The meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. The caloric breakdown of the meal must be provided in the study report. The single dose of IkT-148009 is to be taken after the meal with a large glass of water (240 ml or 8 oz) each day.

7.3. Dose Adjustment Criteria

7.3.1. Safety Review Committee

An SRC will be established, comprised of the Sponsor Study Physician and the outside Drug Safety Physician. The roles and responsibilities of the SRC will be described in the SRC Charter which will be agreed to and signed prior to the first dose of study drug being administered. The role of the SRC is to assess the safety and tolerability concerns that may arise during dosing that may require dosing adjustment and/or termination. In addition, the SRC may stop the study for safety reasons at any time. The Committee will meet after subjects are discharged and all safety, adverse event and pharmacokinetic data are known. If the Committee desires to evaluate the follow-up safety data, that request will be formally made at the SRC meeting following discharge and review of all safety, tolerability and PK data.

7.3.2. Dose Stopping Rules

1. Serious Adverse Event: If any subject has a serious adverse event (SAE) that is not potentially life- threatening but is possibly study drug related, the SRC may stop the study.

2. Multiple moderate AEs in the same subject: If two (2) or more subjects have a severe adverse event that the safety committee determines is related to IkT-148009, the safety committee may stop the study.

3. Clinically significant events observed in at least two (2) subjects exposed to IkT-148009: The SRC may not allow dose continuation if at least two subjects report the same finding. However, if each subject reported a different finding, the SRC could allow dose continuation. In all circumstances, the SRC may allow dose-repetition or dose reduction if:

- Cytopenias (anemia, neutropenia and thrombocytopenia);
- Fluid retention (pleural effusion, pericardial effusion, pulmonary edema and ascites) and edema (unexpected rapid weight gain);
- Congestive heart failure, cardiogenic shock and left ventricular dysfunction;
- Gastrointestinal irritation leading to nausea, vomiting, diarrhea, dyspepsia, abdominal pain, GI hemorrhage;
- A sustained increase (>3X ULN) in alanine aminotransferase (ALT) or aspartate aminotransferase (AST), which must be confirmed elevated within 48 hours (Guideline of Liver Safety Assessment Best Practices Workshop 2014 [Avigan et al., 2014]);
- Total bilirubin (>2X ULN) increase confirmed on repeat testing within 48 hours;
- A sustained increase (> 2X ULN) in alkaline phosphatase (ALP) in association with increased ALT and AST confirmed on repeat testing within 48 hours;
- QTc prolongation defined as QTcF increasing ≥60 msec and persisting for at least 10 minutes or QTcF >500 msec and persisting for at least 30 minutes;
- A sustained increase (> 1.3X ULN) in serum creatinine confirmed on repeat testing within 48 hours.

7.4. Concomitant Medications

Record the name, start date (if known), indication for use and whether ongoing or stopped of medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study. Concomitant medications used for prophylaxis are allowed as is acetaminophen for minor pain (up to 2 grams in 24 hours).

The charts of all study participants will be reviewed for new concomitant medications. Chart reviews will include examination of nursing and physician progress notes, vital signs and medication records in order to identify AEs that may be associated with new concomitant medications. New concomitant medications, ongoing concomitant medications with a change in dose and medical procedures ordered, e.g., laboratory assessments and radiological assessments, will be reviewed to determine if they are associated with an AE not previously identified.

7.5. Treatment Compliance

The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for non-compliance will also be documented, including:

- missed visits;
- interruptions in the schedule of administration;
- non-permitted medications.

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. As this is a Phase I study, it is critical that study activities be carried out per the protocol schedule.

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1. Study Drug

IkT-148009 will be supplied to the pharmacy of the CRU per their SOP by the sponsor per the detailed instructions provided in the pharmacy instructions and given to the subjects as 4x50 mg gelatin capsules.

8.2. Study Drug Packaging and Labeling

The composition and pharmaceutical quality of the investigational product was manufactured according to the current Good Manufacturing Practice (GMP) and the clinical pharmacy will maintain the investigational product using GCP guidelines and clinical research unit SOPs.

8.3. Study Drug Storage

Upon receipt of the medication, the Investigator or designee will inspect the medication and complete and return the acknowledgment of receipt form enclosed with the parcel. A copy of the signed receipt will be kept in the study files.

The study medication must be carefully stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. It should be protected from moisture. Direct contact of the active pharmaceutical ingredient (API) with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references.

The study medication may not be used for any purpose other than the present study. After the study is completed, all unused study medication must be retained, returned as directed or destroyedon site per the Sponsor's instructions.

The Investigator or designee will be responsible for ensuring appropriate storage, compounding, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory must be available for inspection by the designated representatives of the Sponsor or the Sponsor's representatives on request, and must include the information below:

- the identification of the subject to whom the drug was dispensed;
- the date(s) and quantity of the drug dispensed to the subject;

A copy of the inventory record and a record of any clinical supplies that have been destroyed must be documented as directed. This documentation must include at least the information below or as agreed with the Sponsor:

- the number of unused units;
- the number of units destroyed at the end of the study;
- the date, method and location of destruction.

8.4. Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator or designee must keep a record of all study drug received, used and discarded. It must be clear from the records which subject received which dose of treatment.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. Under no circumstances is the Investigator allowed to release study drug supplies to any other physician not named in the FDA Form 1572 or to administer these supplies to a patient not enrolled in this study.

8.5. Study Drug Handling and Disposal

At the end of the study, any unused study drug will be retained or returned to the Sponsor for destruction or destroyed locally per the Sponsor's directions; disposition of study drug will be documented.

9. PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic blood samples will be taken and processed for analysis for concentrations of IkT-148009 at the time points described in the SOE (Appendix 1.) Residual plasma samples willbe used to investigate and identify IkT-148009 metabolites present by LC-MS/MS analysis and perform a semi-quantitative estimate of their abundance; urine samples may also be tested for thispurpose. This metabolite identification and semi-quantification work will be performed under a separate protocol and the study report included as an appendix to this clinical study report.

The following PK parameters will be calculated (Table 6), using a non-compartmental approach from the individual plasma concentration-time profiles of study drug. Actual PK sample collection times relative to dosing will be used to calculate the PK parameters.

Table 6: Pharmacokinetic Parameters of IkT-148009

PK Parameter	Definition
$AUC_{0\text{-}24}$ (ng-h/mL)	Area under the plasma drug concentration-time curve from time zero to 24 hours post dose.
$AUC_{0\text{-}\infty}$(ng-h/mL)	Area under the plasma drug concentration-time curve from time zero to infinity hours post dose.
C_{max} (ng/mL)	Maximum observed plasma concentration.
T_{max} (h)	Time to peak plasma concentration.
C_{trough}(ng/mL)	Plasma concentration observed at trough
$T_{1/2}$ (h)	Terminal half-life

For the purpose of PK parameter calculations, concentration values below the limit of quantification (BLQ) will be set to missing. Pharmacokinetic parameters of the study drug will be computed using a fully validated version of NONMEM. Additional information will be provided in the SAP.

9.1. Blood Sample Collection

Plasma samples for PK analysis will be collected according to the sampling collection times specified in the SOE (Appendix 1). The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. The Investigator or designee will arrange to have the plasma samples processed, stored and transported as directed for bioanalysis.

Selected samples will also be analyzed by LC-MS/MS to investigate and identify metabolites of IkT-148009 that are present and a semi-quantitative estimate of their abundance performed. This work will be conducted under a separate protocol and the study report included as an appendix to this clinical study report.

An additional PK sample may be collected at any time if clinically indicated and at the discretion of the Investigator (e.g., for unusual or severe AEs).

Each sample will be marked with unique identifiers such as the study number, subject number, and the nominal sample time. The date and actual time that the blood sample was taken will be recorded on the case report form or electronically with a bar code or other method.

9.2. Urine Sample Collection

Urine samples will be collected as per the SOE (Appendix 1) and processed for analysis of IkT-148009 concentrations. Urine samples may also be analyzed for IkT-148009 metabolite identification and semi-quantification purposes under a separate protocol. The pre-dose urine sample is to be collected within approximately 60 minutes prior to dosing.

9.3. Storage and Shipment of Pharmacokinetic and Urine Samples

The plasma and urine samples should be kept frozen at approximately -70°C to -80°C until analyzed. They should be packed as directed to avoid breakage during transit and with sufficient

dry ice to prevent thawing for at least 72 hours. A specimen-identification form must be completed and sent to the laboratory with each set of samples. The clinical site will arrange to have the plasma and urine samples transported as directed for bioanalysis as detailed in the PK instructions.

9.4. Sample Analysis

Bioanalysis of plasma samples for the determination of IkT-148009 will be performed utilizing a validated method; and bioanalysis of urine samples for the determination of IkT-148009 will also be performed utilizing a validated method.

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

The safety and tolerability of IkT-148009 will be assessed via treatment emergent adverse event reporting, serious adverse event reporting, vital sign measurement, physical and neurological examination, laboratory data, Safety ECG and C-SSRS.

Physical and neurological examinations, vital signs, daily weights, tracking of fluid intake and urine output volumes, laboratory assessments, Safety ECG evaluations and observations by experienced personnel will be undertaken throughout the study based on the following sections and SOE (Appendix 1). All study assessments may be performed by suitably trained personnel, but the results must be reviewed and signed off by medical personnel.

10.1.1 Demographics

Age, gender, race, and ethnic origin will be recorded at Screening.

10.1.2 Medical History

A full medical history including medication history will be recorded at Screening.

10.1.3 Physical Examination including a neurological exam

A physical examination of all major body systems (general appearance, skin, head, eyes, ears, nose, neck, throat, lungs, heart, abdomen, back, lymph nodes and extremities) will be undertaken and recorded at Screening. Additional exams may be performed if any changes from the screening assessment or symptom driven. This will include body weight and height at the Screening visits. Additional physical examinations will be undertaken and recorded per the SOE (Appendix 1).

Significant findings that are present prior to the first dose of study drug must be included in the Medical History/Current Medical Conditions page of the eCRF. Significant findings made after the first dose of study drug through the End of Study Visit which meet the definition of an AE must be recorded in the Adverse Event CRF summary page.

10.1.4 Screening and Safety Laboratory Tests (Clinical chemistry and CBC)

Clinical chemistry tests will include albumin, alkaline phosphatase, total bilirubin, calcium, cholesterol, creatinine, creatinine clearance, creatinine kinase (CK), gamma-glutamyltransferase (γ-GT), glucose, lactate dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, potassium,

magnesium, total protein, aspartate transaminase (AST), alanine transaminase (ALT), sodium, triglycerides, urea and uric acid, bicarbonate and chloride. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated. TSH levels will also be monitored.

CBC assessments will include hemoglobin, hematocrit, red blood cell (RBC) count, reticulocyte count, white blood cells (WBC) count with differential, platelet count and PT-INR. PT-INR should be reported in both prothrombin time (second) and international normalized ratio (no unit).

Standard urinalysis evaluation is to be performed at the specified intervals in the Schedule of Events.

Urine alcohol or drug abuse screening will be performed to meet subject enrollment criteria. Positive screens for alcohol or controlled substances at the screening or admission visits will disqualify a subject from study participation.

Men and women will undergo additional laboratory tests for reproductive organ function to include leutenizing hormone (LH), follicle stimulating hormone (FSH), testosterone and inhibin B in both genders.

Safety laboratory samples will be collected per the SOE (Appendix 1). Clinical chemistry or complete blood count (CBC) may be collected at any time during the study if clinically indicated.

10.1.5 Echocardiogram

Baseline echocardiogram will be performed prior to dosing on subjects who have completed all other screening events and continue to meet eligibility criterion.

10.2. Vital Signs

Vital signs (VS) for blood pressure and pulse are to be measured after subjects remain supine for 5 min and after 2 min standing. Baseline VS will be measured 3 times at baseline over the course of an hour. Respiratory rate, pulse oximetry and temperature will also be collected. Vital signs measurements outside of the normal range (as per the CRU SOP) should be repeated. All time points are relative to the time of dosing.

VS will be obtained per the SOE (Appendix 1).

10.3. 12-Lead Electrocardiogram (ECG)

The 12-lead Safety ECG assessments (after at least 10 minutes of rest) will be performed and the standard intervals recorded as well as any abnormalities. These Safety ECGs will be obtained per the SOE (Appendix 1) and should be collected at any time if clinically indicated based on vital signs or symptoms at the discretion of the Investigator. ECGs will be performed with subjects resting in a supine position for at least 10 min. All ECG tracings will be reviewed by the PI or designee. ECGs will be interpreted and signed and dated by the PI or designee. The ECGs will be classified as normal, having a non-clinically significant abnormality,or having a clinically significant abnormality. In addition, ECG parameters of ventricular rate, RR or PR

interval, QRS complex, and QTcF interval (corrected and uncorrected) will be noted on the CRF. All clinically significant abnormality findings will be recorded as AEs.

When scheduled post-dose, ECGs will be performed within approximately 20 min of the scheduled time point.. When scheduledat any other time, a standard ECG machine will be used.

10.4. Blood Sample Collection for Pharmacokinetic Assessments

Plasma samples for analysis of IkT-148009 concentrations will be collected at the time points as shown in the SOE (Appendix 1).

The time of study drug administration is time zero and all post-dosing sampling times are relative to dosing time. The investigator will arrange to have the plasma samples processed and transported for bioanalysis as directed by the Sponsor.

An additional plasma sample for analysis of IkT-148009 concentrations may be collected at any time if clinically indicated and at the discretion of the investigator (e.g., for unusual or severe AEs).

Each sample will be marked with unique identifiers as determined by the sponsor or its designee.

10.5. Urine Sample Collection for Pharmacokinetic Assessments

A urine sample will be collected as per the SOE (Appendix 1) and processed for analysis of IkT-148009. An additional urine sample for analysis of IkT- 148009 concentrations may be collected at any time if clinically indicated and at the discretion ofthe investigator (e.g., for unusual or severe AEs).

A “Window Allowance” outlining acceptable windows for intervals between nominal times and actual times for PK sampling times has been included in the SOE (Appendix 1). This will allow flexibility when multiple procedures are scheduled for the same time point.

10.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the study using the C-SSRS. This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicidal ideation and behavior, and a post-baseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes ‘yes’ or ‘no’ responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

The “Baseline/Screening” C-SSRS form will be completed at screening (lifetime history and past 24 months). The “Since Last Visit” C-SSRS form will be completed at all subsequent time points outlined in the SOE (Appendix 1).

10.7. Mini Mental State Exam

The Mini Mental State Examination (MMSE) is a brief test assessing general cognitive function (Folstein et al., 1975) used in the current study to ensure the study participants have no cognitive impairment before being administered IKT-148009 and to evaluate the subject’s cognition after receiving the study drug at subsequent visits per the SOE (Appendix 1). The MMSE consists of

five cognitive components: 1) orientation to time and place; 2) registration of three words; 3) attention and calculation (the investigator can choose in this study whether to administer the "WORLD Backwards" or "Calculation" sub-component); 4) recall of three words; and 5) language. The scores from each of the five components are summed to obtain an overall MMSE score. The score can range from 0-30, with lower scores indicating greater impairment in cognitive functioning. Participants will only be permitted to Screen and Baseline if they score ≥ 28 (representing normal cognition; Larner, 2013) on the MMSE at each of these respective visits.

10.8. Adverse and Serious Adverse Events

10.8.1 Definition of Adverse Events

10.8.1.1 Treatment Emergent Adverse Event (TEAE)

A TEAE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. All TEAEs that occur after any subject has been enrolled, during treatment or within 14 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by Inhibikase Therapeutics or designee. AEs occurring more than once will be reported as a single AE with maximum severity with the onset date recorded as the occurrence ofthe first event.

Examples of TEAEs are as follows:

- Changes in the general condition of the subject
- Subjective symptoms offered by or elicited from the subject
- Objective signs observed by the PI or other study personnel
- All diseases that occur after the first dose of study drug
- All clinically significant abnormalities in laboratory values or clinically significant physical findings that occur after the first dose of study drug

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Suspected adverse reactions are any AEs for which there is a reasonable possibility that the drug caused the AE.

10.8.1.2 Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the investigational product thatfulfils one or more of the following:

- Results in death
- It is immediately life-threatening (see Section 10.8.1.2.1)
- It requires in-subject hospitalization or prolongation of existing hospitalization
- Results in a congenital abnormality or birth defect

- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

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

All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or within 14 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by Inhibikase Therapeutics or designee.

10.8.1.3 Life-threatening

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

10.8.1.4 Unexpected

An AE or suspected adverse reaction is considered "unexpected":

- If it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

In the clinical trial setting, the term "expected" would not mean "anticipated" for the condition being treated or population being studied since "expected" would indicate being "listed in the Investigator's Brochure." For example, some AEs can be anticipated to occur as a result of a disease or condition or in a certain population (e.g., cancer-related deaths in a cancer trial, strokes or acute myocardial infarctions in an older population).

However, for reporting purposes, these anticipated events are not considered "expected" if they are not listed in the Investigator's Brochure (i.e., the investigational drug is not suspected or known to cause them).

10.8.2 Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

10.8.2.1 Pregnancy

Pregnancy in itself is not regarded as an AE. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as an AE. Any pregnancy occurring during this study must be reported to the Investigator. The Investigator will promptly notify the Medical Monitor and withdraw the subject from the study. The Investigator should request permission to contact the subject, the subject's spouse/partner (if the subject is male and his spouse/partner becomes pregnant) or the obstetrician for information about the outcome of the pregnancy, and in the caseof a live birth, about any congenital abnormalities.

10.9. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

Guidelines for Assigning Relationship of the AE to the Study Drug

Not Related:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possibly Related:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probably Related:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product

for the purposes of expedited regulatory reporting.

10.10. Action Taken with Investigational Drug

Action taken with regard to administration of study drug will be recorded.

10.11. Assessment of Outcome

Assessment of outcome of AEs will be categorized as one of the following:

- Recovered/Resolved: The event has improved or recuperated
- Recovering/Resolving: The event is improving
- Not Recovered/Not Resolved: The event has not improved or recuperated
- Recovered/Resolved with Sequelae: The subject recuperated but retained pathological conditions resulting from the prior disease or injury
- Fatal: The termination of life as a result of an adverse event
- Unknown: Not known, not observed, not recorded, or refused

10.12. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs unless they prompt corrective medical action by the Investigator, constitute an SAE or lead to discontinuation of administration of study drug.

Information about AEs will be collected from the signing of the consent form until the final visit of the study for that subject. Adverse events that occur after the first administration of study drug will be denoted Treatment Emergent Adverse Events. All AEs will be followed until they are resolved or have reached a clinical plateau with no expectation of future change.

The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution or clinical plateau (date and time), intensity, causality, action taken, outcome, and whether or not it caused the subjectto discontinue the study.

Severity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 10.8.1.2. An AE of severe intensity may not necessarily be considered serious.

10.13. Reporting Adverse Events

All SAEs (regardless of causality) will be recorded from the signing of the consent form until 14 days following the last dose of study drug. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to Inhibikase Therapeutics or Inhibikase's designee within24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy to Inhibikase Therapeutics or designee.

Additional follow-up information, if required or available, should all be sent (fax, e-mail, etc.) to Inhibikase Therapeutics or designee within 24 hours of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

Inhibikase Therapeutics or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the PI's responsibility to notify the IRB of all SAEs that occur at his or her site if applicable per the IRB's requirements. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB of these additional SAEs.

Reporting to FDA

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32[c][1][i]). Before submitting an IND safety report, the Sponsor will ensure the event meets all 3 of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all 3 of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the AE and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence of serious suspected adverse reactions over that listed in the protocol or Investigator's Brochure.

11. STATISTICS

11.1. General Principles

The below mentioned general principles will be followed throughout the study:

- A detailed description of the analysis methods to be performed in the study will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized andapproved prior to the database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the clinical study report.
- All summaries (safety, tolerability and PK) will be presented by the groups subjects are randomized to and on each schedule time point.
- For vital signs, the baseline value is defined as the last value observed prior to first administration of study medication on Day 1. For other safety variables the baseline value is defined as the value observed on Day -1. If for a subject the Day -1 value is missing, then Screening value will be considered as baseline.
- The change from baseline is defined as the post-baseline value minus the baseline value.
- Missing data will not be imputed but will be analyzed as missing.
- Descriptive statistics will include number of non-missing patients (n), mean, standard deviation (SD), median, minimum, and maximum values for continuous variables, and for categorical variables the frequencies and percentages of patients will be presented.
- For continuous safety data, mean and median will be rounded to 1 additional decimal place, SD will be rounded to 2 additional decimal places compared to the original data and minimum and maximum will be displayed with the same accuracy as the original data, except the baseline and demographic characteristic.
- For continuous baseline and demographic characteristic data, mean and median will be rounded to 1 decimal place, SD will be rounded to 2 decimal places and minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- In addition, for PK data, arithmetic mean, geometric mean, SD and coefficient of variation (CV%) will be rounded to 3 significant figures.
- For the PK analysis, plasma and urine concentrations that are reported as below the limit of quantification of the assay (BLQ) will be treated as zero if they occur before T_{max} and will be treated as missing thereafter.
- The number of BLQ values i.e., the n below lower limit of quantification (LLOQ) will be reported for each time point.
- All study data will be included in study data listings. In general, all data will be listed by time point within subject. All summary tables will present descriptive statistics for the parameters being analyzed.
- No adjustment will be done for multiple comparisons in this study as this is exploratory study.
- SAS® version 9.4 or higher will be used for all analyses.

11.2. Populations

The Pharmacokinetic (PK) Population is defined as all subjects who are administered IkT-148009 and have at least one bioanalysis result for the plasma concentration of IkT-148009.

The Safety Population is defined as all subjects who are administered study drug.

11.3. Sample Size Calculation

No formal sample size calculations have been undertaken for this pharmacokinetic, safety and tolerability study. The number of subjects is thought to besufficient to assess preliminary pharmacokinetic profile of IkT-148009 in addition to safety andtolerability following multiple doses of IkT-148009. No efficacy parameters are beingcollected or analyzed for this Phase I study.

This study is not powered for direct inferential statistical analyses.

11.4. Safety Analysis

Safety assessments will include TEAEs tabulated by cohort; descriptive statistics for continuous variables and frequency counts for discrete variables. No inferential statistical analysis is planned for safety data.

The number and percentage of subjects reporting TEAEs will be tabulated for the safety analyses set by MedDRA preferred term and system organ class with a breakdown by treatment, and further by relationship to study drug, as well as by maximum severity. Listings of deaths, SAEs, and TEAEs that lead to discontinuation of a subject will be presented.

For laboratory data, a treatment-emergent abnormal value is an abnormality that was not present before dosing, but was present after dosing, or one that represents an exacerbation of a pre-existing abnormal value.

All clinical laboratory data will be listed by subject for the safety analysis set, with abnormal lab results presented by subject in another listing. Descriptive statistics will be provided for baseline, end of study and for other times during the study if appropriate.

Vital signs will be listed at each time point for all subjects in the safety analysis set. Clinically significant findings on Safety ECGs will be recorded as TEAEs, coded, listed and tabulated. Physical examination findings including neurological examination findings will belisted for all subjects in the safety analysis set. Clinically significant findings will be included as TEAEs.

No imputation of values for missing data will be performed. Standard clinical monitoring and data management practices will be used to ensure the integrity of data.

AEs will be coded using MedDRA™ with the version used specified in the clinical study report. The overall incidence of AEs will be displayed by System Organ Class (SOC), preferred term, and dose group.Incidence of AEs will also be presented by maximum severity and relationship to study drug. Datafrom vital signs, clinical laboratory measures, Safety ECGs will be summarized using

descriptive statistics by dose group and time point, where applicable. Continuous endpoints will be summarized with n, mean, standard deviation, median, minimum and maximum. In addition, change from baseline values will be calculated at each time point andwill be summarized using descriptive statistics. Out-of-range safety endpoints may be categorizedas low or high, where applicable. For all categorical endpoints, summaries will include counts andpercentages.

11.5. Pharmacokinetic Analysis

PK parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentration (T_{max}) will be summarized using n, mean, standard deviation, median, minimum, and maximum. All other PK parameters will be summarized using n, geometric mean, coefficient of variation, median, minimum, and maximum.

Dose proportionality will be analyzed using a generalized ANOVA model using the logarithm of PK parameter (AUC, C_{max} and C_{trough}) as the dependent variable and the logarithm of the dose as the independent variable (Weerahandi, 1994; Ogenstad, 1998). Point estimates and the corresponding generalized CIs will be estimated for AUC, C_{max} and C_{trough}. For AUC, C_{max} and C_{trough}, the treatment ratio 'test/reference' will be calculated by taking the anti-logarithm of the difference between treatment means. A 90% confidence interval will be constructed for the geometric mean test-to-reference ratio for AUC, C_{max} and C_{trough}. Apparent clearance and apparent volume of distribution will be estimated by using the population pharmacokinetic (PPK) approach. Further details of the above analyses will be provided in the SAP.

Data from subjects who experience emesis will be deleted from statistical analyses if vomiting occurs at or before two times the median T_{max}.

Statistical software for the analysis will be SAS version 9.4 (SAS Institute) or later and XPro (X-Techniques, Inc.).

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Inhibikase Therapeutics or designee will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to the protocol adherence, and the responsibilities of Inhibikase Therapeutics or designee or its representatives. This will be documented in a Clinical Study Agreement between Inhibikase Therapeutics and the Investigator.
- During the study, a monitor from Inhibikase Therapeutics or designee will have regular contacts with the investigational site, for the following:
  - Provide information and support to the Investigator(s)
  - Confirm that facilities remain acceptable
  - Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
  - Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records foreach subject (e.g., clinic charts).
  - Record and report any protocol deviations not previously sent to Inhibikase Therapeutics or designee.
  - Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Inhibikase Therapeutics or designee and those SAEs thatmet criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

12.2. Audits and Inspections

Authorized representatives of Inhibikase Therapeutics, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an Inhibikase Therapeutics or designee audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact Inhibikase Therapeutics immediately if contacted by a regulatory agency about an inspection.

12.3. Institutional Review Board (IRB)

The PI must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

13. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator and institution will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Inhibikase Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

14. ETHICS

14.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form (ICF), must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Inhibikase Therapeutics or designee before he or she can enroll any subject/subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product.

Inhibikase Therapeutics or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

14.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Appendix 8) and are consistent with ICH/Good Clinical Practice and other applicable regulatory requirements.

14.3. Written Informed Consent

The PI will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The PI must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

15. DATA HANDLING AND RECORDKEEPING

15.1. Inspection of Records

Inhibikase Therapeutics or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

15.2. Retention of Records

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Inhibikase Therapeutics or designee or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

15.3. Confidentiality

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Inhibikase Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

16. PUBLICATION POLICY

All information concerning IkT-148009 is considered confidential and shall remain the sole property of Inhibikase Therapeutics.

Inhibikase and the Investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Inhibikase and the Investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the Investigators or their personnel and associates resulting from or relating to this study must be submitted to Inhibikase for review and approval before submission for publication or presentation. If the proposed publication or presentation contains patentable subject matter, which, at Inhibikase' sole discretion, warrants intellectual property protection, Inhibikase may delay any publication or presentation for up to 30 days after approval for the purpose of pursuing such protection.

17. LIST OF REFERENCES

S. Brahmachari, P. Ge, S. H. Lee, D. Kim, S. S. Karuppagounder, M. Kumar, X. Mao, J. H. Shin, Y. Lee, O. Pletnikova, J. C. Troncoso, V. L. Dawson, T. M. Dawson, H. S. Ko, Activation of tyrosine kinase c-Abl contributes to α-synuclein-induced neurodegeneration. J Clin Invest. 126, 2970-88 (2016).

S. Brahmachari, S. S. Karuppagounder, P. Ge, S. Lee, V. L. Dawson, T. M. Dawson, H. S. Ko, c-Abl and Parkinson's Disease: Mechanisms and Therapeutic Potential. J Parkinsons Dis. 7, 589-601 (2017).

