18F-AV-1451-A05 SAP Confirmatory v1.0

An Open Label, Multicenter Study, Evaluating the Safety and Imaging Characteristics of 18F-AV-1451 in Cognitively Healthy Volunteers, Subjects With Mild Cognitive Impairment, and Subjects With Alzheimer's Disease

NCT02016560

Approval date: 05 Jan 2018

Protocol No. 18F-Flortaucipir-A05

An open label, multicenter study, evaluating the safety and imaging characteristics of flortaucipir in cognitively healthy volunteers, subjects with Mild Cognitive Impairment, and subjects with Alzheimer's Disease

Confirmatory (Second Phase)
Statistical Analysis Plan

Prepared for:
Avid Radiopharmaceuticals, Inc

Version 1.0 Date 05Jan2018

Prepared by:

Chiltern International Inc.
[redacted]

Revision History

Version	Date	