G. I. Cancino, E. M. Toledo, N. R. Leal, D. E. Hernandez, L. F. Yévenes, N. C. Inestrosa, A. R., STI571 prevents apoptosis, tau phosphorylation and behavioural impairments induced by Alzheimer's beta-amyloid deposits of article. Brain 131, 2425–2442 (2008).

W. Dauer, S. Przedborski, Parkinson’s disease: mechanisms and models. Neuron. 39, 889–909 (2003).

T. M. Dawson, V. L. Dawson, J. Fan, Cell Death Mechanisms of Neurodegeneration. Adv Neurobiol. 15, 403-425 (2017).

T. M. Dawson, H. S. Ko, V. L. Dawson, Genetic animal models of Parkinson’s disease. Neuron. 66, 646–661 (2010).

G. S. Gaki, A. G. Papavassiliou, Oxidative stress-induced signaling pathways implicated in the pathogenesis of Parkinson's disease. Neuromolecular Med. 16, 217-30 (2014).

M. Goedert, α-Synuclein and neurodegenerative diseases. Nat Rev Neurosci. 2, 492–501 (2001).

M. Goedert, M. G. Spillantini, K. Del Tredici, H. Braak, 100 years of Lewy pathology. Nat Rev Neurol. 9, 13–24 (2013).

M. L. Hebron, I. Lonskaya, C. E. Moussa, Nilotinib reverses loss of dopamine neurons and improves motor behavior via autophagic degradation of α-synuclein in Parkinson's disease models. Hum Mol Genet. 22, 3315-28 (2013).

S. Z. Imam, W. Trickler, S. Kimura, Z. K. Binienda, M. G. Paule, W. Slikker Jr, S. Li, R. A. Clark, S. F. Ali, Neuroprotective efficacy of a new brain-penetrating C-Abl inhibitor in a murine Parkinson’s disease model. *PLoS One*. **8**, e65129 (2013).

S. Z. Imam, Q. Zhou, A. Yamamoto, A. J. Valente, S. F. Ali, M. Bains, J. L. Roberts, P. J. Kahle, R. A. Clark, S. Li, Novel regulation of parkin function through c-Abl-mediated tyrosine phosphorylation: implications for Parkinson’s disease. J Neurosci. 31,157–163 (2011).

K. A. Jellinger, Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. Mov Disord 27, 8–30 (2012).

Z. Jing, J. Caltagarone, R. Bowser Altered subcellular distribution of c-Abl in Alzheimer's disease of article. J Alzheimers Dis. 17,409–422 (2009).

S. S. Karuppagounder, S. Brahmachari, Y. Lee, V. L. Dawson, T. M. Dawson, H. S. Ko,The c-Abl inhibitor, nilotinib, protects dopaminergic neurons in a preclinical animal model of Parkinson's disease. Sci Rep. 4,4874 (2014).35. Weerahandi, S. (1994) Exact Statistical Methods for Data Analysis, New York: Springer-Verlag.

D. Kirik, A. Bjorklund, Modeling CNS neurodegeneration by overexpression of disease-causing proteins using viral vectors. Trends Neurosci 26,386–392 (2003).

H. S. Ko, Y,. Lee, J. H. Shin, S. S. Karuppagounder, B. S. Gadad, A. J. Koleske, O. Pletnikova, J. C. Troncoso, V. L. Dawson, T. M. Dawson, Phosphorylation by the c-Abl protein tyrosine kinase inhibits parkin's ubiquitination and protective function. Proc Natl Acad Sci U S A. 107,16691–16696 (2010).

Kuo YM, Li Z, Jiao Y, Gaborit N, Pani AK, Orrison BM, Bruneau BG, Giasson BI, Smeyne RJ, Gershon MD, Nussbaum RL. Extensive enteric nervous system abnormalities in mice transgenic for artificial chromosomes containing Parkinson disease-associated alpha-synuclein gene mutations precede central nervous system changes. Hum Mol Genet. 19, 1633-50 (2010).

Lacy BE, Levenick JM, Crowell M. Chronic constipation: new diagnostic and treatment approaches. Ther Adv Gastoenterol 5:233-247 (2012).

V. M. Lee, J. Q. Trojanowski, Mechanisms of Parkinson's disease linked to pathological alpha-synuclein: new targets for drug discovery. Neuron. 52, 33–38 (2006).

I. Lonskaya, M. L. Hebron, S. T. Selby, R. S. Turner, C. E. Moussa, Nilotinib and bosutinib modulate pre-plaque alterations of blood immune markers and neuro-inflammation in Alzheimer's disease models. Neuroscience 304, 316-27 (2015).

I. Lonskaya, M. L. Hebron, N. M. Desforges, A. Franjie, C. E. Moussa, Tyrosine kinase inhibition increases functional parkin-Beclin-1 interaction and enhances amyloid clearance and cognitive performance. EMBO Mol Med. 5, 1247-62 (2013).

K. C. Luk, V. Kehm, J. Carroll, B. Zhang, P. O'Brien, J. Q. Trojanowski, V. M. Lee, Pathological α-synuclein transmission initiates Parkinson-like neurode- generation in nontransgenic mice. Science. 338, 949–953 (2012).

X. Mao, M. T. Ou, S. S. Karuppagounder, T. I. Kam, X. Yin, Y. Xiong, P. Ge, G. E. Umanah, S. Brahmachari, J. H. Shin, H. C. Kang, J. Zhang, J. Xu, R. Chen, H. Park, S. A. Andrabi, S. U. Kang, R. A. Gonçalves, Y. Liang, S. Zhang, C. Qi, S. Lam, J. A. Keiler, J. Tyson, D. Kim, N. Panicker,

S. P. Yun, C. J. Workman, D. A. Vignali, V. L. Dawson, H. S. Ko, T. M. Dawson, Pathological α-synuclein transmission initiated by binding lymphocyte-activation gene 3. Science 353, (2016).

E. Masliah, E. Rockenstein, I. Veinbergs, M. Mallory, M. Hashimoto, A. Takeda, Y. Sagara, A. Sisk, L. Mucke, Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders. Science 287,1265– 1269 (2000).

I. Martin, V. L. Dawson, T. M. Dawson, Recent advances in the genetics of Parkinson's disease. Annu Rev Genomics Hum Genet. 12, 301–325 (2011).

Ogenstad, S. The Use of Generalized Tests in Medical Research. Journal of Biopharmaceutical Statistics, 8(4), 497-508, 1998.

C. W. Olanow, P. Brundin, Parkinson's disease and alpha synuclein: is Parkinson's disease a prion-like disorder? Mov Disord. 28, 31-40 (2013)

C. W. Olanow, S. B. Prusiner, Is Parkinson's disease a prion disorder. Proc Natl Acad Sci U. S. A. 106,12571–12572 (2009).

M. H. Polymeropoulos, C. Lavedan, E. Leroy, S. E. Ide, A. Dehejia, A. Dutra, B. Pike, H. Root, J. Rubenstein, R. Boyer, E. S. Stenroos, S. Chandrasekharappa, A. Athanassiadou, T. Papapetropoulos, W. G. Johnson, A. M. Lazzarini, R. C. Duvoisin, G. Di Iorio, L. I. Golbe, R. L. Nussbaum, Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276, 2045–2047 (1997).

Rentz AM, Kahrilas P, Stanghellini V, *et al*. Development and psychometric evaluation of the patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM) in patients with upper gastrointestinal disorders. Qual Life Res. 2004;13:1737‑1749.

J.M. Savitt, V. L. Dawson, T. M. Dawson, Diagnosis and treatment of Parkinson disease: molecules to medicine. J Clin Invest. 116, 1744–1754 (2006).

A. H. V. Schapira, C. W. Olanow, J. T. Greenamyre, E. Bezard, Slowing of neurodegeneration in Parkinson's disease and Huntington's disease: future therapeutic perspectives. Lancet 384, 545-555 (2014).

M. G. Spillantini, M. L. Schmidt, V. M. Lee, J. Q. Trojanowski, R. Jakes, M. Goedert M, Alpha-synuclein in Lewy bodies. Nature 388, 839–840 (1997).

M. A. Tremblay, C. M. Acker, P. Davies, Tau phosphorylated at tyrosine 394 is found in Alzheimer's disease tangles and can be a product of the Abl-related kinase, Arg. J Alzheimers Dis. 19, 721–733 (2010).

Weerahandi, S. Exact Statistical Methods for Data Analysis, New York: Springer-Verlag. 1994.

B. Winner, R. Jappelli, S. K. Maji SK, P. A. Desplats , L. Boyer, S. Aigner , C. Hetzer, T. Loher,

M. Vilar, S. Campioni S, C. Tzitzilonis , A. Soragni, S. Jessberger, H. Mira, A. Consiglio, E. Pham, E. Masliah, F. H. Gage, R. Riek, In vivo demonstration that alpha-synuclein oligomers are toxic. Proc Natl Acad Sci USA 108: 4194–4199 (2011).

X-Techniques, Inc: XPro: Exact Procedures for Parametric Inference, X-Techniques, Inc., Millington, NJ, 1994.

Folstein, M., Folstein, S. E., & McHugh, P. R., Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12, 189-198 (1975).

Larner, A. J. (Ed.) Cognitive screening instruments: A practical approach. NY: Springer. (2013).

Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N; Movement Disorder Society UPDRS Revision Task Force. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008 Nov 15;23(15):2129-70. doi: 10.1002/mds.22340. PMID: 19025984.

Guy, W. "Clinical Global Impressions". *ECDEU Assessment Manual for Psychopharmacology—Revised*. Rockville, MD: U.S. Department of Health, Education, and Welfare; Public Health Service, Alcohol; Drug Abuse, and Mental Health Administration; National Institute of Mental Health; Psychopharmacology Research Branch; Division of Extramural Research Programs. 1976, pp. 218-222. OCLC 2344751. DHEW Publ No ADM 76–338 – via Internet Archive.

Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, Ondo W, Abe K, Macphee G, Macmahon D, Barone P, Rabey M, Forbes A, Breen K, Tluk S, Naidu Y, Olanow W, Williams AJ, Thomas S, Rye D, Tsuboi Y, Hand A, Schapira AH. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. Mov Disord. 2007 Oct 15;22(13):1901-11. doi: 10.1002/mds.21596. PMID: 17674410.

Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Qual Life Res. 1995 Jun;4(3):241-8. doi: 10.1007/BF02260863. PMID: 7613534.

APPENDIX 1. SCHEDULE OF EVENTS

Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Visit Window	**D-28 to D-1**	**D-1**	**0 to +24h**	**+24h to +48h**	**+48h to +72h**	**+72h to +96h**	**+96 to +120h**	**+120 to +144h**	**+144 to +168h**	**+168 to +192h**	**+192 to 216h**			**D14 (±1d) Follow -up**	**D21 (±1d) End of Study**
Visit Days	**Screen**		**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**Follow Up**	**End of Study**
Informed Consent	X														
Inclusion/ Exclusion	X														
Demographics	X														
Medical History	X														
MMSE[9]	X	X							X						X
Physical Examination / Neurological Examination	X	X				X					X				X
Body Weight/Height/Fluid intake/Urine output[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC/Serum Chemistry[1]	X	X	X	X	X	X	X	X		X	X			X	X
FSH/LH/ testosterone/ inhibin B[2]	X	X		X						X				X	X
Urinalysis[1]	X	X		X						X					X
Drug/Alcohol Screen[3]	X	X													
Hepatitis & HIV Screen	X														
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pulse oximetry	X	X	X	X	X	X	X	X	X	X	X	X		X	X

Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Visit Window	**D-28 to D-1**	**D-1**	**0 to +24h**	**+24h to +48h**	**+48h to +72h**	**+72h to +96h**	**+96 to +120h**	**+120 to +144h**	**+144 to +168h**	**+168 to +192h**	**+192 to 216h**			**D14 (±1d) Follow -up**	**D21 (±1d) End of Study**
Visit Days	**Screen**		**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**Follow Up**	**End of Study**
12-Lead Safety ECG[5]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Echocardiogram		X													
Plasma PK Samples[6]			X	X		X		X	X	X	X	X	X		
Urine PK Samples[6]			X						X						
Confined to Unit		X	X	X	X	X	X	X	X	X	X	X	X		
C-SSRS	X		X			X			X					X	X
Administer Study Drug			X	X	X	X	X	X	X						
Adverse Events[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion															X

[1]Screening and Safety Laboratory Tests: V1; V2; V3: pre-dose; V4: pre-dose; V5: pre-dose; V6: pre-dose; V7: pre-dose; V8: pre-dose; V10: 24 hr post-V9dose; V11: 48 hr post-V9 dose; V14 and V15. Urinalysis will be performed at V1, V2, V4: pre-dose; V10: 24 hr post-V9 dose, and V15.

[2]At screening, baseline, 24 hours after D1 dosing but before dosing on D2, 24 hours after last dose, follow-up and end of study. FSH/LH/Inhibin B/Testosteroneto be tested in both genders. Inhibin B results need not be known at screening or baseline prior to dosing.

[3]Urine drug and alcohol screen will be conducted at Visit 1 during Screening and Day -1 (Admission).

[4]Vital Signs: V1, V2, V3: pre-dose and post-dose at: 1hr, 2 hr, 4 hr, 8 hr, 12 hr, 18 hr; V4: pre-dose and post-dose at 4 hr, 8 hr, 12 hr; V5: pre-dose and post- dose 12 hr; V6: pre-dose and post-dose 12 hr; V7: pre-dose and post-dose 12 hr; V8: pre-dose and post-dose 12 hr; V9: pre-dose and post-dose 12 hr; V10: 24hr post-V9 dose; V11: 48 hr post-V9 dose; V12: 72 hours post-V9 dose; V14 and V15.

[5]12-Lead Safety ECG: V1; V2; V3 pre-dose and post-dose at 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, V4: pre-dose and 12 hr post-dose; V5: pre-dose and 12 hr post-dose; V6: pre-dose and 12 hr post-dose; V7: pre-dose and 12 hr post-dose; V8: pre-dose and 12 hr post-dose; V9: pre-dose and 12 hr post-dose; V10: 24 hr post-V9dose; V11: 48 hr post-V9 dose; V12: 72 hr post-V9 dose; V14 and V15.

[6]Plasma PK samples; V3: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), 12 (+/- 30min), 16 (+/-1hr); V4: pre-dose (-15 min), 2 hr (+/- 30 min), 5 hr (+/- 30 min), 8 hr (+/- 30 min); V6: pre-dose (-15 min), 2 hr (+/- 30 min), 5 hr (+/- 30 min), 8hr (+/- 30 min); V8: pre-dose (- 15 min); V9: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), and 16 (+/-1hr); V10: 24 hr post-V9 dose +/- 1 hr; and V11: 48 hr post-V9 dose +/- 1 hr; V12: 72 hr post-V9 dose +/- 2 hr; V13: 96 hr post-V9 dose+/- 2 hr . Urine PK samples will collect 24-hour pooled urines on the indicated

days. The 24-hour collection on Day 1 starts at dosing and collected for 24 hours prior to next day's dose. The 24-hour collection on Day 7 starts at dosing and collected for 24 hours prior to the next day's dose.

[7]Adverse Events and concomitant medications (new or changed) will be collected during Visit 1 at both Screening and Day -1 (Admission) in addition to theother time points noted in the Schedule of Events.

[8]Height is measured only at screening. Weight is collected daily. Fluid intake/Urinary output volumes collected from 0 hour to 192 hour.

[9]The MMSE is administered at screening and repeated pre-dose at V2 to ensure the MMSE inclusion criteria is met. The MMSE is repeated at approximately thesame time of day (+/-1 hour) on V9 as it was administered at V2. The MMSE is administered again at V15 (End of Study) only if the MMSE score at V9 was significantly different, per investigator clinical judgment, than it was at the V2 administration or upon early termination of the subject.

APPENDIX 2. DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964

and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human patients, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human patients to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human patients.

6. The primary purpose of medical research involving human patients is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is patient to ethical standards that promote and ensure respect for all human patients and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research patients.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients. The responsibility for the protection of research patients must always rest with the physician or other health care professionals and never with the research patients, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human patients in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human patients must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.

15. Appropriate compensation and treatment for patients who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human patients may only be conducted if the importance of the objective outweighs the risks and burdens to the research patients.

17. All medical research involving human patients must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the

condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human patients unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human patients must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human patients must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for patients and information regarding provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human patients capable of giving informed consent, each potential patient must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential patient must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information.

After ensuring that the potential patient has understood the information, the physician or another appropriately qualified individual must then seek the potential patient's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research patients should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential patient is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research patient who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential patient, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research patient who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential patient's

dissent should be respected.

30. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the patient or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable;or

where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention;

and

the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be patient to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human patients must be registered in a publicly accessible

database before recruitment of the first patient.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human patients and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

STATISTICAL ANALYSIS PLAN

PROTOCOL: IkT-148009-101

A Phase I, Randomized Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) Study to Determine the Safety, Tolerability and Pharmacokinetics (PK) of Ikt-148009 in Older Adult and Elderly Healthy Volunteers with Extension into Parkinson's Patients

SPONSOR: Inhibikase Therapeutics
3350 Riverwood Pkwy SE
Suite 1900
Atlanta, GA 30339
Telephone: 678 392 3419
Fax: 770 240 1401

PRODUCT: IkT-148009

AUTHORS: Jeffrey S. Finman, Ph.D.
Chief of Biostatistics
Cognitive Research Corporation
200 Central Ave. Suite 1230
Saint Petersburg, FL 33701

Brenda Krogen, M.S.
Biometrics, Manager
Cognitive Research Corporation
200 Central Ave. Suite 1230
Saint Petersburg, FL 33701

Carlos A. Rodríguez, Ph.D.
Director of Clinical Pharmacology and PK/PD
PharmaPolaris International, Inc.
1490 Bellwood Rd
San Marino, CA 91108

DATE: 20 July 2022

STATUS: Final Version 1.0

Statistical Analysis Plan
Protocol: IkT-148009
Final Version: 1.0 Date: 20 July 2022

STATISTICAL CRO REPRESENTATIVE DOCUMENT REVIEWED AND APPROVED BY:	
SIGNATURE:	DATE: 26-July-2022
NAME: Jeffrey S. Finman, PhD	
DEPARTMENT/TITLE: Chief of Biostatistics, Cognitive Research Corporation	

STATISTICAL CRO REPRESENTATIVE DOCUMENT REVIEWED AND APPROVED BY:	
SIGNATURE:	DATE: 21 JUL 2022
NAME: Brenda L. Krogen, M.S.	
DEPARTMENT/TITLE: Biometrics Manager, Cognitive Research Corporation	

PHARMACOKINETICS CRO REPRESENTATIVE DOCUMENT REVIEWED AND APPROVED BY:	
SIGNATURE:	DATE: July 20th 2022
NAME: Emil Samara, Ph.D.	
DEPARTMENT/TITLE: President, PharmaPolaris International Inc.	

SPONSOR COMPANY REPRESENTATIVE DOCUMENT REVIEWED AND APPROVED BY:	
SIGNATURE:	DATE: 7/20/2022
NAME: Milton H. Werner, PhD	
DEPARTMENT/TITLE: President & CEO, Inhibikase	

TABLE OF CONTENTS

IN-TEXT TABLES

AMENDMENT HISTORY

Not applicable

1. LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the time-concentration curve
BLQ	Below the limit of quantitation of assay
BMI	Body mass index
CBC	Complete blood count
CGI-I	Clinical Global Impression of Improvement
CK	Creatinine kinase
C_{max}	Maximum plasma concentration
$C_{max, ss}$	Maximum concentration at steady-state
CNS	Central Nervous System
CRC	Clinical Research Center
CRO	Clinical Research Organization
CRU	Clinical Research Unit
CSBM	Complete Satisfaction with Bowel Movement
CSF	Cerebro-spinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
C_{trough}	Concentration at trough
CV	Coefficient of Variation
ECG	Electrocardiogram
EPQT	Early Precision QT Technique

Abbreviation or Specialist Term	Explanation
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCSI	Gastroparesis Cardinal Symptom Index
GGT or γ-GT	Gamma-glutamyl transferase
GI	Gastrointestinal
HIV	Human immunodeficiency virus
INR	International normalized ratio of prothrombin time
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LLOQ	Lower limit of quantification
MAD	Multiple ascending dose
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
MTD	Maximum tolerated dose
NMSS	Non-Motor Symptom Score
PAGI-SYM	Patient Assessment of Upper GI Disorders Severity Index
PD	Parkinson's Disease
PDQ-39	Parkinson's Disease Questionnaire 39
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PI	Principal Investigator
PK	Pharmacokinetics
PPK	Population Pharmacokinetic
PT	Prothrombin time
PT-INR	Prothrombin time – international normalized ratio
QTcF	QT interval

Abbreviation or Specialist Term	Explanation
RBC	Red blood cell count
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SD	Standard deviation
SOC	System organ class
SOE	Schedule of events
SOP	Standard operating procedure
SRC	Safety Review Committee
$T_{1/2}$	Half-life
TEAE	Treatment emergent adverse event
TFL	Tables, Figures, and Listings
T_{max}	Time at maximum plasma concentration
TSH	Thyroid stimulating hormone
US	United States
VS	Vital signs
WBC	White blood cell count

2. INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses for the study entitled “A Phase I, Randomized Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) Study to Determine the Safety, Tolerability, and Pharmacokinetics (PK) of IkT-148009 in Older Adult and Elderly Healthy Volunteers with Extension to Parkinson’s Patients” (V1.7, 24 January 2022). Mock shells for Appendix 14 of the Clinical Study Report (CSR) will also be produced as a separate working document to facilitate the programming of Tables, Figures, and Listings (TFLs) according to the finalized 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 CSR.

3. STUDY OBJECTIVES

3.1. Primary Objectives

3.1.1. Parts A and B

1. To assess the safety and tolerability of IkT-148009 given as gelatin capsule;
2. To assess the PK profile of single doses and multiple doses (once daily for seven days) of IkT-148009 gelatin capsules in the fed state;
3. To investigate plasma and urine concentrations of IkT-148009.

3.1.2. Part C

4. To assess safety, tolerability, PK, biomarkers, and clinical effects in Parkinson’s Disease (PD) participants

4. STUDY DESIGN

4.1. Duration of Study

The total duration of the study, excluding Screening, will be approximately 15 days (Day -1 through End of Study visit) for Part A, and 22 days (Day -1 through End of Study visit) for Parts B and C. The duration of study treatment (IkT-148009/placebo) is 1 day for Part A and 7 days for Parts B and C.

4.2. Number of Participants (Study Population)

Up to 80 older adult and elderly subjects are planned to be recruited in Part A of this study, depending on the number of cohorts studied, and up to 32 subjects are planned to be recruited in Part B and up to 24 patients in Part C, again depending on the number of cohorts studied.

4.2.1. Replacement of Subjects

Subjects who withdraw or are withdrawn from the study prior to dosing will be replaced, and subjects who withdraw or are withdrawn from the study after study drug dosing may be replaced at the discretion of the sponsor. Additional cohorts may be considered to accommodate dose repetition, slower dose escalation or escalation beyond currently planned doses.

4.3. Design

This is a randomized, Phase I, Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) study to determine the safety, tolerability and pharmacokinetics (PK) of IkT-148009 gelatin capsules in Older and Elderly Healthy Adults with extension to Parkinson's Disease. Escalation to the next dose will be undertaken only after safety, tolerability, and PK data have been reviewed by the Safety Review Committee (SRC) and an agreement has been reached that it is safe to increase the dose. The SRC will not receive any unblinded PK data unless it is agreed upon by the SRC to unblind a subject and/or cohort based on the completed safety review.

4.3.1. Part A (Single Ascending Dose Cohorts)

Cohorts will consist of eight (8) subjects, six (6) of whom will receive treatment with IkT-148009 and two (2) with a matching placebo. The maximum recommended starting dose for this part of the Phase 1 study is 25 mg.

Cohort	Maximum Proposed Escalation from Previous Cohort	IkT-148009 Maximum Planned Dose (mg)
1	N/A	25
2	½ X	12.5
3	3 X	37.5
4	2 X	75
5	1.33 X	100
6	1.33 X	125[1]
7	1.4 X	175[1]
8	1.43 X	250[1]
9	1.3 X	325[1]
10	1.23 X	400[1]

[1]Escalation to these doses or any fraction thereof subject to the determination by the Safety Review Committee

The SAD cohorts will consist of up to 8 visits for up to 28 days prior to dosing and 14 days after dosing.

Sentinel dosing will be employed for each cohort in the SAD part of this study, with one subject randomized to receive IkT-148009 and the other placebo on the first day. These two subjects in each cohort will be monitored for 48 hours after dosing before deciding to dose the remainder of the cohort. As such, the other six subjects in the first cohort will be dosed approximately 48 hours later. Each cohort will be monitored for at least 48 hours before initiating the next (higher dose) cohort. Each cohort will be dosed at approximately weekly intervals to allow adequate time for the collection and review of safety and PK data.

If SAD clinical exposure and PK data through 2 or more cohorts raise no concerns to the SRC, the MAD may commence at the discretion of the SRC while the remaining SAD cohorts are completed.

4.3.2. Part B (Multiple Ascending Dose Cohorts)

Cohorts will consist of eight (8) subjects, six (6) of whom will receive treatment with IkT-148009 and two (2) with a matching placebo. The maximum recommended starting dose and the doses for the dose escalation cohorts for this portion of the Phase I study will be selected based on the available nonclinical data and the pharmacokinetic and safety results from the SAD study.

Cohort	Maximum Proposed Escalation from Previous Cohort	IkT-148009 Maximum Planned Dose (mg)
1	N/A	12.5
2	2 X	25
3	2 X	50[1]
4	2 X	100[1]

[1]Escalation to these doses or fraction thereof subject to the determination by the Safety Review Committee

MAD cohorts will consist of up to 15 visits over 49 days, including 7 days of dosing.

Subjects in each cohort of Part B of the study will be admitted to the unit approximately 24 hours prior to the expected time of dosing. They will be confined to the unit for approximately 12 days in Part B. No subject may be discharged from the unit until the Investigator is satisfied that they have no continuing adverse events related to the study drug.

If SAD clinical exposure and PK data through 2 or more cohorts raise no concerns to the SRC, MAD may commence at the discretion of the SRC while the remaining SAD cohorts are completed. The MAD may be paused or adapted based on the subsequent SAD exposure or safety data.

In the Part B MAD cohorts, optional cerebrospinal fluid (CSF) collection will be offered to eligible participants. To be eligible, participants must have INR values at screening less than or equal to 1.4 and platelets greater than 50. After consent, approximately 4cc of CSF (2cc in each of 2 tubes) will be collected using the standard sterile technique. CSF will be used for PK analysis and banked for future exploratory analysis.

4.3.3. Part C (Multiple Ascending Dose Extension into Parkinson's Disease Patients)

If Part B clinical experience and PK data through 2 or more cohorts raise no concerns to the SRC, the MAD extension into PD participants may commence at the discretion of the SRC while the remaining Part A and Part B cohorts are completed.

Cohorts will consist of eight (8) subjects, six (6) of whom will receive treatment with IkT-148009 and two (2) with a matching placebo. The starting dose and the subsequent doses for this portion of the Phase I study will be selected based on available nonclinical data and the pharmacokinetic and safety results from Parts A and B.

Cohort	Maximum Escalation from Previous Cohort	IkT-148009 Maximum Dose (mg)
1	N/A	50
2	2 X	100[1]
3	2 X	200[1]

[1]Escalation to these doses or fraction thereof subject to the determination by the Safety Review Committee

Subjects in each cohort of Part C of the study will be admitted to the unit approximately 24 hours prior to the expected time of dosing. They will be confined to the unit for up to 12 days in Part C. No subject may be discharged from the unit until the Investigator is satisfied that they have no continuing adverse events that could be related to the study drug.

In the Part C MAD cohorts, optional cerebrospinal fluid (CSF) collection will be offered to eligible participants. To be eligible, participants must have INR values at screening less than or equal to 1.4 and platelets greater than 50. After consent, approximately 4cc of CSF (2 ccs in each of 2 tubes0 will be collected using standard sterile technique. CSF will be used for PK analysis and banked for future exploratory analysis.

Refer Section 4.4 for the schedule of events for the complete list of study assessments and timings for Parts A, B, and C.

4.3.4. Treatment Period

Subjects in Parts A, B, and C will be randomly assigned to either IkT-148009 or a matching placebo according to a randomization schedule prepared by an independent statistician.

4.3.4.1. IKT-148009 Part A SAD Dosing Regimen

IkT-148009 or a matching placebo will be administered once with a meal. The starting dose will be 25 mg (Cohort 1). The doses for the subsequent cohorts will be determined based on the results from the previous cohorts until the MTD has been determined. Refer to Section 4.3.1 for the planned dose escalation schema.

4.3.4.2. IkT-148009 Part B MAD Dosing Regimen

The SRC will determine the overall safety and characterize the PK of SAD dose cohorts through two or more cohorts. If the SRC finds these data to be reassuring at this point, Part B of this study (MAD) may begin. IkT-148009, or a matching placebo, will be administered once with a meal daily for seven days in Part B. The maximum recommended starting dose and the doses for the dose escalation cohorts for this portion of the Phase I study will be selected based on the available nonclinical data and the pharmacokinetic and safety results from the SAD study. Refer to Section 4.3.2 for the planned dose escalation schema.

If the MAD Part B begins before the SAD is completed, the MAD studies may be paused or adapted based on SAD exposure or safety data after two or more SAD cohorts.

4.3.4.3. IkT-148009 Part C PD MAD Dosing Regimen

If Part B clinical exposure and PK data through 2 or more cohorts raise no concerns to the SRC, Part C may commence at the discretion of the SRC while the remaining Part A and Part B cohorts are completed.

IkT-148009 or a matching placebo will be administered once with a meal daily for up to 7 days. The starting dose and subsequent doses for this portion of the Phase I study will be selected based on available nonclinical data and the pharmacokinetic and safety results from Parts A and B. Refer to Section 4.3.3 for the planned dose escalation schema.

4.3.4.4. Dose Adjustment

The SRC will assess the safety, tolerability, and pharmacokinetic information collected for each dose level and determine that the next cohort should:

- advance to the next planned dose level;
- advance to a dose lower than the next planned dose level; or
- repeat the previous dose level.

In addition, the SRC may stop the study for safety reasons at any time. The committee may overrule these stopping criteria by being more conservative, i.e., the next dose lower than planned but may not rule that the next dose should be higher than planned.

The SRC will also review the plasma concentration information (e.g., AUC and C_{max}) from previous cohorts to determine whether to adjust the dose for the next cohort (dose reduction, dose repetition, or reduced dose escalation).

4.4. Schedule of Events and Assessments

Tables 1, 2 and 3 present the schedules of study events and assessments for Parts A, B, and C, respectively.

Table 1: Schedule of Events: Part A (SAD Cohorts)

Visit	V1	V2	V3	V4	V5	V6	V7	V8
Visit Window	**D-28 to D- 1**	**D-1**	**0 to +24h**	**+24h to +48h**	**+48h to +72h**	**+72h to +96h**	**V2+7d (±1d)**	**V2+14d (±1d)**
Visit Days	**Screen**		**D1**	**D2**	**D3**	**D4**	**Follow Up**	**End of Study**
Informed Consent	X							
Inclusion/Exclusion	X							
Demographics	X							
Medical History	X							
Physical Exam /Neurological Exam	X						X	X
MMSE[10]	X	X				X		
Body Weight/Height/Fluid intake/Urine output[9]	X	X	X	X	X	X	X	X
CBC/Serum Chemistry[1]	X	X	X	X		X	X	X
FSH/LH/testosterone/ inhibin B[2]	X	X		X				X
Urinalysis[1]	X	X		X	X		X	
Drug/Alcohol Screen[3]	X	X						
Hepatitis & HIV Screen	X							
Vital Signs[4]	X		X	X	X	X	X	X
Pulse oximetry	X		X	X	X	X	X	X
12-Lead Safety ECG[5]	X	X	X	X	X	X	X	X
Cardiodynamic[6]			X					
Chest x-ray and Echocardiogram		X						
Plasma PK Samples[7]			X	X	X	X	X	X
Urine PK Samples[7]			X	X	X			

Visit	V1	V2	V3	V4	V5	V6	V7	V8
Visit Window	**D-28 to D- 1**	**D-1**	**0 to +24h**	**+24h to +48h**	**+48h to +72h**	**+72h to +96h**	**V2+7d (±1d)**	**V2+14d (±1d)**
Visit Days	**Screen**		**D1**	**D2**	**D3**	**D4**	**Follow Up**	**End of Study**
Confined to Unit			X	X	X	X		
C-SSRS	X		X			X	X	X
Administer Study Drug			X					
Adverse Events[8]	X	X	X	X	X	X	X	X
Concomitant Meds[8]	X	X	X	X	X	X	X	X
Study Completion								X

Notes to the Schedule of Events:

[1]Screening and Safety Laboratory Tests: V1 (Screening and Day -1 [Admission]); V3 pre-dose; V4 24h post-dose; V6 72h post-dose; V7 and V8. To be performed prior to dosing, but after the last baseline cardiodynamic EPQT (early precision QT analysis) 12-lead Safety ECG reading. Urinalysis will be performed at Screening and Day -1, 24 hours and 72 hours post dose, and follow-up V7.

[2]At screening, 24 hr post-dose and at end of study. FSH/LH/Inhibin B/Testosterone to be tested in both genders.

[3]Urine drug screen and alcohol breathalyzer will be conducted at Visit 1 during Screening and Day -1 (Admission).

[4]Vital Signs: V1 (Screening and Day -1 ([Admission]), V3 pre-dose and post-dose 15, 30 and 60 minutes, and 2, 4, 6, 8, 12, 18 and 24 hours; V4: 28, 32, 36, and 48 hours after dosing; V5: 60 and 72 hours after dosing; V6; V7 and V8.

[5]12-Lead Safety ECG: V1 Screening and Day -1 (Admission), V3 pre-dose and post-dose 1, 2, 4, 8, 12 and 24 hours; V4: 36 and 48 hours after dosing; and V5: 72 hours after dosing; V7 and V8. Standardized meal or snack must be completed at least 60 min before any Holter recording extractions and/or safety 12-lead ECG tracings.

[6]Holter monitors will be used to collect continuous cardiodynamic samples on Day 1 over approximately 24 hours. Three pre-dose timepoints will be collected at 45 min, 30 min, and 15 min prior to dosing. EPQT, 12-lead Safety ECG recordings will be extracted from the Holter monitor data within a 5-min time window prior to the PK blood samples collected as close to the exact timepoint as possible. Standardized meal or snack must be completed at least 60 min before any Holter recording extractions and/or safety 12-lead ECG tracings. Cardiodaynamic measurements are to be taken post Safety ECG, but prior to PK blood samples.

[7]Plasma PK samples; V3: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), 12 (+/- 30 min), 16 (+/-1hr) and 24 hours (+/-1hr); V4: 48 hours post dose (+/-2 hr); V5: 72 hours post dose (+/-2h r); V6: 96 hours post dose (+/- 2hr); V7 and V8. To be performed prior to dosing, but after the last baseline cardiodynamic or EPQT 12-lead Safety ECG reading. Urine PK samples will collect 24-hour pooled urines on the indicated days.

[8]Adverse Events and concomitant medications (new or changed) will be collected during Visit 1 at both Screening and Day -1 (Admission) in addition to the other timepoints noted in the Schedule of Events.

[9] Height is measured only at screening. Weight is collected daily. Fluid intake/Urinary output volumes collected from 0 hour to 72 hour.

[10]The MMSE is administered at screening and repeated pre-dose at V2 to ensure the MMSE inclusion criteria is met. The MMSE is repeated at approximately the same time of day (+/-1 hour) on V6 as it was administered at V2. The MMSE is administered again at V8 only if the MMSE score at V6 was considered clinically and meaningfully different then baseline, per Investigator's clinical judgment, than it was at the V2 administration.

Table 2: Schedule of Events: Part B (MAD Cohorts)

Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Visit Window	**D-28 to D-1**	**D-1**	**0 to +24h**	**+24h to +48h**	**+48h to +72h**	**+72h to +96h**	**+96 to +120h**	**+120 to +144h**	**+144 to +168h**	**+168 to +192h**	**+192 to 216h**			**D14 (±1d)**	**D21 (±1d)**
Visit Days	**Screen**		**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**Follow -up**	**End of Study**
Informed Consent	X														
Inclusion/Exclusion	X														
Demographics	X														
Medical History	X														
MMSE[11]	X	X							X						X
Physical Exam/ Neurological Exam	X					X					X				X
Body Weight/Height /Fluid intake/Urine output[10]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
CBC/Serum Chemistry[1]	X	X	X	X	X	X	X	X		X	X			X	X
FSH/LH/ testosterone/ inhibin B[2]	X	X		X						X				X	X
Urinalysis[1]	X	X		X						X					X
Drug/Alcohol Screen[3]	X	X													
Hepatitis & HIV Screen	X														
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pulse oximetry	X		X	X	X	X	X	X	X	X	X	X		X	X
12-Lead Safety ECG[5]	X	X	X	X	X	X	X	X	X	X	X	X		X	X

Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Visit Window	**D-28 to D-1**	**D-1**	**0 to +24h**	**+24h to +48h**	**+48h to +72h**	**+72h to +96h**	**+96 to +120h**	**+120 to +144h**	**+144 to +168h**	**+168 to +192h**	**+192 to 216h**			**D14 (±1d)**	**D21 (±1d)**
Visit Days	**Screen**		**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**Follow -up**	**End of Study**
Chest x-ray and Echocardiogram		X													
Plasma PK Samples[6]			X	X		X		X	X	X	X	X	X		
CSF collection[8]									X						
Biomarker screen[7]		X								X					
Urine PK Samples[6]			X						X						
Confined to Unit			X	X	X	X	X	X	X	X	X	X	X		
C-SSRS	X		X			X			X					X	X
Administer Study Drug			X	X	X	X	X	X	X						
Adverse Events[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion															X

Notes to the Schedule of Events:

[1]Screening and Safety Laboratory Tests: V1; V2; V3: pre-dose; V4: pre-dose; V5: pre-dose; V6: pre-dose; V7: pre-dose; V8: pre-dose; V10: 24 hr post-V9 dose; V11: 48 hr post-V9 dose; V14 and V15. Urinalysis will be performed at V1, V2, V4: pre-dose; V10: 24 hr post-V9 dose, and V15

[2]At screening, baseline, 24 hours after D1 dosing but before dosing on D2, 24 hours after last dose, follow-up and end of study. FSH/LH/Inhibin B/Testosterone to be tested in both genders.

[3]Urine drug screen and alcohol breathalyzer will be conducted at Visit 1 during Screening and Day -1 (Admission).

[4]Vital Signs: V1, V2, V3 pre-dose and post-dose at: 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, 18 hr; V4: pre-dose and post-dose at 4 hr, 8 hr, 12 hr; V5: pre-dose and 12 hr post-dose; V6: pre-dose and 12 hr post-dose; V7: pre-dose and 12 hr post-dose; V8: pre-dose and 12 hr post-dose; V9: pre-dose and 12 hr post-dose; V10: 24 hr post-V9 dose; V11: 48 hr post-V9 dose; V12: 72 hr post-V9 dose; V14 and V15.

[5]12-Lead Safety ECG: V1; V2; V3 pre-dose and post-dose at 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, V4: pre-dose and 12 hr post-dose; V5: pre-dose and 12 hr post-dose; V6: pre-dose and 12 hr post-dose; V7: pre-dose and 12 hr post-dose; V8: pre-dose and 12 hr post-dose; V9: pre-dose and 12 hr post-dose; V10: 24 hr post-V9 dose; V11: 48 hr post-V9 dose; V12: 72 hr post-V9 dose; V14 and V15.

[6]Plasma PK samples: V3: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), 12 (+/- 30 min), 16 (+/- 1hr); V4: pre-dose (-15 min), 2 hr (+/- 30 min), 5 hr (+/- 30 min), 8 hr (+/- 30 min); V6: pre-dose (-15 min), 2 hr (+/- 30 min), 5 hr (+/- 30 min), 8 hr (+/- 30 min); V8: pre-dose (-

15 min); V9: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), and 16 (+/-1hr); V10: 24 hr post-V9 dose +/- 1 hr; and V11: 48 hr post-V9 dose +/- 1 hr; V12: 72 hr post-V9 dose +/- 2 hr; V13: 96 hr post-V9 dose +/- 2 hr . Urine PK samples will collect 24-hour pooled urines on the indicated days. The 24-hour collection on Day 1 starts at dosing and collected for 24 hours prior to next day's dose. The 24-hour collection on Day 7 starts at dosing and collected for 24 hours prior to the next day's dose.

Plasma PK samples for MAD Cohort 1 only; V3: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), 12 (+/- 30 min), 16 (+/-1hr) and 24 hours (+/-1hr); V5: 48 hours post dose (+/-2 hr); V6: 72 hours post dose (+/-2hr); V7: 96 hours post dose (+/- 2hr); V8: 120 hours post dose (+/- 4 hr); V9: 144 hours post-dose (+/- 4 hr); V10: 168 hours post-dose (+/- 4 hr); and V11: 192 hours post-dose (+/- 4 hr); V13.

[7]Biomarker screen for CNS derived exosomes: Day -1 (Admission) pre-dose and V10.

[8]CSF collection V9 **prior** to dose on last dosing day.

[9]Adverse Events and concomitant medications (new or changed) will be collected during Visit 1 at both Screening and Day -1 (Admission) in addition to the other timepoints noted in the Schedule of Events.

[10]Height is measured only at screening. Weight is collected daily. Fluid intake/Urinary output volumes collected from 0 hour to 192 hour.

[11]The MMSE is administered at screening and repeated pre-dose at V2 to ensure the MMSE inclusion criteria is met. The MMSE is repeated at approximately the same time of day (+/-1 hour) on V9 as it was administered at V2. The MMSE is administered again at V15 (End of Study) only if the MMSE score at V9 was significantly different, per investigator clinical judgment, than it was at the V2 administration or upon early termination of the subject.

Table 3: Schedule of Events: Part C (PD MAD Cohorts)

Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Visit Days	**Screen**		**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D14 (±1d) Follow-up**	**D21 (±1d) End of Study**
Informed Consent	X														
Inclusion/Exclusion	X														
Demographics	X														
Medical History	X														
MMSE[11]	X	X							X						X
MDS-UPDRS III[12]		X	X						X					X	X
ON/OFF Diary[12] assessment			X						X						
MDS-UPDRS I + II[12]		X							X					X	X
CGI-I and PGIC[12]										X				X	X
PDQ-39[12]		X								X				X	X
PGI-S[12]		X								X				X	X
CSBM, PAGI-SYM[12]		X								X				X	X
NMSS[13]		X							X					X	X
BDI-II	X	X													
Physical Exam/ Neurological Exam	X					X					X				X
Body Weight/Height/ Fluid intake/Urine output[10]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
FSH/LH/testosterone /inhibin B[2]	X	X		X						X				X	X
CBC/Serum Chemistry[1]	X	X	X	X	X	X	X	X		X	X			X	X

Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Visit Days	**Screen**		**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D14 (±1d) Follow-up**	**D21 (±1d) End of Study**
Urinalysis[1]	X	X		X						X					X
Drug/Alcohol Screen[3]	X	X													
Hepatitis & HIV Screen	X														
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pulse oximetry	X		X	X	X	X	X	X	X	X	X	X		X	X
12-Lead Safety ECG[5]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Chest x-ray and Echocardiogram		X													
Plasma PK Samples[6]			X	X		X		X	X	X	X	X	X		
CSF collection[8]									X						
Biomarker screen[7]		X								X					
Urine PK Samples[6]			X						X						
Confined to Unit			X	X	X	X	X	X	X	X	X	X	X		
C-SSRS	X		X			X			X					X	X
Administer Study Drug			X	X	X	X	X	X	X						
Adverse Events[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion															X

Notes to the Schedule of Events:

[1]Screening and Safety Laboratory Tests: V1; V2; V3: pre-dose; V4: pre-dose; V5: pre-dose; V6: pre-dose; V7: pre-dose; V8: pre-dose; V10: 24 hr post-V9 dose; V11: 48 hr post-V9 dose; V14 and V15. Urinalysis will be performed at V1, V2, V4: pre-dose; V10: 24 hr post-V9 dose, and V15

[2]At screening, baseline, 24 hours after D1 dosing but before dosing on D2, 24 hours after last dose, follow-up and end of study. FSH/LH/Inhibin B/Testosterone to be tested in both genders.

[3]Urine drug screen and alcohol breathalyzer will be conducted at Visit 1 during Screening and Day -1 (Admission).

[4] Vital Signs: V1, V2, V3: pre-dose and post-dose at: 1hr (+/-15 min), 2 hr (+/-15 min), 4 hr (+/-15 min), 8 hr (+/-15 min), 12 hr (+/-15 min), 18 hr (+/-15 min); V4: pre-dose and post-dose at 4 hr (+/-15 min), 8 hr (+/-15 min), 12 hr (+/-15 min); V5: pre-dose and post- dose 12 hr (+/-15 min); V6: pre-dose and post-dose 12 hr (+/-15 min); V7: pre-dose and post-dose 12 hr (+/-15 min); V8: pre-dose and post-dose 12 hr (+/-15 min); V9: pre-dose and post-dose 12 hr (+/-15 min); V10: 24 hr post-V9 dose (+/-15 min); V11: 48 hr post-V9 dose (+/-15 min); V12: 72 hours post-V9 dose (+/-15 min); V14 and V15.

[5]12-Lead Safety ECG: V1; V2; V3 pre-dose and post-dose at 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, V4: pre-dose and 12 hr post-dose; V5: pre-dose and 12 hr post-dose; V6: pre-dose and 12 hr post-dose; V7: pre-dose and 12 hr post-dose; V8: pre-dose and 12 hr post-dose; V9: pre-dose and 12 hr post-dose; V10: 24 hr post-V9 dose; V11: 48 hr post-V9 dose; V12: 72 hr post-V9 dose; V14 and V15.

[5]12-Lead Safety ECG: V1; V2; V3 pre-dose and post-dose at 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, V4: pre-dose and 12 hr post-dose; V5: pre-dose and 12 hr post-dose; V6: pre-dose and 12 hr post-dose; V7: pre-dose and 12 hr post-dose; V8: pre-dose and 12 hr post-dose; V9: pre-dose and 12 hr post-dose; V10: 24 hr post-V9 dose; V11: 48 hr post-V9 dose; V12: 72 hr post-V9 dose; V14 and V15.

[6]Plasma PK samples: V3: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), 12 (+/- 30 min), 16 (+/- 1hr); V4: pre-dose (-15 min), 2 hr (+/- 30 min), 5 hr (+/- 30 min), 8 hr (+/- 30 min); V6: pre-dose (-15 min), 2 hr (+/- 30 min), 5 hr (+/- 30 min), 8 hr (+/- 30 min); V8: pre-dose (-15 min); V9: Pre-dose, post-dose 0.25 (+/-5 min), 0.5 (+/-5 min), 1 (+/-5 min), 2 (+/-5 min), 4 (+/-15 min), 6 (+/-15 min), 8 (+/-30 min), and 16 (+/-1hr); V10: 24 hr post-V9 dose +/- 1 hr; and V11: 48 hr post-V9 dose +/- 1 hr; V12: 72 hr post-V9 dose +/- 2 hr; V13: 96 hr post-V9 dose +/- 2 hr . Urine PK samples will collect 24-hour pooled urines on the indicated days. The 24-hour collection on Day 1 starts at dosing and collected for 24 hours prior to next day's dose. The 24-hour collection on Day 7 starts at dosing and collected for 24 hours prior to the next day's dose.

[7]Biomarker screen for CNS derived exosomes: Day -1 (Admission) pre-dose and V10.

[8]CSF collection V9 **prior** to dose on last dosing day.

[9]Adverse Events and concomitant medications (new or changed) will be collected during Visit 1 at both Screening and Day -1 (Admission) in addition to the other timepoints noted in the Schedule of Events.

[10]Height is measured only at screening. Weight is collected daily. Fluid intake/Urinary output volumes collected from 0 hour to 192 hour (V3 through V11).

[11]The MMSE is administered at screening and repeated pre-dose at V2 to ensure the MMSE inclusion criteria is met. The MMSE is repeated at approximately the same time of day (+/-1 hour) on V10 as it was administered at V2. The MMSE is administered again at V15 (End of Study) only if the MMSE score at V9 was significantly different, per investigator clinical judgment, than it was at the V2 administration or upon early termination of the subject.

[12]In Part C, eligible PD participants will arrive the evening before initiation of study drug dosing. MDS-UPDRS, Part I and Part II will be assessed. No anti-parkinsonian medication will be given after midnight (V2). The following morning (Day 1/V3), they will be clinically assessed in the practically defined OFF state using MDS-UPDRS Part III before administration of IkT-148009. MDS-UPDRS Part III will be administered at 1 (+/- 15 min), 2 (+/- 15 min), 3 (+/- 15 min), 4 (+/- 15 min), and 6 hours (+/- 15 min) after dosing on Day 1. ON, ON with and without troublesome dyskinesias, and OFF will be documented every 30 minutes during waking hours on Day 1. If participants do not turn ON by 6 hours, usual PD medications will resume. If at any point before 6 hours participants and the Investigator feel PD medications are necessary, they may be given. PD medications will be given as usual on Days 2 through up to Day 11, with PD medications held after midnight on the day before the last IkT-148009 dose. On the morning of the last dose, participants will again be evaluated in the practically defined OFF state before resuming usual PD medications that morning. After study activities, they will be discharged from clinic. PD assessments will be conducted at Follow-Up (V14), and the End-Of Study Visit (V15). These will not involve practically defined OFF motor evaluations as done previously, but participants will hold a dose of usual PD medication during the visit to allow for motor assessment in ON and OFF states.

[13]NMSS to be performed at baseline, prior to last dose on Day 7, follow-up and end of study.

4.5. Randomization and Blinding

In Part A (SAD), subjects will be randomly assigned to study drug (IkT-148009 or placebo) based on the randomization scheme on Day 1. Sentinel dosing will be employed for each cohort, and randomization will be 1:1 for the first two subjects, with one subject randomized to receive IkT-148009 and the other placebo on the first day, and then 5:1 for the remaining 6 in each SAD cohort resulting in an overall randomization ratio of 6:2 for each cohort of 8 subjects. In Parts B (MAD) or C (MAD PD), there will be no sentinel dosing. Subjects will be randomized 3:1 for each cohort of 8 subjects. However, dosing will be completed in the initial (or prior) cohort, and subjects will be observed for a minimum of 48 hours after administering the last dose before deciding to initiate the next (higher dose) cohort.

The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the database hard lock has occurred.

4.6. Screening Assessments

4.6.1. Demographics

Age, gender, race, and ethnic origin will be recorded at Screening.

4.6.2. Medical History

A full medical history, including medication history, will be recorded at Screening.

4.7. Safety and Tolerability Assessments

The safety and tolerability of IkT-148009 will be assessed via treatment-emergent adverse event (TEAE) reporting, serious adverse event (SAE) reporting, vital sign measurement, physical and neurological examination, laboratory data, Safety Electrocardiogram (ECG), and Cardiodynamic ECG parameters, and Columbia Suicide Severity Rating Scale (C-SSRS).

Physical and neurological examinations, vital signs, daily weights, tracking of fluid intake and urine output volumes, laboratory assessments, safety and Cardiodynamic ECG evaluations, and observations by experienced personnel will be undertaken throughout the study based on the following sections and SOEs.

4.7.1. Physical Examination

A physical examination of all major body systems (general appearance, skin, head, eyes, ears, nose, neck, throat, lungs, heart, abdomen, back, lymph nodes, and extremities) will be undertaken and recorded at Screening. Additional exams may be performed if any changes from the Screening assessment are symptom-driven. This will include body weight and height at the Screening visits. Additional physical examinations will be undertaken and recorded per the SOEs. Height will be measured on Study Day 1 only.

Significant findings prior to the first dose of the study drug will be recorded under Medical History/Current Medical Conditions. Significant findings made after the first dose of the study drug through the End of Study Visit, which meet the definition of an AE will be recorded as an adverse event.

4.7.2. Screening and Safety Laboratory Tests

Clinical chemistry tests will include albumin, alkaline phosphatase, total bilirubin, calcium, cholesterol, creatinine, creatinine clearance, creatinine kinase (CK), gamma-glutamyltransferase (γ-GT), glucose, lactate dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, potassium, magnesium, total protein, aspartate transaminase (AST), alanine transaminase (ALT), sodium, triglycerides, urea, and uric acid, bicarbonate, and chloride. If the total bilirubin concentration increases above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated. Thyroid stimulating hormone (TSH) levels will also be monitored.

CBC assessments will include hemoglobin, hematocrit, red blood cell (RBC) count, reticulocyte count, white blood cells (WBC) count with differential, platelet count, and PT-INR. PT-INR should be reported in prothrombin time (second) and international normalized ratio (no unit).

Men and women will undergo additional laboratory tests for reproductive organ function to include luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, and inhibin B in both genders.

Safety laboratory samples will be collected per the SOEs. Clinical chemistry or complete blood count (CBC) may be collected at any time during the study if clinically indicated.

4.7.3. Chest X-ray and Echocardiogram

Baseline chest x-ray and echocardiogram will be performed prior to dosing on subjects in Parts A and B who have completed all other screening events and continue to meet eligibility criteria. In Part C, only a chest x-ray will be performed prior to dosing on patients who have completed all other screening events and continue to meet eligibility criteria.

4.7.4. Vital Signs

Vital signs (VS) for blood pressure and pulse will be measured after subjects remain supine for 5 min and after 2 min standing. Baseline VS will be measured 3 times at baseline for an hour. Respiratory rate, pulse oximetry, and temperature will also be collected. Vital signs measurements outside of the normal range (as per the CRU SOP) should be repeated. All time points are relative to the time of dosing.

VS will be obtained per the SOEs.

4.7.5. 12-Lead Electrocardiogram

ECGs will be classified as either Safety ECGs, collected for real-time safety review, or Cardiodynamic ECGs (SAD cohorts only), extracted from the Holter recordings for later analysis. A subject will be withdrawn from the study by the PI or designee if, in their medical judgment, ECG findings are present, which makes continued study participation not in the subject's best interest.

4.7.5.1. Safety Electrocardiogram

The 12-lead Safety ECG assessments (after at least 10 minutes of rest) will be performed, and the standard intervals recorded and any abnormalities. These Safety ECGs will be obtained per the SOEs and should be collected at any time if clinically indicated based on vital signs or symptoms at the discretion of the Investigator. ECGs will be performed with subjects resting supine for at least 10 minutes. All ECGs will be classified as normal, having a non-clinically significant abnormality, or having a clinically significant abnormality. In addition, ECG parameters of ventricular rate, RR or PR interval, QRS complex, and QTcF interval (corrected and uncorrected) will be collected. All clinically significant abnormality findings will be recorded as AEs.

When scheduled post-dose, ECGs will be performed within approximately 20 min of the scheduled timepoint.

4.7.5.2. Cardiodynamic ECGS (SAD only)

Holter monitors will be used to collect continuous 12-lead ECG data on Day 1 for the purpose of collecting Cardiodynamic ECGs. The recording will be started and stopped at logistically optimal times to ensure that all scheduled timepoints are collected. EPQT, 12-lead ECG recordings will be extracted from the Holter monitor data within a 5-min time window around the scheduled time points outlined in the SOE. Timing and recording techniques for ECGs will be standardized for all subjects. Subjects will be required to lie quietly in a supine position with minimal movement and minimal exposure to noise and other environmental stimuli for at least 10 min prior to and 5 min during the ECG extraction window to allow for quality ECG extraction. If targeted ECG timepoints are artifactual and/or of poor quality, analyzable 10-sec ECGs will be extracted as close as possible to the targeted timepoints. The nominal time of the ECG recording will be used for the cardiodynamic analysis.

4.7.6. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. A treatment-emergent AE (TEAE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

All TEAEs that occur after any subject has been enrolled, during treatment or within 14 days following the cessation of treatment, whether or not they are related to the study, will be recorded. AEs occurring more than once will be reported as a single AE with the maximum recorded severity with the onset date recorded as the occurrence of the first event.

4.7.6.1. Serious Adverse Events

A serious adverse event is an AE occurring during any study phase (i.e., baseline, treatment, or follow-up) and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following:

- Results in death
- It is immediately life-threatening (see protocol Section 10.8.1.2.1)
- It requires in-subject hospitalization or prolongation of existing hospitalization
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or within 14 days following the cessation of treatment, whether or not they are related to the study, will be recorded.

4.7.6.2. Relationship to Study Drug

Relationship to the investigational product will be categorized as unrelated, possibly related, or probably related. If the relationship between the AE/SAE and the investigational product is determined to be “possible” or “probable,” the event will be considered to be related to the investigational product for expedited regulatory reporting.

4.7.7. Columbia Suicide Severity Rating Scale

Suicidality will be monitored during the study using the C-SSRS (Oquendo et al., 2003). This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicidal ideation and behavior and a post-baseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes ‘yes’ or ‘no’ responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

The “Baseline/Screening” C-SSRS form will be completed at screening (lifetime history and past 24 months). The “Since Last Visit” C-SSRS form will be completed at all subsequent time points outlined in the SOEs.

4.7.8. Mini Mental State Examination (MMSE)

The Mini Mental State Examination (MMSE) is a brief test assessing general cognitive function (Folstein et al., 1975) used in the current study to ensure the study participants have no cognitive impairment before being administered IkT-148009 and to evaluate the subject's cognition after receiving the study drug at subsequent visits per the SOEs. The MMSE consists of five cognitive components: 1) orientation to time and place; 2) registration of three words; 3) attention and calculation (the investigator can choose in this study whether to administer the "WORLD Backwards" or "Calculation" sub-component); 4) recall of three words; and 5) language. The scores from each of the five components are summed to obtain an overall MMSE score. The score can range from 0-30, with lower scores indicating greater impairment in cognitive functioning. Part A and B participants will only be permitted to Screen and Baseline if they score ≥ 28 (representing normal cognition; Larner, 2013) on the MMSE at each of these respective visits. For Part C (PD participants), the minimum acceptable value will be 26.

4.7.9. Concomitant Medications

Concomitant medications will be reviewed and documented each day during the study.

4.7.10. Concomitant Procedures

Concomitant procedures conducted to diagnose, treat, or follow and AE or SAE will be reviewed and documented each day during the study.

4.8. Pharmacokinetic Assessments

Blood and urine samples to determine IkT-148009 will be collected according to the Schedule of Events (Tables 1 to 3) and analyzed using validated bioanalytical methods.

4.9. Exploratory Assessments

4.9.1. MDS-UPDRS Parts I, II, III

The Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is a well-established tool for characterizing the signs and symptoms of PD (Goetz et al., 2008). The three parts used in this study are Part I (Non-Motor Aspect of Experiences of Daily Living), Part II (Motor Aspects of Experiences of Daily Living), and Part III (Motor Examination). Items in each domain are rated from 0-4, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

4.9.2. Clinical Global Impression of Improvement Score (CGI-I)

The CGI-I is a 7-point scale used to indicate how the clinician views whether a participant has changed since baseline (Guy, 1976). The range includes 1 ("very

much improved"), 2 ("much improved"), 3 ("minimally improved"), 4 ("no change"), 5 ("minimally worse"), 6 ("much worse"), and 7 ("very much worse").

4.9.3. Patient Global Impression of Change Score (PGI-C)

The PGI-C is used to characterize a participant's sense of change compared to baseline. The range includes 1 ("very much improved"), 2 ("much improved"), 3 ("minimally improved"), 4 ("no change"), 5 ("minimally worse"), 6 ("much worse"), and 7 ("very much worse").

4.9.4. Patient Global Impression of Severity Score (PGI-S)

The PGI-S is a single-item tool used to determine how severe a person feels their symptoms are at the time of questioning. It is based on a 4-point scale (1=normal, 2=mild, 3=moderate, 4=severe).

4.9.5. Non-Motor Symptom Score (NMSS)

The NMSS is a 30-item scale divided into 9 domains (cardiovascular, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function, miscellaneous) (Chaudhuri et al., 2007). Each item is rated for frequency (rarely/often/frequent/very frequent) and severity (none/mild/moderate/severe) of symptoms.

4.9.6. Parkinson's Disease Questionnaire 39 (PDQ-39)

The PDQ-39 is a self-administered questionnaire that assesses how often people affected by PD experience difficulties across 8 dimensions of daily living, including relationships, social situations, and communication (Peto et al., 1995). It also assesses the impact of PD on specific dimensions of functioning and well-being. The PDQ-39 is scored on a scale of 0 to 100, with lower scores indicating better health and higher scores for more severe symptoms.

4.9.7. Complete Satisfaction with Bowel Movement Scale (CSBM)

The Complete Satisfaction with Bowel Movement (CSBM) is defined as a bowel movement occurring in the absence of a laxative, enema or suppository use during the previous 24-hour period with the bowel movement accompanied by the patient self-reporting a feeling of complete evacuation. This endpoint is designed with the intent of better identifying a patient experiencing clinically meaningful improvement in symptoms (Lacy et al., 2012).

4.9.8. Patient Assessment of Upper GI Disorders Severity Index (PAGI-SYM)

PAGI-SYM is a clinical assessment composed of a series of questions evaluating the severity of upper GI symptoms and is composed of six subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain. The 20-item questionnaire assesses symptoms of gastroparesis, dyspepsia, and gastroesophageal reflux disease; it includes the 9 symptoms of gastroparesis cardinal symptom index (GCSI). Total

GCSI score equals the mean of nausea/vomiting subscore, postprandial fullness/early satiety subscore, and bloating subscore, where nausea/vomiting subscore = mean of scores for nausea, retching, and vomiting; postprandial fullness/early satiety subscore = mean of scores for stomach fullness, inability to finish the meal, excessive fullness, and loss of appetite; and bloating subscore = mean of scores for bloating and large stomach. The upper abdominal pain subscore was the average of upper abdominal pain and upper abdominal discomfort. Patients are asked to assess the severity of their symptoms during the previous 2 weeks using a 0 to 5 scale where no symptoms = 0, very mild = 1, mild = 2, moderate = 3, severe = 4, and very severe = 5 (Rentz et al., 2004).

4.9.9. Biomarker Screen in CNS Derived Exosomes (if available)

Antibody selection for CNS-derived exosomes will be isolated by FACS from up to 100 ml of peripheral blood to examine biomarkers of c-Abl activity in Parkinson's disease participants.

4.10. COVID-19 Impact

The impact of the COVID-19 pandemic on study assessments and procedures will be recorded.

5. STUDY ENDPOINTS

5.1. Primary Endpoints

5.1.1. Parts A, B, and C

1. Safety (vital sign measurements, clinical laboratory data, ECG parameters and C-SSRS)
2. Tolerability (adverse event reporting)
3. PK of IkT-148009 by determining the PK parameters (such as C_{max}, T_{max} and AUC)

5.2. Exploratory Endpoints

5.2.1. Part B

1. IkT-148009 drug concentration in the CSF at steady-state, if available.

5.2.2. Part C

1. Change from Baseline to Final Visit in the MDS-UPDRS Motor Subscale (Part III) Score
2. Change from Baseline to Final Visit in the MDS-UPDRS Non-motor aspects of experiences of daily living (Part I) score and in the MDS-UPDRS Motor aspects of experiences of daily living (Part II) score.

3. Change in Clinical Global Impression of Improvement (CGI-I) Score and the Patient Global Impression of Change (PGI-C) Score.
4. Change in Non-Motor Symptom Score (NMSS).
5. Change from Baseline to Final Visit in Parkinson's Disease Questionnaire 39 (PDQ-39).
6. Change from Baseline to Final Visit in the Patient Global Impression of Severity Score (PGI-S).
7. Change from Baseline to Final Visit in Complete Bowel Movement Score (CSBM).
8. Change in Patient Assessment of Upper GI Disorders Severity Index (PAGI-SYM).
9. IkT-148009 drug concentration in the CSF at steady-state, if available.
10. Biomarker analysis form CNS-derived exosomes, if available.

6. STATISTICAL ANALYSES

6.1. General Considerations

- Data will be summarized separately for Parts A, B, and C, with placebo subjects, generally pooled within each study part.
- All summaries (safety, tolerability, and PK) will be presented by groups of subjects defined as treated at each scheduled time point. Data from unplanned visits will be included in listings but omitted from summary statistics.
- Summary tables will include the following descriptive statistics: For continuous variables, the number of non-missing subjects (n), mean, standard deviation (SD), median, minimum, and maximum values, and for categorical variables, the frequencies, and percentages of subjects.
- For vital signs, the baseline value is defined as the last value observed prior to the first administration of study medication on Day 1. For other safety variables, the baseline value is defined as the value observed on Day -1. If the Day -1 value is missing for a subject, then Screening value will be considered as baseline.
- Change from baseline values will be calculated at each time point and summarized using descriptive statistics. The change from baseline is defined as the post-baseline value minus the baseline value.
- For continuous safety data, mean and median will be rounded to 1 additional decimal place, SD will be rounded to 2 additional decimal places compared to the original data, and minimum and maximum will be

displayed with the same accuracy as the original data, except baseline and demographic characteristics.

- For continuous baseline and demographic characteristic data, mean and median will be rounded to 1 decimal place, SD will be rounded to 2 decimal places, and minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- In addition, for PK data, arithmetic mean, geometric mean, SD, and coefficient of variation (CV%) will be rounded to 3 significant figures.
- All study data will be included in study data listings for CSR Appendix 16.2. In general, all data will be listed by time point within the subject. All summary tables will present descriptive statistics for the parameters being analyzed.
- No adjustment will be made for multiple comparisons in this study as this is an exploratory study.
- SAS® version 9.4 or higher will be used for all statistical analyses.

6.2. Statistical Methodology

6.2.1. Sample Size Determination

No formal sample size calculations have been undertaken for this pharmacokinetic, safety, and tolerability study. The number of subjects in each cohort and at each dose level is thought to be sufficient to assess the preliminary pharmacokinetic profile of IkT-148009 in addition to safety and tolerability following single or multiple doses of IkT-148009.

This study is not powered for direct inferential statistical analyses.

6.2.2. Populations for Statistical Analysis

The following are analysis populations for the study:

- PK Population: All subjects who receive the study drug have no major protocol violations and have sufficient pharmacokinetic data to obtain reliable estimates of the key pharmacokinetic variables. Subjects who vomited or who did not comply with dosing requirements or with incomplete PK data, will be assessed on a case-by-case basis as to their inclusion in the analysis.
- Safety Population (SP): All subjects who are administered study drug, are analyzed as treated.

6.2.3. Procedures for Handling Missing Data

Missing data will not be imputed.

6.2.4. Interim Analyses

Interim analyses are not anticipated for this study.

6.3. Screening and Baseline Characteristics

Summary tables will be constructed by treatment for the Safety Population for Screening or Baseline (Pre-Dose) data: demographic characteristics of age, sex, race, ethnicity, weight, height and body mass index (BMI), medical history, laboratory examinations, vital signs, and ECG.

Listings will be provided for eligibility criteria violations, demographics, and medical history.

6.4. Subject Disposition

Subject disposition will include the number of subjects who enroll in the study and the number and percentage of subjects included in each analysis population by treatment. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will be summarized by treatment. Subject-level listings will be provided.

All reported major protocol deviations and determined exclusions from any analysis population(s) will be documented and included in the CSR.

6.5. Study Treatment Administration

Study drug administration data will be listed by subject.

6.6. Safety Analyses

The placebo dose group will be pooled across cohorts for all safety analyses. The number of subjects treated in each dose group will be included in the summary tables.

Out-of-range safety endpoints may be categorized as low or high, where applicable.

No inferential statistical analyses are planned for safety data.

6.6.1. Adverse Events

The number and percentage of subjects reporting TEAEs will be tabulated using MedDRA™ version 23.1 preferred term and system organ class, with a breakdown by treatment and further by relationship to study drug, as well as by maximum severity.

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 percentage of subjects who experience TEAEs will be summarized by treatment group for the following:

- By system organ class and preferred term
- By severity, system organ class, and preferred term
- By relationship to Study Medication (related, not related), system organ class, and preferred term
- Serious adverse events (Grade ≥ 3) by system organ class and preferred term
- Serious adverse events by relationship to Study Medication, system organ class, and preferred term
- Adverse events resulting in discontinuation of Study Medication by system organ class and preferred term

Listings of deaths, SAEs, and TEAEs that lead to the discontinuation of a subject from the study will be presented.

6.6.2. Clinical Laboratory Assessments

For laboratory data, a treatment-emergent abnormal value is an abnormality that was not present before dosing but was present after dosing or one that represents an exacerbation of a pre-existing abnormal value. All clinical laboratory data will be listed by subject for the safety analysis set, with abnormal lab results (based on reference ranges) presented by the subject in another listing. Descriptive statistics will be provided for baseline, end of the study, and for other times during the study if appropriate. The change from baseline values will also be summarized.

6.6.3. Vital Signs

Vital signs (blood pressure, pulse, respiratory rate, temperature, pulse oximetry, fluid intake, and urine output) will be tabulated and listed at each time point for all subjects in the safety analysis set. Supine, standing, and postural change from supine to standing values will be reported where applicable. The change from baseline values will also be summarized. Only the second measurement will be included in the descriptive statistics for any vital signs measured in triplicate.

6.6.4. Electrocardiogram

The change from baseline in heart rate and ECG intervals (PR, QT, QTcF, QRS, and RR) to each scheduled assessment will be summarized descriptively by treatment group. Frequencies and percentages of ECG interpretations (Normal/Abnormal, Clinically Significant/Not Clinically Significant) will be

tabulated by treatment group. Clinically significant findings on Safety and Cardiodynamic ECG will be recorded as TEAEs, coded, listed, and tabulated.

6.6.5. Other Assessments

A listing of abnormal physical and neurological examination findings will be provided by the subject. Reproductive organ function, alcohol screening, and drug testing results will be provided by the subject. BDI-II scores will be provided by the subject. Clinically significant findings will be included as TEAEs.

6.6.6. Columbia Suicide Severity Rating Scale

The C-SSRS data will be summarized descriptively. Individual subject data will be provided in a listing. Only the following specific suicidal ideation and behavior category questions with any “Yes” responses will be summarized in a frequency distribution table at each post-randomization visit:

- Any Suicidal Ideation Category:
    - Wish to be Dead
    - Non-Specific Active Suicidal Thoughts
    - Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
    - Active Suicidal Ideation with Some Intent to Act, without Specific Plan
    - Active Suicidal Ideation with Specific Plan and Intent
- Any Suicidal Behavior Category:
    - Completed Suicide
    - Non-Fatal Suicide Attempt
    - Interrupted Attempt
    - Aborted Attempt
    - Preparatory Acts or Behavior
    - Any Suicidal Ideation or Behavior Category

6.6.7. MMSE

MMSE scores will be tabulated for each treatment group and visit using descriptive statistics and listed by subject.

6.6.8. Concomitant Medications

Concomitant medications will be summarized (n and %) by anatomical therapeutic chemical (ATC) class and preferred term (coded by WHO Drug coding dictionary September 2020) for each treatment group. Concomitant medications for individual subjects will be provided in a listing.

6.6.9. Concomitant Procedures

Concomitant procedures will be listed by subject.

6.6.10. Study Medication Administration

Study medication administration data will be listed by subject.

6.7. Pharmacokinetic Analysis

6.7.1. Plasma Concentrations

Plasma concentrations of IkT-148009 will be summarized and tabulated for each treatment and separate for each part of the study (SAD, MAD, PD) using descriptive statistics that include the sample size (N), arithmetic mean, standard deviation, minimum, median, maximum, coefficient of variation (CV%), and the geometric mean. Individual and average IkT-148009 plasma concentrations will be plotted by treatment. Nominal times will be used for summary statistics and plotting of concentration-time data.

PK parameter estimates for IkT-148009 will be determined using model-independent analysis in Phoenix WinNonlin (Version 8.2 or later). Actual sampling times will be used in these analyses. PK parameters will be summarized using descriptive statistics that include the sample size (N), arithmetic mean, standard deviation, minimum, median, maximum, coefficient of variation (CV%), and the geometric mean. Additional PK parameters may be calculated as appropriate and will be documented in the final report. Any exceptions or special handling of data will be clearly documented within the final study report.

6.7.2. Plasma PK Parameters

The following plasma PK parameters will be calculated in the SAD Cohorts (Part A), where appropriate:

C_{max}	Maximum plasma concentration, obtained by inspection.
t_{max}	Time of maximum plasma concentration, obtained by inspection.
λ_z	Terminal rate constant, estimated by log-linear regression of the terminal phase.
$t_{1/2}$	Terminal half-life, calculated as $\ln(2)/\lambda_z$.
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration, calculated by the linear trapezoidal rule.
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity, calculated as $AUC_{0-t} + C_t/\lambda_z$, where C_t is the last quantifiable concentration.
C_{max}/D	Dose-normalized Cmax.
$AUC_{0-\infty}/D$	Dose-normalized $AUC_{0-\infty}$.

The following plasma PK parameters will be calculated in the MAD Cohorts of Parts B and C of the study, where appropriate:

C_{min}	Predose concentration on Day 7, obtained by inspection (Day 7 only)
C_{max}	Maximum plasma concentration, obtained by inspection.
t_{max}	Time of maximum plasma concentration, obtained by inspection.
λ_z	Terminal rate constant, estimated by log-linear regression of the terminal phase.
$t_{1/2}$	Terminal half-life, calculated as $\ln(2)/\lambda_z$.
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration, calculated by the linear trapezoidal rule.
$AUC_{0-\tau}$	Area under the plasma concentration-time curve under the dosing interval τ.
C_{max}/D	Dose-normalized C_{max}.
$AUC_{0-\tau}/D$	Dose-normalized $AUC_{0-\tau}$.
ARC_{max}	Accumulation ratio based on C_{max}, calculated as the C_{max} ratio of Day 7 to Day 1 (Day 7 only).
ARAUC	Accumulation ratio based on AUC, calculated as the $AUC_{0-\tau}$ ratio of Day 22 to Day 1 (Day 7 only).

In the MAD portions on the study (Parts B and C), steady-state achievement will be assessed by comparing predose concentrations on Days 2 to 7. Accumulation on Day 7 will be assessed by comparing $AUC_{0-\tau}$ and C_{max} of the last and first doses and comparing predose (C_{min}) concentrations on Day 7 to the 24-hour sample on Day 1 (predose on Day 2).

6.7.3. Urine PK Parameters

The cumulative amount of IkT-148009 in urine from 0 to 72 hours, $A_{e,72}$, in Part A (SAD), will be calculated as the sum between 0 and 72 hours of the product of the urine concentration and the urine volume. In addition, the cumulative amount of IkT-148009 in urine from 0 to 24 hours on Days 1 and 7, $A_{e,24}$, in Parts B and C will be calculated as the product of the urine concentration and the urine volume collected in each day.

The % of the dose excreted in urine (f_e%) will be calculated as $A_{e,72}$/Dose for Part A and as Day 7 $A_{e,24}$/Dose for Parts B and C.

6.7.4. Handling of Missing Data and Below the Limit of Quantitation Samples

Missing samples will not be assigned a concentration value and there will be no imputation methods for missing data. Observed data will be summarized.

All plasma concentration below the limit of quantitation (BLQ) values occurring before the first quantifiable concentration will be imputed as zero (0). All BLQ values occurring after the first quantifiable concentration will be treated as missing.

6.7.5. General Calculation Rules for PK Parameters

Actual sampling times will be used in the final analyses of individual PK parameters. Predose sampling times will be set to zero.

C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.

AUC_{0-t} will be calculated using the linear trapezoidal rule.

Half-life ($t_{1/2}$) will be calculated, when appropriate, based on the slope of the terminal log-linear portion of the plasma concentration-time curve (λ_z). The start of the terminal phase for each subject will be determined automatically (best fit) by Phoenix WinNonlin™. At least 3 plasma concentrations after the peak concentration on the terminal phase, spanning at least one half-life, will be used to determine λ_z. Half-life and other parameters dependent on λ_z, such as $AUC_{0-\infty}$, will only be calculated when a reliable estimate of λ_z can be calculated.

The Uniform Weighting Option will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

If a value is considered inconsistent with the expected PK profile, it may be appropriate to exclude this point from PK analysis. However, the exclusion of such data will be justified and documented in the report.

6.7.6. Statistical Analysis

Dose proportionality analysis will be performed using a linear regression model with natural logarithm of dose normalized C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ (Part A), C_{min} (Parts B and C, Day 7), and $AUC_{0-\tau}$ (Parts B and C) as response variable (Y) and dose (Dose) as an explanatory variable in the regression framework of SAS (SAS Institute; version 9.4 or higher). Gender and body weight may be included as covariates in the model if warranted. A linear model Y= a + b*Dose + error will be used, and 95% confidence intervals (CI) for b will be constructed. The exposure PK parameter will be declared dose proportional if the slope parameter b is not significantly different from 0 or the 95% CI for b contains 0.

6.8. Exploratory Analyses (Part C)

Descriptive statistics will be presented by dose group with the placebo pooled across cohorts.

6.8.1. MDS-UPDRS Score - Part III

MDS-UPDRS Motor Subscale (Part III) score will be tabulated and listed at each time point for all subjects. Descriptive statistics at each visit (including change from baseline) will be provided.

6.8.2. MDS-UPDRS Score - Parts I and II

MDS-UPDRS Non-motor aspects of experiences of daily living (Part I) score and the MDS-UPDRS Motor aspects of daily living experiences (Part II) scores will be tabulated and listed at each time point for all subjects. Descriptive statistics at each visit (including change from baseline) will be provided.

6.8.3. CGI-I AND PGI-C Scores

CGI-I score and PGI-C score between baseline and final visit will be tabulated and listed at each time point for all subjects and summarized descriptively.

6.8.4. NMSS

NMSS score will be tabulated and listed at each time point for all subjects. Descriptive statistics at each visit (including change from baseline) will be provided.

6.8.5. PDQ-39

PDQ-39 score will be tabulated and listed at each time point for all subjects. Descriptive statistics at each visit (including change from baseline) will be provided.

6.8.6. PGI-S

PGI-S score will be tabulated and listed at each time point for all subjects. Descriptive statistics at each visit (including change from baseline) will be provided.

6.8.7. CSBM

CSBM score will be tabulated and listed at each time point for all subjects. Descriptive statistics at each visit (including change from baseline) will be provided.

6.8.8. PAGI-SYM

PAGI-SYM score will be tabulated and listed at each time point for all subjects. Descriptive statistics at each visit (including change from baseline) will be provided.

6.9. Biomarker and CSF Analysis (Parts B and C)

Biomarker screen in CNS-derived exosomes and IkT-148009 drug concentrations in the CSF at steady state will be tabulated and provided in a listing for the MAD portion of this study only. It will not be subjected to model-independent analyses.

7. REFERENCES

Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, Ondo W, Abe K, Macphee G, Macmahon D, Barone P, Rabey M, Forbes A, Breen K, Tluk S, Naidu Y, Olanow W, Williams AJ, Thomas S, Rye D, Tsuboi Y, Hand A, Schapira AH. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. Mov Disord. 2007 Oct 15;22(13):1901-11. doi: 10.1002/mds.21596. PMID: 17674410.

Folstein M, Folstein SE, McHugh PR. Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12, 189-198 (1975).

Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N; Movement Disorder Society UPDRS Revision Task Force. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008 Nov 15;23(15):2129-70. doi: 10.1002/mds.22340. PMID: 19025984.

Guy, W. "Clinical Global Impressions". *ECDEU Assessment Manual for Psychopharmacology—Revised*. Rockville, MD: U.S. Department of Health, Education, and Welfare; Public Health Service, Alcohol; Drug Abuse, and Mental Health Administration; National Institute of Mental Health; Psychopharmacology Research Branch; Division of Extramural Research Programs. 1976, pp. 218-222. OCLC 2344751. DHEW Publ No ADM 76–338 – via Internet Archive.

Lacy BE, Levenick JM, Crowell M. Chronic constipation: new diagnostic and treatment approaches. Ther Adv Gastoenterol 5:233-247 (2012).

Larner, A. J. (Ed.) Cognitive screening instruments; A practical approach. NY: Springer. (2013).

Oquendo MA, Halberstam B, Mann JJ. Colombia Suicide Severity Rating Scale (C-SSRS) – Risk Factors for Suicidal Behavior: The Utility and Limitations of Research Instruments, in Standardized Evaluation in Clinical Practice. First MB, editor. American Psychiatric Publishing; Washington, DC: 2003: 103-131.

Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Qual Life Res. 1995 Jun;4(3):241-8. doi: 10.1007/BF02260863. PMID: 7613534.

Rentz AM, Kahrilas P, Stanghellini V, *et al*. Development and psychometric evaluation of the patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM) in patients with upper gastrointestinal disorders. Qual Life Res. 2004;13:1737–1749.

8. TABLES, LISTINGS, AND FIGURES

A separate document containing the list of tables, listings, and figures (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 an update to
the SAP.

STATISTICAL ANALYSIS PLAN

A Phase I, 7-Day Dosing Study of 200 mg IkT-148009 to Determine the Safety, Tolerability and Pharmacokinetics (PK) of IkT-148009 in Older Adult and Elderly Healthy Volunteers

Protocol No: IkT-148009-102
Final Protocol Date: 03 February 2023
Compound Name: IkT-148009

Celerion Project CA38832
Final Version 1.0
Date: 10 April 2023

Inhibikase Therapeutics
3350 Riverwood Pkwy SE Suite 1900
Atlanta, Georgia 30339, USA

Celerion
621 Rose Street
Lincoln, Nebraska 68502, USA

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Compound Name: IkT-148009

Protocol: IkT-148009-102

Study Title: A Phase I, 7-Day Dosing Study of 200 mg IkT-148009 to Determine the Safety, Tolerability and Pharmacokinetics (PK) of IkT-148009 in Older Adult and Elderly Healthy Volunteers

Issue Date: 10 April 2023

Signature: DocuSigned by:
Jing Jin
Signer Name: Jing Jin
Signing Reason: I approve this document
Signing Time: 10-Apr-2023 | 21:59:48 BST
160EAEA400444EA4B3917D59104D6797

Jing Jin, MS
Biostatistician II, Data Management and Biometrics
Celerion, Lincoln, Nebraska, USA

Signature: DocuSigned by:
Gregory Armaos
Signer Name: Gregory Armaos
Signing Reason: I approve this document
Signing Time: 10-Apr-2023 | 21:47:01 BST
C1C90C304BEE4E4CBCC3A8B08D4C0832

Gregory Armaos, MSc
Pharamacokinetic Scientist II, Clinical Pharmacology and Pharmacometrics, Data Management and Biometrics
Celerion, Montreal, Quebec, Canada

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Compound Name: IkT-148009

Protocol: IkT-148009-102

Study Title: A Phase I, 7-Day Dosing Study of 200 mg IkT-148009 to Determine the Safety, Tolerability and Pharmacokinetics (PK) of IkT-148009 in Older Adult and Elderly Healthy Volunteers

Issue Date: 10 April 2023

Signature: DocuSigned by:
Milton Werner
Signer Name: Milton Werner
Signing Reason: I approve this document
Signing Time: 10-Apr-2023 | 14:22:08 PDT
00586028F08B42228DB199F7118A4D37

Milton Werner, PhD
President and CEO
Inhibikase Therapeutics

TABLE OF CONTENTS

1. INTRODUCTION

The following statistical analysis plan (SAP) provides the framework for the analysis and presentation of the data from this study. Any changes made from the planned analysis described in the protocol or after finalization of this SAP will be documented in the Clinical Study Report (CSR). The section referred to as "Table, Figure, and Listing Shells" within this SAP describes the Clinical Data Interchange Standards Consortium (CDISC) input in order to provide traceability to the corresponding tables, figures, and listings (TFLs). Analysis data model (ADaM) is the source for tables and figures (as well as listings that may contain derived data) and study data tabulation model (SDTM) is the source for the data listings.

Any additional exploratory analyses not addressed within this SAP and/or driven by the data, or requested by Inhibikase Therapeutics, will be considered out of scope and must be described in the CSR.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the safety and tolerability of IkT-148009 given as gelatin capsule	Safety (adverse event [AE] reporting, vital sign measurements, clinical laboratory data, electrocardiogram [ECG] parameters and Columbia-Suicide Severity Rating Scale [C-SSRS]) Tolerability (percent completers)
To assess the pharmacokinetic (PK) profile of 200 mg (once daily for seven days) of IkT-148009 delivered as 4 × 50 mg gelatin capsules in the fed state	Assess the PK of IkT-148009 by determining the following parameters on Days 1 and 7: <u>Day 1:</u> $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, C_{max}, T_{max}, and $t_{½}$ <u>Day 7:</u> AUC_{tau}, $C_{max,ss}$, $T_{max,ss}$, $t_{½}$
To investigate plasma and urine concentrations of IkT-148009	Assess the plasma and urine concentrations of IkT-148009

3. STUDY DESIGN

This study is designed to meet the objectives outlined in Section 2.

This is a Phase I, 7-day dosing study to determine the safety, tolerability, and PK of IkT-148009 gelatin capsules in older and elderly healthy adults at 200 mg IkT-148009.

The cohort will consist of 6 subjects. The cohort will consist of up to 15 visits over a period of 29 days including 7 days of dosing and 14 days of follow-up after the last dose. Subjects in the cohort will be admitted to the unit approximately 24 hours prior to the expected time of dosing and will be confined to the unit for approximately 12 days. Subjects will be administered multiple once-daily (QD) doses of 200 mg IkT-148009 as gelatin capsules under fed conditions. No subject may be discharged from the unit until the investigator is satisfied that they have no continuing adverse events that could be related to study drug.

4. ANALYSIS POPULATIONS

Safety Population

The Safety Population is defined as all subjects who are administered study drug

Pharmacokinetic Concentration Population

The PK Concentration Population is defined as all subjects who are administered IkT-148009 and have at least one bioanalysis result for the plasma or urine concentration of IkT-148009. All available data will be included in the concentration tables to the extent possible.

Pharmacokinetic Analysis Population

The PK Analysis Population, a subset of the PK Concentration Population, will include all subjects who comply sufficiently with the protocol and have ample PK data to display an evaluable PK profile (e.g., exposure to treatment, availability of measurements, and absence of major protocol violations). The PK Analysis Population will be used in concentration summaries, PK parameter summaries, and statistical analyses.

Note: If subjects experience issues that affect exposure to study drug (e.g., emesis*, dosing errors, incomplete data, significant drug carryover, important protocol violation, sample processing errors), data will be reviewed by the study pharmacokineticist and evaluated for exclusion from the PK Analysis Population on a case-by-case basis. All subjects excluded from the PK Analysis Population will be documented.

*Additional notes on emesis: Data from subjects who experience emesis at or before 2 times median T_{max} (i.e., at or before 8 hours post-dose) during the PK sampling period on Day 1 and Day 7 will be excluded from the summary statistics of plasma IkT-148009 PK parameters. Additionally, subjects who experience emesis at or before 2 times median T_{max} (i.e., at or before 8 hours post-dose) following dosing on Days 2, 3, 4, 5, and 6 will be evaluated on a case by case basis for potential exclusion from the summary statistics of C_{trough} values and the analysis of steady state.

All available data will be included in the concentration and PK parameter listings/tables to the extent possible.

5. TREATMENT DESCRIPTIONS

Study treatment is described as follows:

Short Description	Long Description (Table and Listing Footnotes)
IkT-148009 QD	Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects

6. PHARMACOKINETIC ANALYSIS

6.1 Investigational Product and Pharmacokinetic Analyte Information for IkT-148009

The molecular formula of IkT-148009 is $C_{37}H_{40}N_8O_6$ and its molecular weight is 692.78 g/mol.

No dose corrections are required for the calculation of dose-dependent parameters.

6.2 Bioanalytical Method for IkT-148009

6.2.1 Plasma

Plasma concentrations of IkT-148009 will be determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods validated with respect to accuracy, precision, linearity, sensitivity, and specificity at Celerion, Lincoln, Nebraska. The analytical range (lower limit of quantitation [LLOQ] – upper limit of quantitation [ULOQ]) for IkT-148009 in plasma is expected to be 3.00 – 750 ng/mL.

6.2.2 Urine

Urine concentrations of IkT-148009 will be determined using LC-MS/MS methods validated with respect to accuracy, precision, linearity, sensitivity, and specificity at Celerion, Lincoln, Nebraska. The analytical range (LLOQ – ULOQ) for IkT-148009 in urine is expected to be 3.00 – 750 ng/mL.

6.3 Pharmacokinetic Concentrations of Plasma IkT-148009

Measurements and Collection Schedule

Plasma IkT-148009

Blood samples for the determination of plasma IkT-148009 will be collected at the following time points:

- Day 1: Pre-dose, and 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16 hours post-dose
- Day 2: Pre-dose, and 2, 5, and 8 hours post-dose
- Day 4: Pre-dose, and 2, 5, and 8 hours post-dose
- Day 6: Pre-dose
- Day 7: Pre-dose, and 0.25, 0.5, 1, 2, 4, 6, 8, 16, 24, 48, 72, and 96 hours post-dose

Urine IkT-148009

Urine samples will be collected as 24-hour pooled samples on Day 1 and Day 7.

Plasma and Urine IkT-148009

All concentration data will be listed by subject and nominal time in an appendix. If there are any significant protocol deviations (e.g., significant time deviations from nominal sample times), some individual concentration data may be excluded from mean data presentations (e.g., descriptive statistics for concentrations at specific nominal time points and mean concentration-time plots). All deviations and excluded data will be provided and discussed in the CSR.

6.4 Noncompartmental Pharmacokinetic Analysis and Parameter Calculation

6.4.1 Plasma IkT-148009 Pharmacokinetic Parameters

Plasma concentrations of IkT-148009, as determined per the bioanalytical method and the collection times described in Section 6.2.1 and Section 6.3, respectively, will be used for the calculation of the plasma IkT-148009 PK parameters.

The appropriate noncompartmental PK parameters will be calculated from the plasma IkT-148009 concentration-time data using Phoenix® WinNonlin® Version 8.3.4 or higher. Actual sample times will be used in the calculations of the PK parameters. The calculation of the actual time for IkT-148009 will be in respect to the dose administration time of IkT-148009 on Day 1 and Day 7. All PK parameters included in the protocol are listed in Table 6-1 (for Day 1) and Table 6-2 (for Day 7) below, and are defined as appropriate for study design.

Table 6–1 Noncompartmental Plasma IkT-148009 Pharmacokinetic Parameters to be Calculated on Day 1

Parameter*	Label to be Used in the Text, Tables, and Figures	Definition	Method of Determination
AUC_{0-24}	AUC0-24	Area under the plasma concentration-time curve from time 0 to 24 hours post-dose Note: if the 24-hour plasma concentration is missing, below limit of quantification (BLQ), or not reportable, then extrapolation will be conducted, as appropriate. If extrapolation cannot be reliably performed, then this parameter will not be calculated.	Calculated using the Linear Trapezoidal with Linear Interpolation Method
AUC_{0-last}	AUC0-last	Area under the concentration-time curve from time 0 to the time of the last observed/measured non-zero concentration	Calculated using the Linear Trapezoidal with Linear Interpolation Method
$AUC_{0-\infty}$	AUC0-inf	Area under the concentration-time curve from time 0 extrapolated to infinity	Calculated as: $AUC_{0-last} + (C_{last}/K_{el})$ where C_{last} is the last observed/measured concentration
$AUC_{\%extrap}$	AUC%extrap	percent of $AUC_{0-\infty}$ extrapolated	Calculated as: $(1- AUC_{0-last}/AUC_{0-\infty}) \times 100$
C_{max}	Cmax	Maximum observed concentration	Taken directly from bioanalytical data
T_{max}	Tmax	Time to reach C_{max}; if C_{max} occurs at more than one time point, T_{max} is defined as the first time point with this value	Derived from clinical data as the difference in the time of the blood draw which is associated with the C_{max} and the time of administration
K_{el}	Kel	Apparent first-order terminal elimination rate constant	Calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., 3 or more non-zero concentrations)
$t_{1/2}$	t1/2	Apparent terminal elimination half-life of drug in plasma	Calculated as: $ln(2)/K_{el}$
AUC_{0-24}/D	AUC0-24/D	Dose-normalized AUC_{0-24}	Calculated as: AUC_{0-24}/Dose
AUC_{0-last}/D	AUC0-last/D	Dose-normalized AUC_{0-last}	Calculated as: AUC_{0-last}/Dose

Parameter*	Label to be Used in the Text, Tables, and Figures	Definition	Method of Determination
$AUC_{0-\infty}/D$	AUC0-inf/D	Dose-normalized $AUC_{0-\infty}$	Calculated as: $AUC_{0-\infty}$/Dose
C_{max}/D	Cmax/D	Dose-normalized C_{max}	Calculated as: C_{max}/Dose

*In the text of the CSR, subscripts and symbols will be used in parameter names, as appropriate. However, in post-text tables and listings, subscripts and symbols will not be used in parameter names.

Table 6–2 Noncompartmental Plasma IkT-148009 Pharmacokinetic Parameters to be Calculated on Day 7

Parameter*	Label to be Used in the Text, Tables, and Figures	Definition	Method of Determination
AUC_{tau}	AUCtau	Area under the concentration-time curve during a dosing interval, tau (τ), at steady state	Calculated using the Linear Trapezoidal with Linear Interpolation Method
$C_{max,ss}$	Cmax,ss	Maximum observed concentration at steady state	Taken directly from bioanalytical data
$T_{max,ss}$	Tmax,ss	Time to reach $C_{max,ss}$	Derived from clinical data as the difference in the time of the blood draw which is associated with the $C_{max,ss}$ and the time of administration
K_{el}	Kel	Apparent first-order terminal elimination rate constant	Calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., 3 or more non-zero concentrations)
$t_{½}$	t1/2	Apparent terminal elimination terminal half-life of drug at steady state in plasma	Calculated as: $ln(2)/K_{el}$
AR AUC	AR AUC	Accumulation ratio calculated from AUC_{tau} (on Day 7) and AUC_{0-24} following the first dose (on Day 1)	Calculated as: AUC_{tau}/AUC_{0-24} (from Day 1)
AR C_{max}	AR Cmax	Accumulation ratio calculated from $C_{max,ss}$ at steady state and C_{max} following the first dose (on Day 1)	Calculated as: $C_{max,ss}/C_{max}$ (from Day 1)
AUC_{tau}/D	AUCtau/D	Dose-normalized AUC_{tau}	Calculated as: AUC_{tau}/Dose
$C_{max,ss}/D$	Cmax,ss/D	Dose-normalized $C_{max,ss}$	Calculated as: C_{max}/Dose

Parameter*	Label to be Used in the Text, Tables, and Figures	Definition	Method of Determination
CL_{ss}/F	CLss/F	Apparent total body clearance estimated at steady state after oral administration	Calculated as: $Dose/AUC_{tau}$
V_z/F	Vz/F	Apparent volume of distribution as steady state after oral administration	Calculated as: $Dose/(AUC_{tau} \times K_{el})$

*In the text of the CSR, subscripts and symbols will be used in parameter names, as appropriate. However, in post-text tables and listings, subscripts and symbols will not be used in parameters.

PK parameters will not be calculated for subjects with less than 3 consecutive post-dose time points with quantifiable concentrations. Subjects for whom there are insufficient data to calculate the PK parameters will be included in the concentration tables, concentration summaries, and individual concentration-time figures.

For the calculation of concentration summary statistics and PK parameters on Day 1, plasma concentrations below the limit of quantitation (BLQ) prior to the first quantifiable concentration will be set to 0 and plasma concentrations BLQ after the first quantifiable concentration will be treated as missing. If plasma IkT-148009 trough concentrations (C_{trough}) are BLQ on Days 1, 3, 5, and 6 (corresponding to pre-dose values on Days 2, 4, 6, and 7), these values will be set to ½ the LLOQ for the calculation of concentration summary statistics and steady-state analysis. Additionally, BLQ concentrations on Day 7 will be treated as follows: if multiple consecutive BLQ concentrations are observed, then the first BLQ will be set to ½ the LLOQ and any subsequent BLQ concentrations will be set to missing for the calculation of concentration summary statistics and PK parameters. If only 1 BLQ concentration is observed on Day 7, then it will be set to ½ the LLOQ.

The K_{el} will be determined using linear regressions composed of at least 3 data points. Furthermore, the K_{el} will not be assigned if 1) the terminal elimination phase is not apparent, 2) T_{max} is one of the last 3 data points, or 3) the R^2 value is less than 0.75. In cases where the K_{el} interval is not assigned, the values of K_{el} and K_{el}-dependent parameters (i.e., $AUC_{0-\infty}$, $AUC_{\%extrap}$, $t_{½}$, V_z/F, and AUC_{0-24}, if applicable) are considered not calculable and will not be reported. Wherever the resulting $t_{½}$ is more than half as long as the sampling interval, the K_{el} value and K_{el}-dependent parameters (i.e., $AUC_{0-\infty}$, $AUC_{\%extrap}$, $t_{½}$, V_z/F, and AUC_{0-24}, if applicable) may not be presented, as judged appropriate and in accordance with Celerion SOPs.

6.4.2 Urine IkT-148009 Pharmacokinetic Parameters

The following PK parameters will be calculated from urine IkT-148009 excretion data on Day 1 and Day 7 using SAS® Version 9.4 or higher. All urine PK parameters to be calculated are listed in Table 6-3, and are defined as appropriate for study design.

Table 6–3 Urine IkT-148009 Pharmacokinetic Parameters to be Calculated on Day 1 and Day 7

Parameter*	Label to be Used in the Text, Tables, and Figures	Definition	Method of Determination
A_e	Ae	Total amount of drug excreted unchanged in the urine over the 24-hour collection interval	Calculated as: Conc × Vol
Conc	Conc	Drug concentration in the urine during the urine over the 24-hour collection interval	Taken directly from bioanalytical data
Vol	Vol	Volume of urine collected over the 24-hour collection interval	Taken directly from case report form (CRF) data
F_e	Fe	Fraction (in percentage) of drug dose excreted unchanged in urine	Calculated as: (A_e/Dose) × 100

*In the text of the CSR, subscripts and symbols will be used in parameter names, as appropriate. However, in post-text tables and listings, subscripts and symbols will not be used in parameters.

For the calculation of descriptive statistics and urine PK parameters, urine concentrations that are BLQ will be set to zero. Urine PK samples will collect 24-hour pooled urines on Day 1 and Day 7. The 24-hour collection on Day 1 starts at dosing and collected for 24 hours (i.e., prior to Day 2 dose). The 24-hour collection on Day 7 starts at dosing and collected for 24 hours. The amount of IkT-148009 excreted in urine (A_e) and fraction (in percentage) of IkT-148009 dose excreted in urine (F_e) after a deviation affecting sample collection (e.g., lost part of void, volume not recorded, etc.) will be presented, but may be excluded from summary statistics and footnoted accordingly.

6.5 Data Summarization and Presentation

6.5.1 Plasma

All IkT-148009 PK concentrations and PK parameters descriptive statistics will be generated using SAS® Version 9.4 or higher.

The plasma concentrations of IkT-148009 will be listed and summarized by study day and time point for all subjects in the PK Population. Plasma concentrations of IkT-148009 will be presented with the same level of precision as received from the bioanalytical laboratory. Summary statistics, including sample size (n), number of samples below the lower limit of quantitation (nLLOQ), arithmetic mean (mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum will be calculated for all nominal concentration time points. Excluded subjects will be included in the concentration listings, but will be excluded from the summary statistics and noted as such in the tables. All BLQ values will be presented as “BLQ” in the concentration listings and tables but will be set to zero (0) or missing, as described in Section 6.4.1 and footnoted accordingly.

Mean plasma IkT-148009 concentration-time profiles will be presented on linear and semi-log scales for the entire PK sampling profile as well as Day 1 and Day 7 overlaid. Linear mean plots will be presented with and without SD. Superimposed individual concentration-time profiles will be created for Days 1 and 7 separately, on linear and semi-log scales; different colors will be used for each subject's profiles on each day. Individual superimposed concentration-time profiles will be based on actual sample times, and mean concentration-time profiles will be based on nominal sample times.

Plasma IkT-148009 C_{trough} will be summarized by trough day with descriptive statistics, including n, mean, SD, CV%, minimum, median, maximum, geometric mean, and geometric CV%. Mean C_{trough}-time profile will also be presented on linear scale. The following $C_{troughs}$ will be presented:

- Day 1 C_{trough}, corresponding to the pre-dose concentration on Day 2
- Day 3 C_{trough}, corresponding to the pre-dose concentration on Day 4
- Day 5 C_{trough}, corresponding to the pre-dose concentration on Day 6
- Day 6 C_{trough}, corresponding to the pre-dose concentration on Day 7
- Day 7 C_{trough}, corresponding to the 24-hour post-Day 7 dose

Plasma IkT-148009 PK parameters will be listed and summarized by study day for all subjects in the PK Analysis Population. PK parameters will be reported to 3 significant figures for individual parameters, with the exception of C_{max}, $C_{max,ss}$, and C_{trough}, which will be presented with same level of precision as received from the bioanalytical laboratory and T_{max} and $T_{max,ss}$ which will be presented with 2 decimal places. Summary statistics (n, mean, SD, CV%, SEM, minimum, median, and maximum, geometric mean, and geometric CV% will be presented for all PK parameters. Excluded subjects will be listed in the PK parameter tables, but will be excluded from the summary statistics and noted as such in the tables.

The level of precision for each concentration and PK parameter statistic will be presented as follows:

- minimum/maximum in same precision as in bioanalytical data and/or parameter output,
- mean/median/geometric mean/SD/SEM/CV%/geometric CV% will be rounded to 3 significant figures, and
- n and nLLOQ will be presented as an integer

6.5.2 Urine

Descriptive statistics for all urine excretion intervals will be generated using SAS® Version 9.4 or higher.

The A_e and F_e over each 24-hour interval following dosing will be summarized by day and collection interval with descriptive statistics, including n, mean, SD, CV%, minimum, median, and maximum.

The level of precision for each concentration and PK parameter statistic will be presented as follows:

- minimum/maximum in same precision as in bioanalytical data,
- mean/median/geometric mean/SD/SEM/CV%/geometric CV% will be rounded to 3 significant figures,
- n and nLLOQ will be presented as an integer

6.6 Steady-State Analysis of Pharmacokinetic Parameters

A steady-state analysis will be performed on the ln-transformed C_{trough} values for plasma IkT-148009. The C_{trough} parameters on Days 1, 3, 5, 6, and 7 will be used. The repeated analysis of variance (ANOVA) model will be performed and will include Day as a fixed effect. The best variance-covariance matrix structure will be chosen to model the correlation within each subject using the Akaike's Burnham and Anderson criterion (AICC, smaller is better).

Helmert contrasts are constructed such that each time point is compared to the mean of the subsequent time points. Steady state will be concluded at the time point where no more statistical difference (alpha=5%, two-sided) can be observed.

The contrasts will be:

- Comparison 1: Day 1 C_{trough} versus mean of (Day 3 C_{trough}, Day 5 C_{trough}, Day 6 C_{trough}, and Day 7 C_{trough}^{*})
- Comparison 2: Day 3 C_{trough} versus mean of (Day 5 C_{trough}, Day 6 C_{trough} and Day 7 C_{trough}^{*})
- Comparison 3: Day 5 C_{trough} versus mean of (Day 6 C_{trough} and Day 7 C_{trough}^{*})
- Comparison 4: Day 6 C_{trough} versus Day 7 C_{trough}^{*}

*Note: The C_{trough} on Day 7 corresponds to the concentration obtained at 24 hours post-Day 7 dose.

The steady-state analysis will be conducted using PROC MIXED of SAS®. The following SAS® code will be used:

```
PROC MIXED;
CLASS SUBJECT DAY;
MODEL LN_ CONC = DAY/DDFM=KR;
REPEATED DAY/TYPE=&TYPE SUB= SUBJECT;
LSMEAN DAY;
RUN;
```

Where &TYPE is UN. Note: A SAS® macro will be used to run Helmert contrasts.

Programmer Note: UN will be tested first and if the UN correlation structure model does not converge, the following additional correlation structures will be tested: CS, CSH, AR(1), ARH(1), and ARMA(1,1); then AICC (smaller is better) will be used to determine the final model.

6.7 Preliminary Analysis

Celerion Biometrics will perform a preliminary analysis following completion of all subjects to provide Inhibikase Therapeutics with expedited PK data. Details for the preliminary analysis are described in a separate document (i.e., the Preliminary Analysis Plan).

7. SAFETY

All relevant CRF data will be listed by subject and chronologically by assessment time point. This will include rechecks, unscheduled, and early termination assessments.

Applicable continuous variables will be summarized using n, mean, SD, minimum, median, and maximum.

The level of precision will be presented as follows:

For demographic characteristic data, mean and median will be rounded to one decimal place, SD will be rounded to two decimal places and minimum and maximum will be in the same precision as the original data in the database, and n will be presented as an integer.

For other continuous safety data, mean and median will be in one more decimal places than original data in database, SD will be in two more decimal places than original data in database, minimum and maximum will be in the same precision as original data in the database, and n will be presented as an integer.

Percentages will be rounded to one decimal place.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

Baseline will be the result closest and prior to the first dose of study product which is generally the Day 1 pre-dose value unless otherwise stated. Summaries for post-baseline time points will not include rechecks, unscheduled, or early termination measurements.

Tables summarizing safety data by assessment time point will only include summaries for baseline and post-baseline time points.

7.1 Subject Disposition

Subjects will be summarized by the number and percent of subjects dosed, completed the study, discontinued the study (with discontinuation reasons), completed treatment, and discontinued from treatment (with treatment discontinuation reasons) by overall.

7.2 Protocol Deviations

Protocol deviations are captured by the clinical site and provided in the CSR in a similar format to that provided by the clinical site. Protocol deviations are not edited or processed in SAS®.

7.3 Demographics

Descriptive statistics will be calculated for continuous variables (age, body mass index, height, and weight) by overall. Age will be approximated by subtracting the year of birth from the year of informed consent. If year of informed consent – year of birth is one more than the protocol maximum age then the age approximation will be year of informed consent – year of birth – 1. Descriptive statistics for body mass index, height, and weight will be calculated using screening measurements.

Frequency counts will be provided for categorical variables (sex, race, and ethnicity) by overall.

7.4 Adverse Events

All AEs occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 25.1.

All AEs captured in the database will be listed in a by-subject data listing including verbatim term, coded term, treatment, start date/time, end date/time, frequency, severity, seriousness, outcome, relationship to study product, and action; however, only treatment-emergent AEs (TEAEs) will be summarized.

A TEAE is defined as an AE that is starting at the time of or after study product administration. Each TEAE will be attributed to the treatment based on the start date and time of the AE compared to that of the respective treatment administration date and time.

If the onset time of an AE is missing and the onset date is the same as or occurs after the treatment dosing date, then the AE will be considered treatment emergent. If the onset date of an AE is missing, then the AE will be considered treatment emergent.

TEAEs will be tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include the number of subjects reporting the TEAE and as a percent of the number of subjects dosed by overall. The number of TEAEs will be tabulated in a similar manner. A table, which summarizes the number of TEAEs by Preferred Term, severity, and relationship to study product, will also be included.

Serious adverse events (SAEs), if present, will also be listed. Applicable narratives will be included in the CSR.

7.5 Clinical Laboratory Tests (Serum Chemistry, Hematology, Coagulation, Urinalysis and Other)

Clinical laboratory tests will be measured at the following time points:

Clinical Laboratory Panels	Time Point		
	Period	CRF/Listing Day and Hour	Table
Serum Chemistry, Hematology, Coagulation, Urinalysis and Tests for Reproductive Organ Function	Screening^		NA
	1	Day -1 Hour -18.00* and -17.75^	NA
		Day 1 Hour -0.83	Baseline
		Day 2 Hour 23.17^ and 23.83*	Day 2 pre-dose
		Day 3 Hour 47.17	Day 3 pre-dose
		Day 4 Hour 71.17	Day 4 pre-dose
		Day 5 Hour 95.17	Day 5 pre-dose
		Day 6 Hour 119.17	Day 6 pre-dose
		Day 8 Hour 167.92* and 168.00^	Day 8
		Day 9 Hour 192.00	Day 9
		Day 14 Hour 312.00^	Follow-up
		Day 21 Hour 479.50* and 480.00^	End of Study

Time points in the CRF/Listing column are approximated/based on the blank CRF and it should be noted that the data listings will reflect the data found in the final subject CRFs.
If applicable, an early termination assessment will be performed.
*Time points only applies to urinalysis.
^Time points includes tests for reproductive organ function (leutenizing hormone [LH], follicle stimulating hormone [FSH], testosterone and inhibin B)
NA = Not applicable

Clinical laboratory results will be presented as extracted from the clinical laboratory database, which is in conventional units. Out-of-reference range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results.

Out-of-reference range values and corresponding recheck results will be listed.

For all numeric laboratory values, descriptive statistics will be presented for each laboratory test by assessment time point. Change from baseline will be summarized in a similar manner. For all numeric laboratory tests, the mean value calculated for each assessment time point will be compared to the reference range and flagged if outside of the reference range (* if above the reference range and ^ if below the reference range). In the event there is more than one reference range for a laboratory test, the comparison will be made against the lowest of the lower ranges and the highest of the higher ranges.

For each laboratory test, a shift table will be developed to compare the frequency of the results at baseline (above reference range, within reference range, or below reference range) with the respective post-dose results. For urinalysis tests, the categories are within reference range and outside reference range.

7.6 Vital Signs

Vital signs will be measured at the following time points:

Parameter	Time Point		
	Period	CRF/Listing Day and Hour	Table
Blood Pressure (Supine for 5 minutes, Standing for 2 minutes), Heart Rate (Supine for 5 minutes, Standing for 2 minutes), Respiration, Temperature, Oxygen	Screening		NA
	1	Day -1 Hour -16.50	NA
		Day 1 Hour -1.33/-1.17/-1.00	Baseline
		Day 1 Hour 0.83	Day 1 Hour 1
		Day 1 Hour 1.83	Day 1 Hour 2
		Day 1 Hour 3.83	Day 1 Hour 4
		Day 1 Hour 7.83	Day 1 Hour 8
		Day 1 Hour 11.83	Day 1 Hour 12
		Day 2 Hour 18.00	Day 2 Hour 18
		Day 2 Hour 23.08	Day 2 pre-dose
		Day 2 Hour 28.00	Day 2 Hour 4*
		Day 2 Hour 31.83	Day 2 Hour 8*
		Day 2 Hour 36.00	Day 2 Hour 12*
		Day 3 Hour 47.08	Day 3 pre-dose
		Day 3 Hour 60.00	Day 3 Hour 12*
		Day 4 Hour 71.08	Day 4 pre-dose
		Day 4 Hour 84.00	Day 4 Hour 12*
		Day 5 Hour 95.08	Day 5 pre-dose
		Day 5 Hour 108.00	Day 5 Hour 12*
		Day 6 Hour 119.08	Day 6 pre-dose
		Day 6 Hour 132.00	Day 6 Hour 12*
		Day 7 Hour 143.17	Day 7 pre-dose
		Day 7 Hour 156.00	Day 7 Hour 12*
		Day 8 Hour 167.83	Day 8
		Day 9 Hour 191.83	Day 9
		Day 10 Hour 215.83	Day 10
		Day 14 Hour 311.83	Follow-up
		Day 21 Hour 479.83	End of Study

Parameter	Time Point		
	Period	CRF/Listing Day and Hour	Table
Weight	Screening		NA
	1	Day -1 Hour -17.75| Day 1 Hour -2.25 Day 2 Hour 22.50 Day 3 Hour 46.50 Day 4 Hour 70.00 Day 5 Hour 94.50 Day 6 Hour 118.50 Day 7 Hour 142.25 Day 8 Hour 167.50 Day 9 Hour 191.25 Day 10 Hour 215.50 Day 11 Hour 239.58 Day 14 Hour 312.08 Day 21 Hour 480.08	NA Baseline Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 9 Day 10 Day 11 Follow-up End of Study

Time points in the CRF/Listing column are approximated/based on the blank CRF and it should be noted that the data listing will reflect the data found in the final subject CRFs.
If applicable, an early termination assessment will be performed.
*Hours are relative to dosing on respective Day.
NA = Not applicable

Descriptive statistics will be presented for vital signs measurements (supine blood pressure, standing blood pressure, supine heart rate, standing heart rate, respiration, temperature, oxygen and weight) by assessment time point. Change from baseline will be summarized in a similar manner. Baseline for vital signs that was measured three times on Day 1 pre-dose is defined as the average of three measurements. Rechecks or unscheduled assessments results may be used as baseline when applicable.

Orthostatic change will be calculated and listed for blood pressure and heart rate at the time points listed previously by subtracting the supine measurement from the standing measurement (i.e. orthostatic change = standing measurement – supine measurement). Baseline for orthostatic change is defined as the average of three orthostatic result obtained on Day 1 pre-dose. At postdose time points, the first complete orthostatic assessment (i.e. assessment with supine result and corresponding standing result) will be used during analysis. If the first complete orthostatic assessment is not the original assessment at a given postdose time point (e.g., original assessment has supine result and no corresponding standing result), the first complete orthostatic assessment will only be used if this assessment starts within 15 minutes of the original incomplete assessment. Post-dose unscheduled and early termination measurements will not be included in listing of orthostatic change.

7.7 Electrocardiogram

ECGs will be measured at the following time points:

Parameter	Time Point		
	Period	CRF/Listing Day and Hour	Table
HR, PR, QRS, QT, QTcF, RR	Screening		NA
	1	Day -1 Hour -17.00	NA
		Day 1 Hour -1.50	Baseline
		Day 1 Hour 0.68	Day 1 Hour 1
		Day 1 Hour 1.68	Day 1 Hour 2
		Day 1 Hour 3.68	Day 1 Hour 4
		Day 1 Hour 7.68	Day 1 Hour 8
		Day 1 Hour 11.68	Day 1 Hour 12
		Day 2 Hour 23.00	Day 2 pre-dose
		Day 2 Hour 35.83	Day 2 Hour 12*
		Day 3 Hour 47.00	Day 3 pre-dose
		Day 3 Hour 59.83	Day 3 Hour 12*
		Day 4 Hour 71.00	Day 4 pre-dose
		Day 4 Hour 83.83	Day 4 Hour 12*
		Day 5 Hour 95.00	Day 5 pre-dose
		Day 5 Hour 107.83	Day 5 Hour 12*
		Day 6 Hour 119.00	Day 6 pre-dose
		Day 6 Hour 131.83	Day 6 Hour 12*
		Day 7 Hour 143.00	Day 7 pre-dose
		Day 7 Hour 155.83	Day 7 Hour 12*
		Day 8 Hour 167.68	Day 8
		Day 9 Hour 191.68	Day 9
		Day 10 Hour 215.68	Day 10
		Day 14 Hour 311.68	Follow-up
		Day 21 Hour 479.68	End of Study

Time points in the CRF/Listing column are approximated/based on the blank CRF and it should be noted that the data listing will reflect the data found in the final subject CRFs.
If applicable, an early termination assessment will be performed.
*Hours are relative to dosing on respective Day.
NA = Not applicable

Descriptive statistics will be presented for ECG measurements by assessment time point. Change from baseline will be summarized in a similar manner.

All ECG data will be listed by subject and QTc values > 450 msec and increase from baseline > 30 msec will be flagged.

7.8 Prior and Concomitant Medications

Prior and concomitant medications recorded during the study will be coded with the World Health Organization (WHO) Drug Dictionary Version 01-Sep-2022 b3 and listed.

7.9 Physical and Neurological Examination

Abnormal physical examination findings will be reported as medical history or AEs. All data found in the CRF will be listed.

8. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

The final protocol (dated 03 February 2023) describes a dose-proportionality analysis that is to be performed in Section 11.5. However, since only 1 dose of study drug will be administered, a dose-proportionality analysis cannot be performed. An analysis of steady state, as described in Section 6.6, will be completed instead.

The final protocol (dated 03 February 2023) describes different precision principles in Section 11.1 on continuous baseline and other continuous data. However, the same precision principles will be used for all non-demographic continuous data. Demographic data will use the same precision principles as described in the protocol.

The final protocol (dated 03 February 2023) describes different definition on baseline for vital signs and other safety variables in Section 11.1. However, one same baseline will be used.

9. SUMMARY TABLES, FIGURES, AND LISTINGS

Summary tables and figures are numbered following the International Council on Harmonization (ICH) structure but may be renumbered as appropriate during the compilation of the tables and figures for the CSR. Note that all summary tables and figures will be generated using SAS® Version 9.4 or higher.

In-text tables and figures will be generated as RTF and all other tables and listings will be generated as SAS® LST format and converted to MS Word for Inclusion in the CSR. In compliance Celerion SOP/PG, SAS® outputs will not be manually edited.

9.1 In-text Summary Tables and Figures

The following is a list of table and figure titles that will be included in the text of the CSR. Tables and figures will be numbered appropriately during compilation of the CSR.

Section 10:

Number	Title	Shell
Table 10-1	Disposition Summary (Safety Population)	IDS

Section 11:

Number	Title	Shell
Table 11-1	Demographic Summary (Safety Population)	IDEM
Table 11-2	Summary of Plasma IkT-148009 Pharmacokinetic Parameters on Day 1 Following Administration of the First Oral Dose of IkT-148009 and on Day 7 Following Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)	ITPPAR1
Table 11-3	Summary of Steady-State Assessment of Plasma IkT-148009 Using Helmert Contrasts Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)	ITCPSS1
Figure 11-1	Arithmetic Mean Plasma IkT-148009 Concentration-Time Profile on Days 1 to 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Linear Scale) (Pharmacokinetic Analysis Population)	PFPCONC2
Figure 11-2	Arithmetic Mean Plasma IkT-148009 Concentration-Time Profiles on Day 1 Following Administration of the First Oral Dose of IkT-148009 and on Day 7 Following Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Linear Scale) (Pharmacokinetic Analysis Population)	PFPCONC2
Figure 11-3	Arithmetic Mean Plasma IkT-148009 Ctrough-Time Profile Following Administration on Days 1 to 7 of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Linear Scale) (Pharmacokinetic Analysis Population)	PFPCONC2

Section 12:

Number	Title	Shell
Table 12-1	Treatment-Emergent Adverse Event Frequency - Number of Subjects Reporting the Event (% of Subjects Dosed) (Safety Population)	IAES

9.2 Section 14 Summary Tables and Figures

The following is a list of table and figure titles that will be included in Section 14 of the report. Table and figure titles may be renumbered as appropriate during the compilation of the report.

14.1 Demographic Data Summary Tables

Number	Title	Shell
Table 14.1.1	Disposition Summary (Safety Population)	CDS
Table 14.1.2	Demographic Summary (Safety Population)	CDEM

14.2 Pharmacokinetic Data Summary Tables and Figures

14.2.1 Plasma IkT-148009 Tables

Number	Title	Shell
Table 14.2.1.1	Plasma IkT-148009 Concentrations (ng/mL) Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers on Days 1 to 7 (Pharmacokinetic Analysis Population)	CPCONC1
Table 14.2.1.2	Plasma IkT-148009 Pharmacokinetic Parameters on Day 1 Following Administration of the First Oral Dose of IkT-148009 in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)	CPPAR1
Table 14.2.1.3	Plasma IkT-148009 Pharmacokinetic Parameters on Day 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)	CPPAR1
Table 14.2.1.4	Steady-State Assessment of Plasma IkT-148009 Using Helmert Contrasts Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)	CPSS1

14.2.2 Plasma IkT-148009 Figures

Number	Title	Shell
Figure 14.2.2.1	Arithmetic Mean (SD) Plasma IkT-148009 Concentration-Time Profile on Days 1 to 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Linear Scale) (Pharmacokinetic Analysis Population)	PFPCONC 1
Figure 14.2.2.2	Arithmetic Mean Plasma IkT-148009 Concentration-Time Profile on Days 1 to 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Linear Scale) (Pharmacokinetic Analysis Population)	PFPCONC 2
Figure 14.2.2.3	Arithmetic Mean (SD) Plasma IkT-148009 Concentration-Time Profile on Days 1 to 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Semi-Log Scale) (Pharmacokinetic Analysis Population)	PFPCONC 4
Figure 14.2.2.4	Arithmetic Mean Plasma IkT-148009 Concentration-Time Profile on Days 1 to 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Semi-Log Scale) (Pharmacokinetic Analysis Population)	PFPCONC 3
Figure 14.2.2.5	Arithmetic Mean (SD) Plasma IkT-148009 Concentration-Time Profiles on Day 1 Following Administration of the First Oral Dose of IkT-148009 and on Day 7 Following Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Linear Scale) (Pharmacokinetic Analysis Population)	PFPCONC 1
Figure 14.2.2.6	Arithmetic Mean Plasma IkT-148009 Concentration-Time Profiles on Day 1 Following Administration of the First Oral Dose of IkT-148009 and on Day 7 Following Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Linear Scale) (Pharmacokinetic Analysis Population)	PFPCONC 2

Number	Title	Shell
Figure 14.2.2.7	Arithmetic Mean (SD) Plasma IkT-148009 Concentration-Time Profiles on Day 1 Following Administration of the First Oral Dose of IkT-148009 and on Day 7 Following Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Semi-Log Scale) (Pharmacokinetic Analysis Population)	PFPCONC 4
Figure 14.2.2.8	Arithmetic Mean Plasma IkT-148009 Concentration-Time Profiles on Day 1 Following Administration of the First Oral Dose of IkT-148009 and on Day 7 Following Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Semi-Log Scale) (Pharmacokinetic Analysis Population)	PFPCONC 3
Figure 14.2.2.9	Arithmetic Mean (SD) Plasma IkT-148009 Ctrough-Time Profile Following Administration on Days 1 to 7 of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Linear Scale) (Pharmacokinetic Analysis Population)	PFPCONC 1
Figure 14.2.2.10	Arithmetic Mean Plasma IkT-148009 Ctrough-Time Profile Following Administration on Days 1 to 7 of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Linear Scale) (Pharmacokinetic Analysis Population)	PFPCONC 2

14.2.3 Urine IkT-148009 Tables

Number	Title	Shell
Table 14.2.3.1	Urine Excretion of IkT-148009 on Day 1 Following Administration of the First Oral Dose of IkT-148009 and on Day 7 Following Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)	CUPAR3

14.3 Safety Data Summary Tables

14.3.1 Displays of Adverse Events

Number	Title	Shell
Table 14.3.1.1	Treatment-Emergent Adverse Event Frequency – Number of Subjects Reporting the Event (% of Subjects Dosed) (Safety Population)	CAES
Table 14.3.1.2	Treatment-Emergent Adverse Event Frequency – Number of Adverse Events (% of Total Adverse Events) (Safety Population)	CAEE
Table 14.3.1.3	Treatment-Emergent Adverse Event Frequency by Severity and Relationship to Study Product – Number of Adverse Events (Safety Population)	CAESR

14.3.2 Listings of Deaths, other Serious and Significant Adverse Events

Number	Title	Shell
Table 14.3.2.1	Serious Adverse Events (Safety Population)	16.2.7.2

14.3.3 Narratives of Deaths, other Serious and Certain other Significant Adverse Events

14.3.4 Abnormal Laboratory Value Listing (each subject)

Number	Title	Shell
Table 14.3.4.1	Out-of-Range Values and Recheck Results – Serum Chemistry (Safety Population)	CLBO
Table 14.3.4.2	Out-of-Range Values and Recheck Results – Hematology (Safety Population)	
Table 14.3.4.3	Out-of-Range Values and Recheck Results – Coagulation (Safety Population)	
Table 14.3.4.4	Out-of-Range Values and Recheck Results – Urinalysis (Safety Population)	

14.3.5 Displays of Other Laboratory, Vital Signs, Electrocardiogram, Physical Examination, and Other Safety Data

Number	Title	Shell
Table 14.3.5.1	Clinical Laboratory Summary and Change From Baseline – Serum Chemistry (Safety Population)	CLBD
Table 14.3.5.2	Clinical Laboratory Shift From Baseline – Serum Chemistry (Safety Population)	CLBS
Table 14.3.5.3	Clinical Laboratory Summary and Change From Baseline – Hematology (Safety Population)	CLBD
Table 14.3.5.4	Clinical Laboratory Shift From Baseline – Hematology (Safety Population)	CLBS
Table 14.3.5.5	Clinical Laboratory Summary and Change From Baseline – Coagulation (Safety Population)	CLBD
Table 14.3.5.6	Clinical Laboratory Shift From Baseline – Coagulation (Safety Population)	CLBS
Table 14.3.5.7	Clinical Laboratory Summary and Change From Baseline – Urinalysis (Safety Population)	CLBD
Table 14.3.5.8	Clinical Laboratory Shift From Baseline – Urinalysis (Safety Population)	CLBS
Table 14.3.5.9	Clinical Laboratory Summary and Change From Baseline – Reproductive Organ Function (Safety Population)	CLBD
Table 14.3.5.10	Clinical Laboratory Shift From Baseline – Reproductive Organ Function (Safety Population)	CLBS
Table 14.3.5.11	Vital Sign Summary and Change From Baseline (Safety Population)	CVS
Table 14.3.5.12	12-Lead Electrocardiogram Summary and Change From Baseline (Safety Population)	CEG

9.3 Section 16 Data Listings

Note: Hepatitis and HIV results that are provided by the clinical laboratory will not be presented in subject data listings and will not be included in any database transfer. All data will be presented as outline in the CRF (i.e., time point information will be consistent with the CRF data).

Data listings are numbered following the ICH structure but may be renumbered as appropriate during the compilation of the TFLs for the CSR. The following is a list of appendix numbers and titles that will be included as data listings:

16.1 Study Information

16.1.9 Statistical Methods

Number	Title
Appendix 16.1.9.1	Statistical Analysis Plan
Appendix 16.1.9.2	Statistical Methods – Pharmacokinetics

16.1.10 Clinical Laboratory Reference Ranges

Number	Title
Appendix 16.1.10.1	Clinical Laboratory Reference Ranges

16.2 Subject Data Listings

16.2.1 Subject Discontinuation

Number	Title	Shell
Appendix 16.2.1.1	Subject Disposition (Safety Population)	DISP

16.2.2 Protocol Deviations

Number	Title
Appendix 16.2.2	Protocol Deviations

16.2.3 Subjects Excluded From the Pharmacokinetic Analysis

Number	Title
Appendix 16.2.3	Subjects Excluded From the Pharmacokinetic Analysis

Note: Appendices 16.2.2 and 16.2.3 are generated in MS Word for inclusion in the study report.

16.2.4 Demographic Data

Number	Title	Shell
Appendix 16.2.4.1	Demographics (Safety Population)	LDEM
Appendix 16.2.4.2	Physical and Neurological Examination (Safety Population)	LPE

Number	Title	Shell
Appendix 16.2.4.3	Medical History (Safety Population)	LMH
Appendix 16.2.4.4	Substance Use (Safety Population)	LSU

16.2.5 Compliance and/or Drug Concentration Data

Number	Title	Shell
Appendix 16.2.5.1	Subject Eligibility (Safety Population)	LSE
Appendix 16.2.5.2	Test Compound Description	CPDE
Appendix 16.2.5.3	Test Compound Administration Times (Safety Population)	CPAD
Appendix 16.2.5.4	Meal Times (Safety Population)	LML
Appendix 16.2.5.5	Fluid Intake (Safety Population)	LFI
Appendix 16.2.5.6	Prior and Concomitant Medications (Safety Population)	LCM
Appendix 16.2.5.7	Pharmacokinetic Blood Draw Times and Concentration Data (Pharmacokinetic Concentration Population)	PK_BLD
Appendix 16.2.5.8	Pharmacokinetic Urine Collection Times, Weight, and Concentration Data (Pharmacokinetic Concentration Population)	PK_URN

16.2.6 Individual Pharmacokinetic Response Data

Number	Title	Shell
Appendix 16.2.6.1	Individual Superimposed Plasma IkT-148009 Concentration-Time Profiles on Day 1 Following Administration of the First IkT-148009 Oral Dose in Older Adult and Elderly Healthy Volunteers (Linear Scale)	PFPCONC6a
Appendix 16.2.6.2	Individual Superimposed Plasma IkT-148009 Concentration-Time Profiles on Day 1 Following Administration of the First IkT-148009 Oral Dose in Older Adult and Elderly Healthy Volunteers (Semi-Log Scale)	PFPCONC7a
Appendix 16.2.6.3	Individual Superimposed Plasma IkT-148009 Concentration-Time Profiles on Day 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Linear Scale)	PFPCONC6a

Number	Title	Shell
Appendix 16.2.6.4	Individual Superimposed Plasma IkT-148009 Concentration-Time Profiles on Day 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Semi-Log Scale)	PFPCONC7a
Appendix 16.2.6.5	Intervals (Hours) Used for Determination of Plasma IkT-148009 Kel Values on Days 1 and 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)	CPKEL1

16.2.7 Adverse Events Listings

Number	Title	Shell
Appendix 16.2.7.1	Adverse Events (Safety Population)	LAE
Appendix 16.2.7.2	Details for Serious Adverse Events (Safety Population) *This listing will be removed if no serious adverse events are reported.*	DSAE

16.2.8 Clinical Laboratory Reports

Number	Title	Shell
Appendix 16.2.8.1	Clinical Laboratory Report - Serum Chemistry (Safety Population)	LBR
Appendix 16.2.8.2	Clinical Laboratory Report - Hematology (Safety Population)	LBR
Appendix 16.2.8.3	Clinical Laboratory Report - Coagulation (Safety Population)	LBR
Appendix 16.2.8.4	Clinical Laboratory Report - Urinalysis (Safety Population)	LBR
Appendix 16.2.8.5	Clinical Laboratory Report - Urine Drug Screening (Safety Population)	LBR
Appendix 16.2.8.6	Clinical Laboratory Report - Reproductive Organ Function (Safety Population)	LBR
Appendix 16.2.8.7	Vital Signs (Safety Population)	LVS

Number	Title	Shell
Appendix 16.2.8.8	Orthostatic Vital Signs (Safety Population)	LOVS
Appendix 16.2.8.9	12-Lead Electrocardiogram (Safety Population)	LECG
Appendix 16.2.8.10	Echocardiogram (Safety Population)	LECO
Appendix 16.2.8.11	Columbia-Suicide Severity Rating Scale (C-SSRS) Questions – Baseline/Screening (Safety Population)	LCSBQ
Appendix 16.2.8.12	Columbia-Suicide Severity Rating Scale (C-SSRS) Questions – Since Last Visit (Safety Population)	LCSLQ
Appendix 16.2.8.13	Columbia-Suicide Severity Rating Scale (C-SSRS) Responses – Baseline/Screening (Safety Population)	LCSBR
Appendix 16.2.8.14	Columbia-Suicide Severity Rating Scale (C-SSRS) Responses – Since Last Visit (Safety Population)	LCSLR
Appendix 16.2.8.15	Mini-Mental State Exam Questions (Safety Population)	LMSEQ
Appendix 16.2.8.16	Mini-Mental State Exam Responses (Safety Population)	LMSER

10. TABLE, FIGURE, AND LISTING SHELLS

The following table shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the tables that will be presented and included in the final report. Unless otherwise noted, all in-text tables will be presented in Times New Roman font size 9 and post-text tables will be presented in Courier New font size 9. In-text tables and figures will be generated as RTF and all other tables and listings will be generated as SAS® LST format and converted to MS Word for inclusion in the CSR. In compliance Celerion SOP/PG, SAS® outputs will not be manually edited. Tables will be generated from ADaM datasets created in accordance with CDISC guidance (ADaM Model 2.1 and ADaM implementation Guide 1.1).

10.1 In-text Summary Tables Shells

In-text Shells will be in the following RTF formats:

Table IDS Disposition Summary (Safety Population)

Category	Overall
Dosed	XX (XX.X%)
Completed Study	XX (XX.X%)
Discontinued From Study	XX (XX.X%)
<Reason>	XX (XX.X%)
Completed Treatment	XX (XX.X%)
Discontinued From Treatment	XX (XX.X%)
<Reason>	XX (XX.X%)
All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects. Source: Table 14.1.1 Program: /CAXXXXX/sas_prg/stsas/intext/t_disp.sas DDMMMYYYY HH:MM	

Programmer Note: Percentages will be rounded to one decimal place.

Table IDEM Demographic Summary (Safety Population)

Trait	Category/Statistic	Overall
Sex	Female	XX (XX.X%)
	Male	XX (XX.X%)
Race	Asian	XX (XX.X%)
	Black or African American	XX (XX.X%)
	White	XX (XX.X%)
Ethnicity	Hispanic or Latino	XX (XX.X%)
	Not Hispanic or Latino	XX (XX.X%)
Age (yr)	n	X
	Mean	X.X
	SD	X.XX
	Minimum	XX
	Median	X.X
	Maximum	XX
Body Mass Index (kg/m²)	n	X
	Mean	X.X
	SD	X.XX
	Minimum	XX
	Median	X.X
	Maximum	XX
Height (cm)	n	X
	Mean	X.X
	SD	X.XX
	Minimum	XX
	Median	X.X
	Maximum	XX
Weight (kg)	n	X
	Mean	X.X
	SD	X.XX
	Minimum	XX
	Median	X.X
	Maximum	XX

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
Descriptive statistics for body mass index, height, and weight are calculated using Screening measurements.

Source: Table 14.1.2
Program: /CAXXXXX/sas_prg/stsas/intext/t_dem.sas DDMMMYYYY HH:MM

Programmer Note: Percentages will be rounded to one decimal place. Mean and median will be rounded to one decimal place, SD will be rounded to two decimal places and minimum and maximum will be in the same precision as the original data in the database.

Table ITPPAR1 Summary of Plasma IkT-148009 Pharmacokinetic Parameters on Day 1 Following Administration of the First Oral Dose of IkT-148009 and on Day 7 Following Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)

Pharmacokinetic Parameters	Day 1	Day 7
Param1 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param2 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param3 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param4 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects AUCs, C_{max}, and $C_{max,ss}$ values are presented as geometric mean and geometric CV%. T_{max} values are presented as median (min, max). Other parameters are presented as arithmetic mean (± SD). Source: Tables 14.2.1.2 and 14.2.1.3		

Notes for Generating the Actual Table:

Presentation of Data:

- The following PK parameters will be presented in the following order and with following units for Day 1: AUC_{0-24} (ng*hr/mL), AUC_{0-24}/D (ng*hr/mL/mg), AUC_{0-last} (ng*hr/mL), AUC_{0-last}/D (ng*hr/mL/mg), $AUC_{0-\infty}$ (ng*hr/mL), $AUC_{0-\infty}/D$ (ng*hr/mL/mg), $AUC_{\%extrap}$ (%), C_{max} (ng/mL), C_{max}/D (ng/mL/mg), T_{max} (hr), and $t_{½}$ (hr)
- The following PK parameters will be presented in the following order and with the following units for Day 7: AUC_{tau} (ng*hr/mL), AUC_{tau}/D (ng*hr/mL/mg), $C_{max,ss}$ (ng/mL), $C_{max,ss}/D$ (ng/mL/mg), $T_{max,ss}$ (hr), $t_{½}$, AR AUC, AR C_{max}, CL_{ss}/F (L/hr), and Vz/F (L)
- n will be presented as an integer (with no decimal);
- Summary statistics will be presented with same precision as defined in post-text shells
- For parameters that will not be calculated for the specified PK day, use "NC" and footnote "Not calculated".

Program: /CAXXXXX/sas_prg/pksas/intext-pk-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas DDMMMYYYY HH:MM

Table ITCPSS1 Summary of Steady-State Assessment of Plasma IkT-148009 Using Helmert Contrasts Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)

Trough Days	Geometric LSM	p-value
Day 1	X.XXX	X.XXXX
Day 3	X.XXX	X.XXXX
Day 5	X.XXX	X.XXXX
Day 6	X.XXX	X.XXXX
Day 7	X.XXX	.

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects

The C_{trough} on Days 1, 3, 5, and 6 correspond to the pre-dose concentration obtained on Days 2, 4, 6, and 7 respectively. The C_{trough} on Day 7 corresponds to the concentration obtained at 24 hours post-Day 7 dose.

Concentrations were ln-transformed prior to analysis.

Geometric least-squares means (LSMs) were obtained by taking exponential of the LSMs from ANOVA.

p-value corresponds to the Helmert contrast, i.e., the comparison of that day versus the average of the remaining days.

Source: Table 14.2.1.4

Notes for Generating the Actual Table:

Presentation of Data:

- Geometric LSM will be presented with 4 significant figures
- p-value will be presented to 4 decimals

Program: DM_PX:[HLXXXXX.PKSAS]STEADYSTATE-HELMERT.SAS XXAPRXXXX HH:MM

Table IAES Treatment-Emergent Adverse Event Frequency - Number of Subjects Reporting the Event (% of Subjects Dosed) (Safety Population)

Adverse Event	Overall (N = X)
Number of Subjects With TEAEs	XX (XX.X%)
Number of Subjects Without TEAEs	XX (XX.X%)
Eye disorders	XX (XX.X%)
Visual blurred	XX (XX.X%)
Gastrointestinal disorders	XX (XX.X%)
Dyspepsia	XX (XX.X%)
Nausea	XX (XX.X%)
Musculoskeletal and connective tissue disorders	XX (XX.X%)
Back pain	XX (XX.X%)
Muscle cramps	XX (XX.X%)
Musculoskeletal pain	XX (XX.X%)
Nervous system disorders	XX (XX.X%)
Headache	XX (XX.X%)
Reproductive system and breast disorders	XX (XX.X%)
Vaginal discharge	XX (XX.X%)
Respiratory, thoracic and mediastinal disorders	XX (XX.X%)
Epistaxis	XX (XX.X%)
Skin and subcutaneous tissue disorders	XX (XX.X%)
Sweating increased	XX (XX.X%)

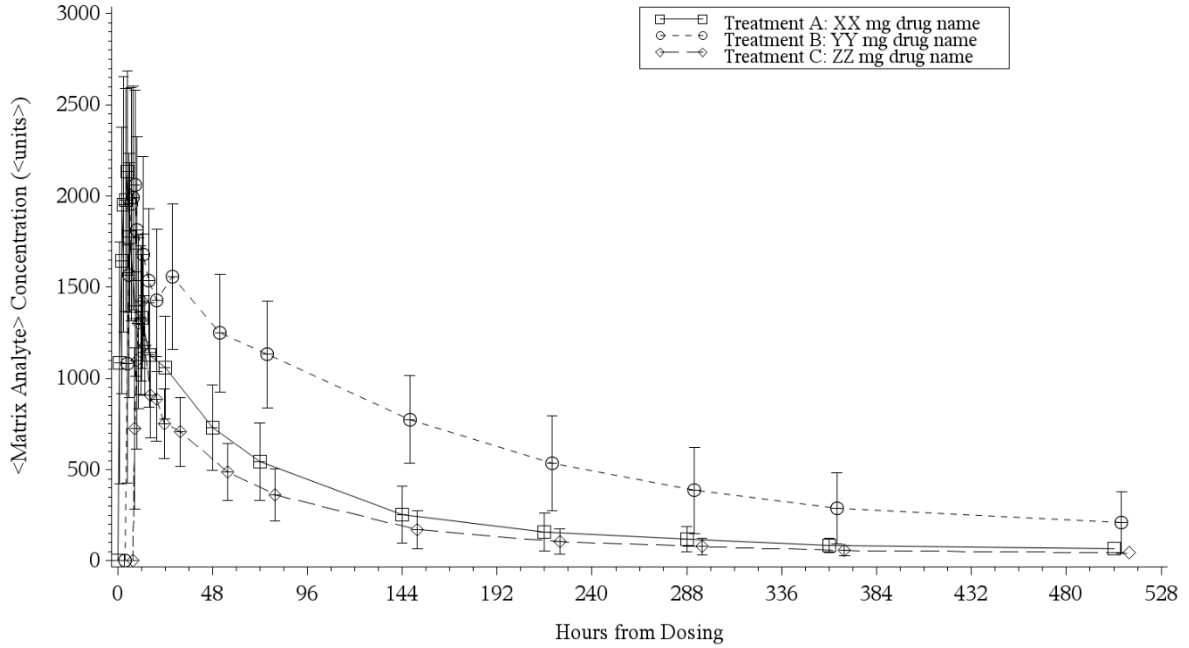
All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
Although a subject may have had 2 or more adverse events, the subject is counted only once within a category. The same subject may appear in different categories.
Adverse events are classified according to MedDRA Version 25.1.
TEAEs = Treatment-emergent adverse events

Source: Table 14.3.1.1
Program: /CAXXXXX/sas_prg/stsas/intext/t_ae.sas DDMMMYYYY HH:MM

10.2 Figures Shells

Figure PFPCONC1

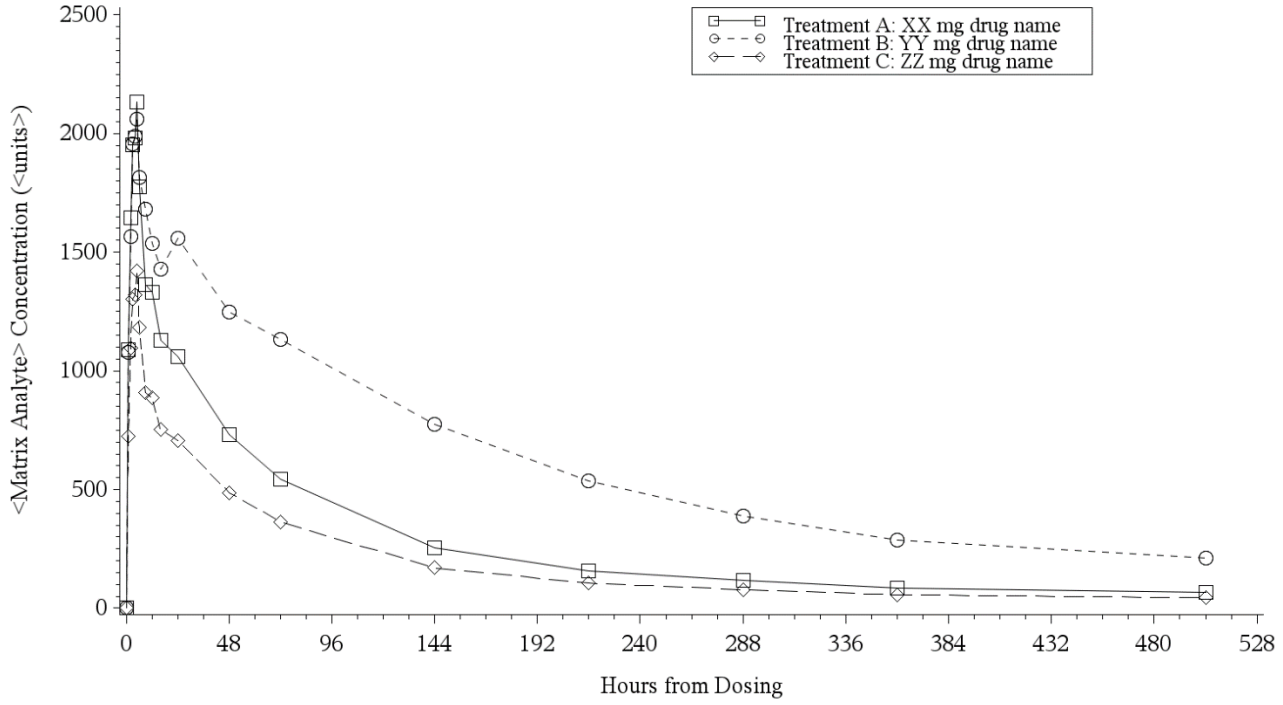
Arithmetic Mean (SD) Plasma IkT-148009 Concentration-Time Profile on Days 1 to 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Linear Scale) (Pharmacokinetic Analysis Population)



Program: /CAXXXXX/sas_prg/pksas/meangraph.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_meangraph.sas DDMMMYYYY HH:MM

Figure PFPCONC2

Arithmetic Mean Plasma IkT-148009 Concentration-Time Profile on Days 1 to 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Linear Scale) (Pharmacokinetic Analysis Population)

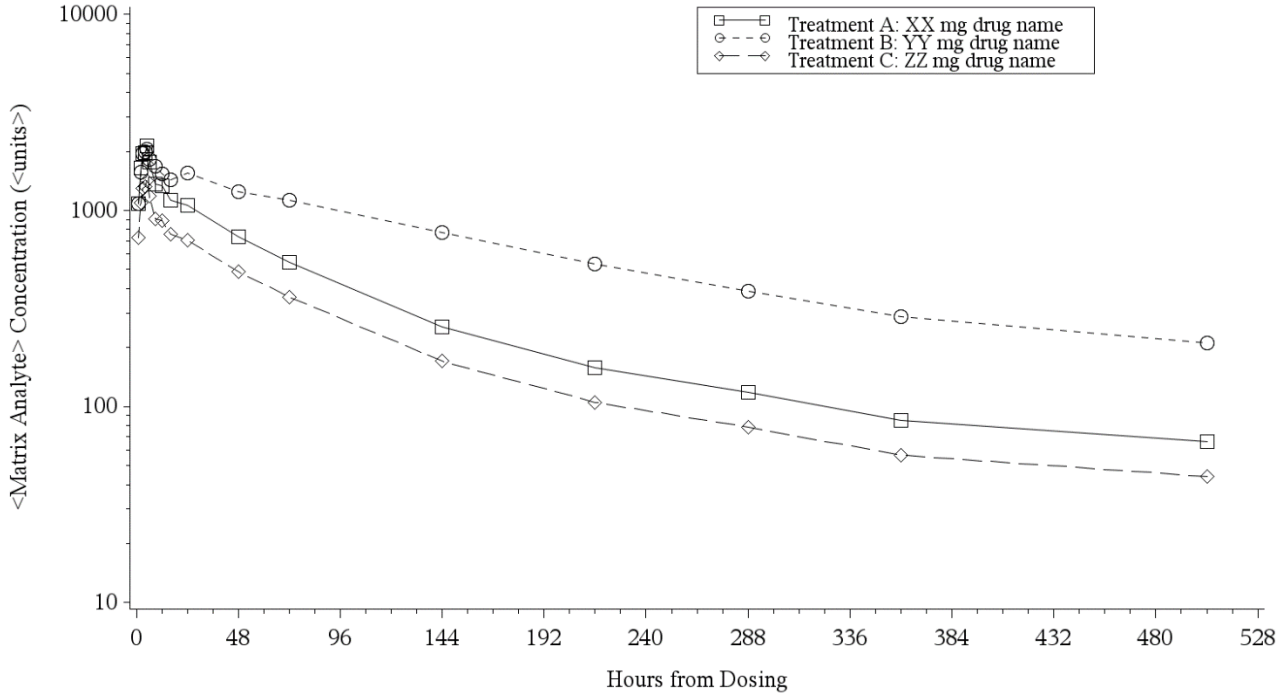


Program: /CAXXXXX/sas_prg/pksas/adam_meangraph.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/meangraph.sas DDMMMYYYY HH:MM

Program: /CAXXXXX/sas_prg/pksas/meangraph.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_meangraph.sas DDMMMYYYY HH:MM

Figure PFPCONC3

Arithmetic Mean Plasma IkT-148009 Concentration-Time Profile on Days 1 to 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Semi-Log Scale) (Pharmacokinetic Analysis Population)

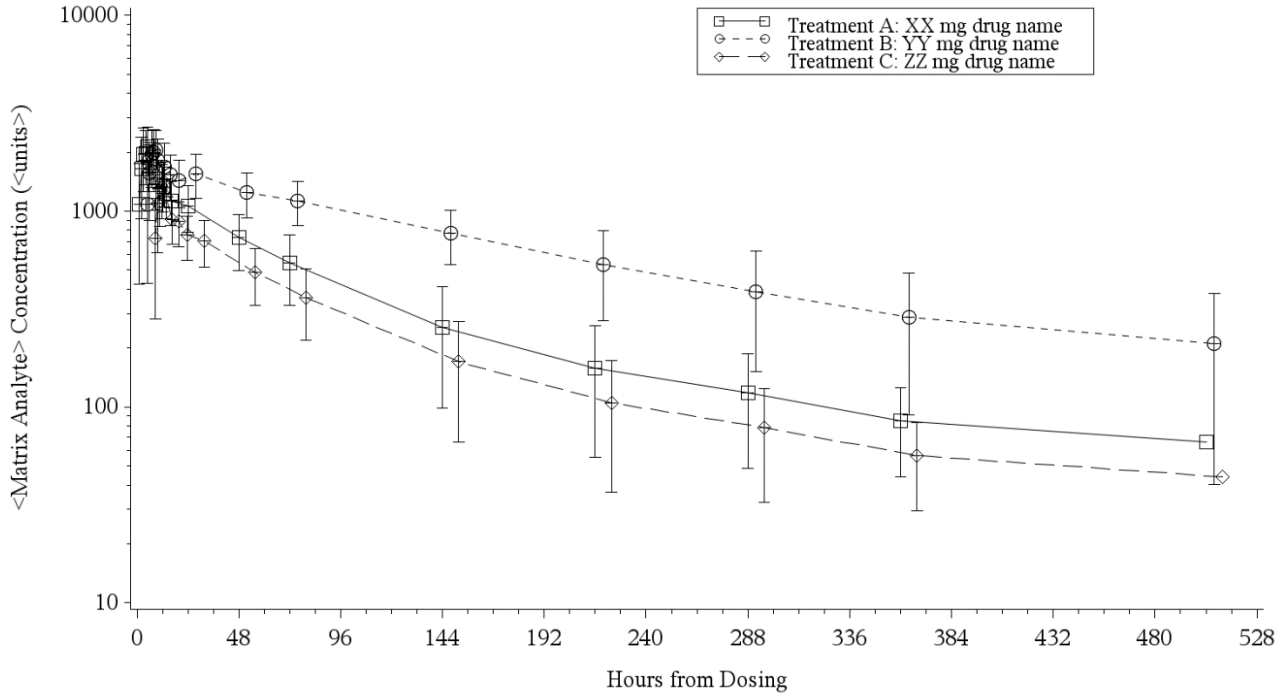


Program: /CAXXXXX/sas_prg/pksas/adam_meangraph.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/meangraph.sas DDMMMYYYY HH:MM

Program: /CAXXXXX/sas_prg/pksas/meangraph.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_meangraph.sas DDMMMYYYY HH:MM

Figure PFPCONC4

Arithmetic Mean (SD) Plasma IkT-148009 Concentration-Time Profile on Days 1 to 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Semi-Log Scale) (Pharmacokinetic Analysis Population)



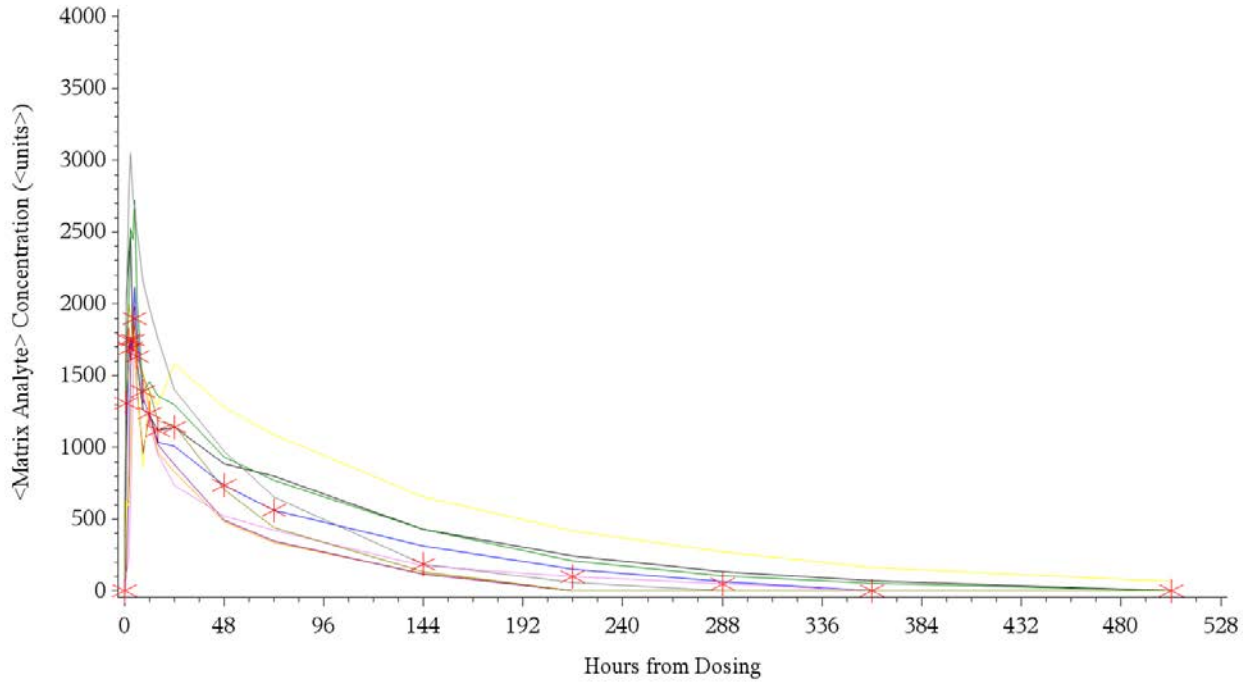
Program: /CAXXXXX/sas_prg/pksas/meangraph.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_meangraph.sas DDMMMYYYY HH:MM

Notes for Generating the Actual Mean Figure:

- Legend will be "IkT-148009 QD" for all figures
- Y axis label will be "Plasma IkT-148009 Concentration (ng/mL)"
- X axis label will be "Hours From Dosing"
- Note regarding figures being presented:
    - Figures 11-1, 14.2.2.1, 14.2.2.2, and 14.2.2.3, 14.2.2.4 will present the entire PK sampling period from Days 1 to 7 inclusively
    - Figures 11-2, 14.2.2.5, 14.2.2.6, 14.2.2.7, and 14.2.2.8 will present the Day 1 and Day 7 PK profiles in the same figure.
    - Figures 11-3, 14.2.2.9, and 14.2.2.10 will present the Ctrough values on Days 1, 3, 5, 6, and 7

Figure PFPCONC6a

Individual Superimposed Plasma IkT-148009 Concentration-Time Profiles on Day 1 Following Administration of the First IkT-148009 Oral Dose in Older Adult and Elderly Healthy Volunteers (Linear Scale)



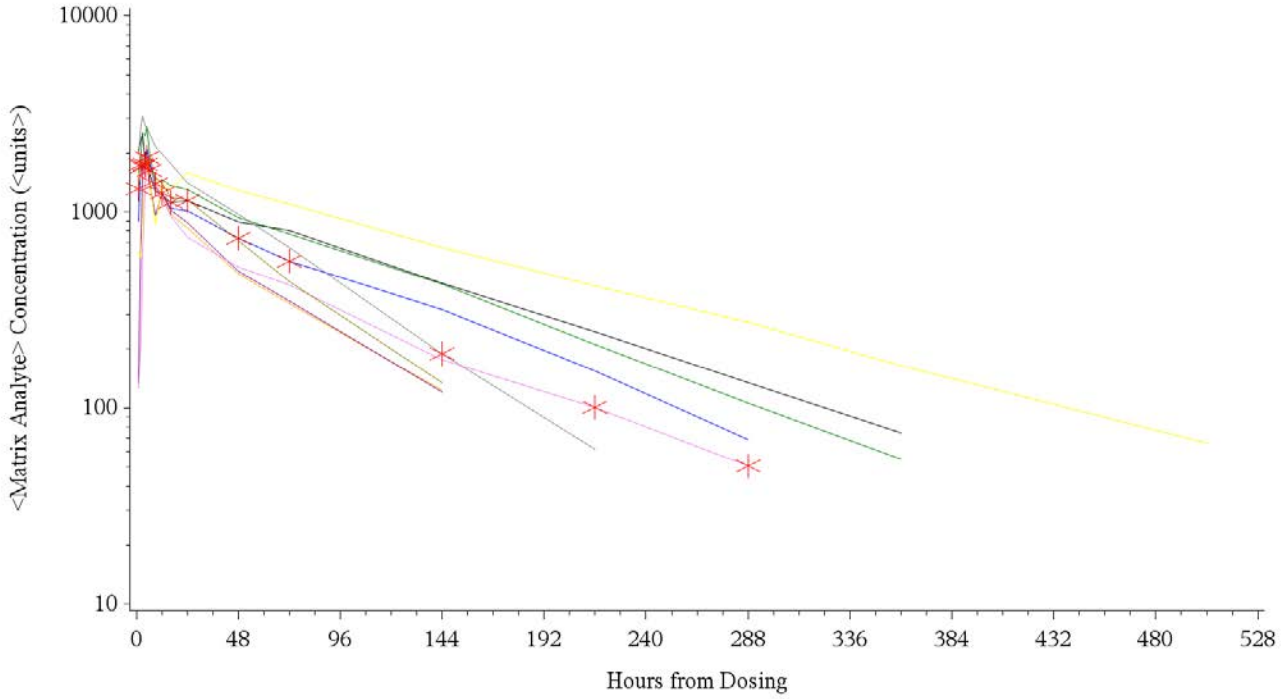
Notes for Generating the Actual Spaghetti Plots Figure:

- All profiles will be presented with the same line type (with color)
- Y-axis label will be "Plasma IkT-148009 Concentration (ng/mL)"
- X-axis label will be "Hours From Dosing"
- Appendix 16.2.6.1 will present the Day 1 data
- Appendix 16.2.6.3 will present the Day 7 data
- Present each subject number as the legend to associate color of each line to corresponding subject number.

Program: /CAXXXXX/sas_prg/pksas/spaggraph.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_spaggraph.sas DDMMMYYYY HH:MM

Figure PFPCONC7a

Individual Superimposed Plasma IkT-148009 Concentration-Time Profiles on Day 1 Following Administration of the First IkT-148009 Oral Dose in Older Adult and Elderly Healthy Volunteers (Semi-Log Scale)



Notes for Generating the Actual Spaghetti Plots Figure:

- All profiles will be presented with the same line type (with color)
- Y axis label will be "Plasma IkT-148009 Concentration (ng/mL)"
- X axis label will be "Hours From Dosing"
- Appendix 16.2.6.2 will present the Day 1 data
- Appendix 16.2.6.4 will present the Day 7 data
- Present each subject number as the legend to associate color of each line to corresponding subject number.

Program: /CAXXXXX/sas_prg/pksas/spaggraph.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_spaggraph.sas DDMMMYYYY HH:MM

10.3 Section 14 Summary Tables Shells

Table CDS Disposition Summary (Safety Population)

Category	Overall
Dosed	XX (100.0%)
Completed Study	XX (XX.X%)
Discontinued From Study	X (XX.X%)
<Reason>	X (XX.X%)
Completed Treatment	XX (XX.X%)
Discontinued From Treatment	X (XX.X%)
<Reason>	X (XX.X%)

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1programname2022Q1.sas DDMMMYYYY HH:MM

Programmer Note: Percentages will be rounded to one decimal place.

Table CDEM Demographic Summary (Safety Population)

Trait	Category/Statistic	Overall
Sex	Male	X (XX.X%)
	Female	X (XX.X%)
Race	Asian	X (XX.X%)
	Black or African American	X (XX.X%)
	White	X (XX.X%)
Ethnicity	Hispanic or Latino	X (XX.X%)
	Not Hispanic or Latino	X (XX.X%)
Age (yr)	n	X
	Mean	X.X
	SD	X.XX
	Minimum	XX
	Median	X.X
	Maximum	XX
Body Mass Index (kg/m^2)	n	X
	Mean	X.X
	SD	X.XX
	Minimum	XX
	Median	X.X
	Maximum	XX

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
Descriptive statistics for body mass index, height, and weight are calculated using screening measurements.

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Programmer Note:
- Please include height and weight to this table.
- Percentages will be rounded to one decimal place. Mean and median will be rounded to one decimal place, SD will be rounded to two decimal places and minimum and maximum will be in the same precision as the original data in the database.

Table CPCONC1 Plasma IkT-148009 Concentrations (ng/mL) Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers on Days 1 to 7 (Pharmacokinetic Analysis Population)

Subject	Sample Times (hr)								
Number	Predose	XX	XX	XX	XX	XX	XX	XX	XX
X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
n	XX	XX	XX	XX	XX	XX	XX	XX	XX
nLLOQ	XX	XX	XX	XX	XX	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SD	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
CV%	.	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SEM	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Minimum	XX	XX	XX	XX	XX	XX	XX	XX	XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Maximum	XX	XX	XX	XX	XX	XX	XX	XX	XX

<add BLQ rule footnote>
. = Value missing or not reportable.

Notes for Generating the Actual Table:

Presentation of Data:
Concentrations will be presented to same precision as in bio data.
Summary statistics presentation will be presented as follows: n and nLLOQ = integer; Mean, Median, SD, SEM, and CV% will be rounded to 3 significant figures; Minimum and Maximum will be presented to the same precision as in bio data

Programmer Note:
PK Time points are as follows:
Day 1: Pre-dose, and 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16 hours post-dose
Day 2: Pre-dose, and 2, 5, and 8 hours post-dose
Day 4: Pre-dose, and 2, 5, and 8 hours post-dose
Day 6: Pre-dose
Day 7: Pre-dose, and 0.25, 0.5, 1, 2, 4, 6, 8, 16, 24, 48, 72, and 96 hours post-dose
Note: wrap concentrations for all days into 1 table with a Day column header.

Program: /CAXXXX/sas_prg/pksas/pk-conc-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXX/sas_prg/pksas/pk-conc-tables-sig.sas DDMMMYYYY HH:MM
Program: /CAXXXX/sas_prg/pksas/adam_conc.sas DDMMMYYYY HH:MM

Table CPPAR1 Plasma IkT-148009 Pharmacokinetic Parameters on Day 1 Following Administration of the First Oral Dose of IkT-148009 in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)

	Parameters					
Subject Number	param1 (units)	param2 (units)	param3 (units)	param4 (units)	param5 (units)	param6 (units)
X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
X	X.XX	X.XX	XXX	XXX	XX.X	X.XXX
X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
n	XX	XX	XX	XX	XX	XX
Mean	XXX.X	X.XXX	XXX.X	XXX.X	XX.XX	X.XXXX
SD	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SEM	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Minimum	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
Median	XX.XX	X.XXX	XXX.X	XXX.X	XX.XX	X.XXXX
Maximum	XXX	X.XX	XXX	XXX	XX.X	X.XXX
Geom Mean	XXX.X	X.XXX	XXX.X	XXX.X	XX.XX	X.XXXX
Geom CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

. = Value missing or not reportable.

Notes for Generating the Actual Table:

Presentation of Data:

- PK Parameters will be presented in the following order and with following units for Day 1: AUC0-24 (ng*hr/mL), AUC0-24/D (ng*hr/mL/mg), AUC0-last (ng*hr/mL), AUC0-last/D (ng*hr/mL/mg), AUC0-inf (ng*hr/mL), AUC0-inf/D (ng*hr/mL/mg), AUC%extrap (%), Cmax (ng/mL), Cmax/D (ng/mL/mg), Tmax (hr), Kel (1/hr), and t1/2 (hr)
- PK Parameters will be presented in the following order and with following units for Day 7: AUCtau (ng*hr/mL), AUCtau/D (ng*hr/mL/mg), Cmax,ss (ng/mL), Cmax,ss/D (ng*hr/mL/mg), Tmax,ss (hr), Kel (1/hr), t1/2 (hr), AR AUC, AR Cmax, CLss/F (L/hr), and Vz/F (L)
- n will be presented as an integer (with no decimal);
- Parameter values for exposure based parameters (i.e., AUCs, Cmax, Cmax,ss, CLss/F, Vz/F) will be presented with the same level of precision as received from the bioanalytical laboratory. Summary statistics for exposure based parameters will be presented as described in Section 6.5.1.
- Values for Tmax and Tmax,ss will be presented with 2 decimal places. Summary statistics for Tmax and Tmax,ss will be presented as described in Section 6.5.1.
- Values for t1/2 and AUC%extrap will be presented with 3 significant figures. Summary statistics for Tmax and Tmax,ss will be presented as described in Section 6.5.1.
- Values for rate constants (i.e. Kel) will be presented with 3 significant figures. Summary statistics for Kel will be presented as described in Section 6.5.1.

Program: /CAXXXX/sas_prg/pksas/pk-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXX/sas_prg/pksas/adam_pkparam.sas DDMMMYYYY HH:MM

Table CPSS1 Steady-State Assessment of Plasma IkT-148009 Using Helmert Contrasts Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)

Trough Days	Geometric LSM	p-value
DAY 1	X.XXX	X.XXXX
DAY 3	X.XXX	X.XXXX
DAY 5	X.XXX	X.XXXX
DAY 6	X.XXX	X.XXXX
DAY 7	X.XXX	.

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
The Ctrough on Days 1, 3, 5, and 6 correspond to the pre-dose concentration obtained on Days 2, 4, 6, and 7 respectively. The Ctrough on Day 7 corresponds to the concentration obtained at 24 hours post-Day 7 dose.
Concentrations were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) were obtained by taking exponential of the LSMs from ANOVA.
p-value corresponds to the Helmert contrast, i.e., the comparison of that day versus the average of the remaining days.

Notes for Generating the Actual Table:

Presentation of Data:

- Geometric LSM will be presented to 4 significant figures
- p-value will be presented to 4 decimals

Program: /CAXXXXX/sas_prg/pksas/programmingname.sas

Table CUPAR3 Urine Excretion of IkT-148009 on Day 1 Following Administration of the First Oral Dose of IkT-148009 and on Day 7 Following Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)

	Parameters					
	Predose		X – X Hours			
Subject Number	Conc (units)	Vol (units)	Conc (units)	Vol (units)	Ae (units)	Fe (%)
X	X.XX	X.XX	XX.XX	X.XX	X.XX	X.XX
X	X.XX	X.XX	XX.XX	X.XX	X.XX	X.XX
X	X.XX	X.XX	XX.XX	X.XX	X.XX	X.XX
n	X	X	X	X	X	X
Mean	X.XXX	X.XXX	XX.XXX	X.XXX	X.XXX	X.XXX
SD	X.XXXX	X.XXXX	XX.XXXX	X.XXXX	X.XXXX	X.XXXX
CV%	X.X	X.X	XX.X	X.X	X.X	X.X
SEM	X.XXXX	X.XXXX	XX.XXXX	X.XXXX	X.XXXX	X.XXXX
Minimum	X.XX	X.XX	XX.XX	X.XX	X.XX	X.XX
Median	X.XXX	X.XXX	XX.XXX	X.XXX	X.XXX	X.XXX
Maximum	X.XX	X.XX	XX.XX	X.XX	X.XX	X.XX
Geom Mean	X.XXX	X.XXX	XX.XXX	X.XXX	X.XXX	X.XXX
Geom CV%	X.X	X.X	XX.X	X.X	X.X	X.X

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
. = Value missing or not reportable.

Notes for Generating the Actual Table:

Presentation of Data:

- Concentrations will be presented to same precision as the bio concentration data. Volume will be presented to same precision as on the CRF. Fe will be presented to 2 decimal places. Ae will be presented to 3 significant figures.
- Summary statistics for exposure based parameters will be presented as described in Section 6.5.2.
- Add an additional column to this table to present "Day 1" and "Day 7" in separate column stratifications.

Programmers Note:
Intervals are: Predose, 0-24 Hours on Day 1 and 0-24 hours on Day 7. Add a "Day" variable to table header to present both days in the same table.
PK Parameters for each postodse interval are: Conc, Vol, Ae, and Fe; predose: Conc, Vol

Program: DM_PX:[HLXXXXX.PKSAS]URINE-CONC-TABLES.SAS DDMMMYYYY HH:MM

Table CAES Treatment-Emergent Adverse Event Frequency –
Number of Subjects Reporting the Event (% of Subjects Dosed) (Safety Population)

Adverse Event	Overall (N = X)
Number of Subjects With TEAEs	X (XX.X%)
Number of Subjects Without TEAEs	XX (XX.X%)
Eye disorders	X (X.X%)
Vision blurred	X (X.X%)
Gastrointestinal disorders	X (X.X%)
Dyspepsia	X (X.X%)
Nausea	X (X.X%)
Musculoskeletal and connective tissue disorders	X (X.X%)
Back pain	X (X.X%)
Muscle cramps	X (X.X%)
Musculoskeletal pain	X (X.X%)
Nervous system disorders	X (X.X%)
Headache	X (X.X%)
Reproductive system and breast disorders	X (X.X%)
Vaginal discharge	X (X.X%)
Respiratory, thoracic and mediastinal disorders	X (X.X%)
Epistaxis	X (X.X%)
Skin and subcutaneous tissue disorders	X (X.X%)
Sweating increased	X (X.X%)

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
Although a subject may have had 2 or more adverse events, the subject is counted only once within a category. The same subject may appear in different categories.
Adverse events are classified according to MedDRA Version 25.1.
TEAEs = Treatment-emergent adverse event

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Programmer Note: Percentages will be rounded to one decimal place.

Table CAEF Treatment-Emergent Adverse Event Frequency-
Number of Adverse Events (% of Total Adverse Events) (Safety Population)

Adverse Event	Overall
Number of TEAEs	X
Eye disorders	X (X.X%)
Vision blurred	X (X.X%)
Gastrointestinal disorders	X (X.X%)
Dyspepsia	X (X.X%)
Nausea	X (X.X%)
Musculoskeletal and connective tissue disorders	X (X.X%)
Back pain	X (X.X%)
Muscle cramps	X (X.X%)
Musculoskeletal pain	X (X.X%)
Nervous system disorders	X (X.X%)
Headache	X (X.X%)
Reproductive system and breast disorders	X (X.X%)
Vaginal discharge	X (X.X%)
Respiratory, thoracic and mediastinal disorders	X (X.X%)
Epistaxis	X (X.X%)
Skin and subcutaneous tissue disorders	X (X.X%)
Sweating increased	X (X.X%)

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
Adverse events are classified according to MedDRA Version 25.1.
TEAEs = Treatment-emergent adverse events

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Programmer Note: Percentages will be rounded to one decimal place.

Table CAESR Treatment-Emergent Adverse Event Frequency by Severity and Relationship to Study Product - Number of Adverse Events (Safety Population)

Adverse Event	Number of Subjects With TEAEs	Number of TEAEs	Severity			Relationship to Study Product		
			Mild	Moderate	Severe	Not Related	Possibly Related	Probably Related
Abdominal pain	X	X	X	X	X	X	X	X
Constipation	X	X	X	X	X	X	X	X
Dry throat	X	X	X	X	X	X	X	X
Dysmenorrhoea	X	X	X	X	X	X	X	X
Dyspepsia	X	X	X	X	X	X	X	X
Headache	X	X	X	X	X	X	X	X
Myalgia	X	X	X	X	X	X	X	X
Nasal congestion	X	X	X	X	X	X	X	X
Skin laceration	X	X	X	X	X	X	X	X
Overall	X	X	X	X	X	X	X	X

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
Adverse events are classified according to MedDRA Version 25.1.
TEAEs = Treatment-emergent adverse events

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Table 14.3.2.1 Serious Adverse Events (Safety Population)

Will match format of Appendix 16.2.7

Or contain statement as follows:

"There were no events that met this criteria."

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Table CLBO Out-of-Range Values and Recheck Results - <Clinical Laboratory Panel> (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Parameter1 <Range> (Unit)	Parameter2 <Range> (Unit)	Parameter3 <Range> (Unit)	Parameter4 <Range> (Unit)
X	XX/X	Screen			DDMMMYYYY	HH:MM:SS	XX H		XX L	XX H
		1	-X	-X.XX	DDMMMYYYY	HH:MM:SS	XX L	XX L		XX L

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
F = Female; M = Male
H = Above reference range; L = Below reference range

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Programmer Note:
- Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled assessment and early termination chronologically with other scheduled assessments and rechecks. Recheck should be sorted with the scheduled time point the recheck is for. Unscheduled and Early Termination records should only be included if they are out of range or recheck results.
- For table on reproductive organ function, please include leutenizing hormone [LH], follicle stimulating hormone [FSH], testosterone and inhibin B

Table CLBD Clinical Laboratory Summary and Change From Baseline - <Clinical Laboratory Panel> (Safety Population)

Laboratory Test (units)	Reference Range	Time Point	Statistic	Summary	Change From Baseline
Testname (unit)	< - >#	Baseline	n	X	
			Mean	X.X*	
			SD	X.XX	
			Minimum	XX	
			Median	X.X	
			Maximum	XX	
		Day 2 pre-dose	n	X	X
			Mean	X.X^	X.X
			SD	X.XX	X.XX
			Minimum	XX	XX
			Median	X.X	X.X
			Maximum	XX	XX
		Day 3 pre-dose	n	X	X
			Mean	X.X	X.X
			SD	X.XX	X.XX
			Minimum	XX	XX
			Median	X.X	X.X
			Maximum	XX	XX

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
Baseline is the result closest and prior to the first dose of study product which is generally the Day 1 pre-dose value.
= Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1 for the breakdown.
* = Above reference range; ^ = Below reference range

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Programmer Note:
- Treatment means at specific time points will be flagged (with a *) if they are above or below the reference range. This only applies to the clinical laboratory treatment results (i.e., not the change from baseline or any other endpoints). Time Point column will match those found in Section 7.5 of the SAP.

- Mean and median will be in one more decimal places than original data in database, SD will be in two more decimal places than original data in database, minimum and maximum will be in the same precision as original data in the database
- For summary table on reproductive organ function, please include leutenizing hormone [LH], follicle stimulating hormone [FSH], testosterone and inhibin B

Table CLBS Clinical Laboratory Shift From Baseline - Serum Chemistry (Safety Population)

		Baseline L			Baseline N			Baseline H		
		Post-dose			Post-dose			Post-dose		
Laboratory Test (units)	Time Point	L	N	H	L	N	H	L	N	H
Testname (unit)	Day 2 pre-dose	X	XX	X	X	XX	X	X	XX	X
	Day 3 pre-dose	X	XX	X	X	XX	X	X	XX	X
	Day 4 pre-dose	X	XX	X	X	XX	X	X	XX	X

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
Baseline is the result closest and prior to the first dose of study product which is generally the Day 1 pre-dose value.
N = Within reference range; L = Below reference range; H = Above reference range

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Programmer Note:
- Time Point column will match those found in Section 7.5 of the SAP. For urinalysis, the following footnote is used since the categories of N and O will be used instead of L, N, H: N = Within reference range; O = Outside reference range
- For shift table on reproductive organ function, please include leutenizing hormone [LH], follicle stimulating hormone [FSH], testosterone and inhibin B

Table CVS Vital Sign Summary and Change From Baseline (Safety Population)

			Summary		Change From Baseline	
Vital Sign (units)	Time Point	Statistic	Supine5	Standing2	Supine5	Standing2
SBP (mmHg)	Baseline	n	X	X		
		Mean	X.X	X.X		
		SD	X.XX	X.XX		
		Minimum	XX	XX		
		Median	X.X	X.X		
		Maximum	XX	XX		
	Day 1 Hour 1	n	X	X	X	X
		Mean	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX
	Day 1 Hour 2	n	X	X	X	X
		Mean	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
For weight, baseline is the result closest and prior to the first dose of study product which is generally the Day 1 pre-dose value. For rest vital sign parameters, baseline is the average of three measurements on Day 1 pre-dose.
*Weight result is presented under column 'Supine5' but the position of supine for 5 minutes or standing for 2 minutes is not applied for weight measurement.
Standing2 = Standing for 2 minutes; Supine5 = Supine for 5 minutes

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Programmer Note:

- Time Point column will match those found in Section 7.6 of the SAP.
- Mean and median will be in one more decimal places than original data in database, SD will be in two more decimal places than original data in database, minimum and maximum will be in the same precision as original data in the database
- Temperature, oxygen and respiration are only taken at one position, so please present result using the position in source data
- Weight is not taken in supine5 nor standing2 position, but please present the result under column 'Supine5'.

Table CEG 12-Lead Electrocardiogram Summary and Change From Baseline (Safety Population)

Measurement (units)	Time Point	Statistic	Summery	Change From Baseline
Testname (unit)	Baseline	n	X	
		Mean	X.X	
		SD	X.XX	
		Minimum	XX	
		Median	X.X	
		Maximum	XX	
	Day 1 Hour 1	n	X	X
		Mean	X.X	X.X
		SD	X.XX	X.XX
		Minimum	XX	XX
		Median	X.X	X.X
		Maximum	XX	XX
	Day 1 Hour 2	n	X	X
		Mean	X.X	X.X
		SD	X.XX	X.XX
		Minimum	XX	XX
		Median	X.X	X.X
		Maximum	XX	XX

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
Baseline is the result closest and prior to the first dose of study product which is generally the Day 1 pre-dose value.

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Programmer Note:
- Time Point column will match those found in Section 7.7 of the SAP.
- Mean and median will be in one more decimal places than original data in database, SD will be in two more decimal places than original data in database, minimum and maximum will be in the same precision as original data in the database.

11. LISTING SHELLS

The following listing shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the listings that will be presented and included in the final report. Listings will generated from data created in accordance with SDTM Model 1.4 with Implementation Guide 3.2 or CDASH data structure. Listings with derived data (i.e., triplicate vital signs) may be created from the ADaM data. All listings will be presented in Courier New size font 9. Time point information (period, day, hour) will match that found in the CRF.

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

Laboratory Group	Test Name	Sex	Age Category	Reference Range	Unit
Serum Chemistry	Testname1	MALE		XX - XXX	mEq/L
	Testname2	MALE	0-25	XX - XXX	U/L
			26-99	XX - XXX	U/L
<similar for all other tests, note that age will only be presented when different reference range exists>					
Hematology	<similar to serum chemistry>				
Urinalysis	Testname	MALE		NEGATIVE	
Urine Drug Screening	Amphetamines	MALE		NOT DETECTED	

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix DISP Subject Disposition (Safety Population)

	End of Treatment				End of Study			
Subject Number	Did Subject Prematurely Discontinue?	Treatment Discontinuation Date	Primary Treatment Discontinuation Reason	Specify	Did Subject Complete the Study?	Date of Last Contact	Primary Study Discontinuation Reason	Specify
1	No				Yes	DDMMMYYYY		
2	No				No	DDMMMYYYY	Personal Reason	XXXXXXXXXXX
3	Yes	DDMMMYYYY	Adverse Event	XXXXXXXXXXX	No	DDMMMYYYY	Other	XXXXXXXXXXX

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LDEM Demographics (Safety Population)

Subject Number	Year of Birth	Age (yr)	Sex	Race	Ethnicity	Height (cm)	Weight (kg)	Body Mass Index (kg/m²)	Informed Consent Date
1	YYYY	47	Male	< >	Not Hispanic or Latino	XXX	XX.X	XX.XX	DDMMMYYYY
2	<similar to above.>								

Age is approximated as year of informed consent – year of birth. There will be a subtraction of 1 if the difference in years is 1 more than the age specified in the inclusion criteria.

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LPE Physical and Neurological Examination (Safety Population)

Subject Number	Study Period	Day	Hour	Date	Question	Answer
1	Screen			DDMONYYYY	Was PNE performed?	YES
	1	-1	-17.75	DDMONYYYY	Was PNE performed?	NO
2	<similar to above>					

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
PNE = Physical and neurological examination

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LMH Medical History (Safety Population)

Subject Number	Any History?	Condition or Event	Date		Ongoing?
			Start	End	
1	No				
2	Yes	< >	YYYY		YES

<note date can be YYYY, MONYYYY, or DDMONYYYY based on individual subject data>

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LSU Substance Use (Safety Population)

Subject Number	Substance	Description of Use	Start Date	End Date
1	Tobacco Use	0-4 CIGARETTES WEEK	DDMONYYYY	DDMONYYYY
		NON-SMOKER	DDMONYYYY	
2	Tobacco Use	NON-SMOKER	DDMONYYYY	

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LSE Subject Eligibility (Safety Population)

Subject Number	Study Period	Did subject meet all eligibility criteria?	Criterion Not Met	Specify
1	Screen	YES		
2	Screen	NO	Exclusion 5	<specify and criterion not met will only be presented if populated>

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix CPDE Test Compound Description

CRF Treatment Description	Form	Route
< >	CAPSULE	ORAL

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix CPAD Test Compound Administration Times (Safety Population)

Subject Number	Study Period	Day	Hour	Dose Date	Dose Time	Compound	Planned Dosage	Comments
1	1	1	0.00	DDMONYYYY	HH:MM:SS	< >	500 NCI	<This column prints only if data is presented>

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LML Meal Times (Safety Population)

Subject Number	Study Period	Day	Hour	Interval	Event	Start Date	Start Time	Stop Date	Stop Time	Comments
1	1	1	-0.75	-0.75 TO -0.25	BREAKFAST	DDMONYYYY	HH:MM:SS	DDMONYYYY	HH:MM:SS	
		2	23.25	23.25 TO 23.75	BREAKFAST	DDMONYYYY	HH:MM:SS	DDMONYYYY	HH:MM:SS	

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LFI Fluid Intake (Safety Population)

Subject Number	Study Period	End Day	Start Date	End Date	Interval	Total Amount Consumed in mL
1	1	2	DDMONYYYY	DDMONYYYY	0.00 – 24.00	XXXX
		3	DDMONYYYY	DDMONYYYY	24.00 – 48.00	XXXX

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LCM Prior and Concomitant Medications (Safety Population)

Subject Number	Prior?	Medication (WHO DD)	Dosage	Route	Start Date	Start Time	End Date	End Time	Frequency	Indication	Ongoing?
1		None									
2		None									
3	Yes	CETIRIZINE (CETIRIZINE)	X MG	BY MOUTH	DDMONYYYY		DDMONYYYY	HH:MM	XXXXXXX	XXXXXXX	NO
	No	PARACETAMOL (PARACETAMOL)	X MG	XXXXXXXXX	DDMONYYYY	HH:MM	XXXXXXXXX	HH:MM	XXXXXXXX	XXXXXXXX	XX

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
Concomitant medications are coded with WHO Drug Dictionary Version 01-Sep-2022 b3.
Prior is defined as a medication administered prior to the first study drug administration.
WHO DD = World Health Organization Drug Dictionary

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix PK_BLD Pharmacokinetic Blood Draw Times and Concentration Data (Pharmacokinetic Concentration Population)

Subject Number	CRF Day	CRF Hour	Blood Draw Date	Blood Draw Time	Elapsed Time From Last Dose (Hour)	Plasma IkT-148009 Concentration (units)	Comments
1	1	-0.05	DDMONYYYY	HH:MM:SS	0.0	X.XX	
		0.25	DDMONYYYY	HH:MM:SS	0.265	X.XX	
		0.50	DDMONYYYY	HH:MM:SS	0.590	X.XX	Late Draw
	< >						
	<similar for all other time points and subjects>						

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.

Program: /CAXXXXX/sas_prg/pksas/standardlis/pk_bld.sas DDMMMYYYY HH:MM

Appendix PK_URN Pharmacokinetic Urine Collection Times, Weight, and Concentration Data (Pharmacokinetic Concentration Population)

Subject Number	CRF Collection: End Day	CRF Collection: Interval	Urine Collection: Start Date	Urine Collection: Start Time	Urine Collection: Stop Date	Urine Collection: Stop Time	Urine IkT-148009 Concentration (units)	Urine Weight (g)	Comments
1	1	-0.92	DDMONYYYY	HH:MM:SS	DDMONYYYY	HH:MM:SS	XXXX	X.XX	No void
		-.18	DDMONYYYY	HH:MM:SS	DDMONYYYY	HH:MM:SS	XXXX	X.XX	XXXXXXXX
		-0.17 - 23.83	DDMONYYYY	HH:MM:SS	DDMONYYYY	HH:MM:SS	XXXX	X.XX	Unknown amount of urine spilled
	<similar to above for all time points and subjects>								

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.

Program: /CAXXXXX/sas_prg/pksas/standardlis/pk_urn.sas DDMMMYYYY HH:MM

Appendix CPKEL1 Intervals (Hours) Used for Determination of Plasma IkT-148009 Kel Values on Days 1 and 7 Following Administration of Multiple Oral Doses of IkT-148009 QD in Older Adult and Elderly Healthy Volunteers (Pharmacokinetic Analysis Population)

Subject Number	Treatment Sequence	Day 1 Interval	Day 1 R2	Day 1 n	Day 7 Interval	Day 7 R2	Day 7 n
X	XX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
X	XX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
X	XX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
X	XX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
X	XX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X
X	XX	XX.X - XX.X	X.XXX	X	XX.X - XX.X	X.XXX	X

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
R2 = Coefficient of determination
n = Number of points used in Kel calculation
. = Kel value not reportable.

Notes for Generating the Actual Listing:

Presentation of Data:

- Interval start and stop times will be presented to 1 decimal or 3 sig figures min;
- R2 will be presented to 3 decimals;
- n will be presented as an integer (with no decimal)
- Present the Day 1 and Day 7 data in separate columns side-by-side.

Program: /CAXXXXX/sas_prg/pksas/kel-tables-parallel.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_kel.sas DDMMMYYYY HH:MM

Appendix LAE Adverse Events (Safety Population)

Subject Number	Age/ Sex	TE?	System Organ Class/ Preferred Term (Verbatim)	Time From Last Dose (DD:HH:MM)	Date:Time Start/ End Duration (DD:HH:MM)	Serious/ Outcome	Severity/ Frequency	Study Product Relationship/ Action
1	XX/F		None					
2	XX/M		None					
3	52/M	Yes	XXXXXXXXXXXXX/ XXXXXXXXXXXXXXXXX (XXXXXXXXXXXX)	XX:XX:XX	DDMONYYYY:HH:MM/ DDMONYYYY:HH:MM 00:23:15	No/ Recovered/ Resolved	Moderate/ Intermittent	Probably Related/ Drug Withdrawn
		Yes	<similar to above>					

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
Adverse events are classified according to MedDRA Version 25.1.
F = Female; M = Male; TE = Treatment-emergent

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Programmer Note: AEs should be presented start date/time order for each subject.

Appendix DSAE Details for Serious Adverse Events (Safety Population)

Subject Number	Age/ Sex	TE?	System Organ Class/ Preferred Term (Verbatim)	Date:Time Start/ End Duration (DD:HH:MM)	Serious Event?	Congenital Anomaly/ Birth Defect?	Hospital- ization?	Life- Threat?	Important Medical Event?	Death?
3	52/M	Yes	XXXXXXXXXXXX/ XXXXXXXXXXXXXXXXX (XXXXXXXXXXX)	DDMONYYYY:HH:MM/ DDMONYYYY:HH:MM 00:23:15	Yes	No	Yes	No	Yes: < >	No

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
Adverse events are classified according to MedDRA Version 25.1.
F = Female; M = Male; TE = Treatment-emergent

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Programmer Note: If Serious = Yes then present AEs in this listing otherwise please do not include this listing.

Appendix LBR Clinical Laboratory Report - Serum Chemistry (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Chloride M: 97-105 (mEq/L)	Potassium M: 3.7-5.2 (mEq/L)	Phosphorus M: 2.4-4.4 (mg/dL)	Sodium M: 135-143 (mEq/L)
1	XX/M	Screen			DDMONYYYY	HH:MM:SS	XXX	X.X	X.X	XXX H
		1	1	-XX.00	DDMONYYYY	HH:MM:SS	XXX H	X.X	X.X	XXX H
		Recheck			DDMONYYYY	HH:MM:SS	XXX	X.X	X.X	XXX
	<similar to above for all subjects/time points>									

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
F = Female; M = Male
H = Above reference range

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Programmer Note: For listing on reproductive organ function, please include leutenizing hormone [LH], follicle stimulating hormone [FSH], testosterone and inhibin B

Appendix LVS Vital Signs (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Blood Pressure (mmHg) Position	Blood Pressure (mmHg) Sys/Dia	Pulse (bpm)	Respiration (brpm)	Temperature (°C)	Weight (kg)	Oxygen (%)
1	XX/F	Screen			DDMONYYYY	HH:MM:SS						XX.X	
							SUP5	XXX/ XX	XX	XX	XX.X		XX
						HH:MM:SS	STD2	XXX/ XX	XX				
				R		HH:MM:SS	STD2	XXX/ XX	XX				
		1	-1	-17.75	DDMONYYYY	HH:MM:SS						XX.X	
				-16.50		HH:MM:SS	SUP5	XXX/ XX	XX				
							STD2	XXX/ XX	XX	XX	XX.X		XX

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
F = Female; M = Male
bpm = beats/min; brpm = breaths/min; R = Recheck value; SUP5 = 5-minute supine; STD2 = 2-minute standing

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LOVS Orthostatic Vital Signs (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Blood Pressure (mmHg) Systolic	Blood Pressure (mmHg) Diastolic	Heart Rate (bpm)
1	XX/F	1		Baseline	XX	-XX	XX
			1	1.00	XX	XX	XX
			<similar to above>				

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
This listing only presents orthostatic changes.
Baseline for orthostatic change is defined as the average of three orthostatic result obtained on Day 1 pre-dose.
Orthostatic Change = standing - supine
F = Female; M = Male
bpm = beats/min

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LECG 12-Lead Electrocardiogram (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Result	Heart Rate (bpm)	RR (msec)	PR (msec)	QRS (msec)	QT (msec)	QTcF (msec)	Specify/Comments
1	XX/F	Screen			DDMONYYYY	X:XX:XX	WNL	XX	XXX	XX	XX	XXX	XXX	EARLY REPOLARIZATION; LEFT AXIS DEVIATION
		1	-1	-X.XX	DDMONYYYY	XX:XX:XX	ANCS	XX	XXX	XX	XX	XXX	410	LEFT AXIS DEVIATION
			1	-X.XX	DDMONYYYY	XX:XX:XX	< >	XX	XXX	XX	XX	XXX	441 @	SINUS BRADYCARDIA
				X.XX	DDMONYYYY	XX:XX:XX	< >	XX	XXX	XX	XX	XXX	451#@	

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
# = QTc value greater than 450 msec; @ = QTc change from baseline greater than 30 msec
F = Female; M = Male
ANCS = Abnormal, not clinically significant; QTcF = QT corrected for heart rate using Fridericia's correction; WNL = Within normal limits

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LECO Echocardiogram (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Question	Answer (Yes/No)
1	XX/F	1	-1	-XX.XX	DDMONYYYY	Was Echocardiogram performed?	Yes

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
F = Female; M = Male

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LCSBQ Columbia Suicide Severity Rating Scale (C-SSRS) Questions – Baseline/Screening (Safety Population)

Questions Number	Description
1.0	(Lifetime) Have you wished you were dead or wished you could go to sleep and not wake up? (YES/NO)
1.1	(Lifetime) If yes, describe:
1.2	(Past 24 Months) Have you wished you were dead or wished you could go to sleep and not wake up? (YES/NO)

<Similar for other questions>

Program: /CAXXXXX/sas_prg/stsas/lis/programname.sas DDMONYYYY HH:MM

Appendix LCSLQ Coloumbia Suicide Severity Rating Scale (C-SSRS) Questions – Since Last Visit (Safety Population)

Questions Number	Description
1.0	Have you wished you were dead or wished you could go to sleep and not wake up? (YES/NO)
1.1	If yes, describe:
2.0	Have you actually had any thoughts of killing yourself?(YES/NO)

<Similar for other questions>

Program: /CAXXXXX/sas_prg/stsas/lis/programname.sas DDMONYYYY HH:MM

Appendix LCSBR Columbia-Suicide Severity Rating Scale (C-SSRS) Responses – Baseline/Screening (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Question* 1.0	1.1	1.2
1	XX/M	Screen			DDMMMYYYY	XXX	XXX	<Similar for other questions>

*Refer to Appendix LCSBQ for the question descriptions.

F = Female; M = Male

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LCSLR Columbia-Suicide Severity Rating Scale (C-SSRS) Responses – Since Last Visit (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Question* 1.0	1.1	2.0
1	XX/F	1	1	-2.00	DDMMMYYYY	XXX	XXX	<Similar for other questions>
			4	70.25	DDMMMYYYY	XXX	XXX	<Similar for other questions>

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
*Refer to Appendix LCSLQ for the question descriptions.
F = Female; M = Male

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix LMSEQ Mini-Mental State Exam Questions (Safety Population)

Dimension	Questions Number	Description
ORIENTATION	I1	What is today's date?
	I2	What is today's year?
	I3	What is the mouth?
	<Similar for other questions>	
IMMEDIATE RECALL	II1	<Similar for other questions>
ATTENTION AND CALCULATION	III1	
RECALL	IV1	
LANGUAGE	V1	
COPYING	VI1	

Program: /CAXXXXX/sas_prg/stsas/lis/programname.sas DDMONYYYY HH:MM

Appendix LMSER Mini-Mental State Exam Responses (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Question* I1	I2	I3
1	XX/F	Screening 1	-1	-14.00	DDMMMYYYY	XXX	XXX	<Similar for other questions>
			7	154.00	DDMMMYYYY	XXX	XXX	<Similar for other questions>

All subjects received the following treatment: Administration of multiple oral doses of 200 mg IkT-148009 once daily on Days 1 to 7 following a high-fat, high-calorie meal in older adult and elderly healthy subjects.
*Refer to Appendix LMSEQ for the question descriptions.
F = Female; M = Male

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM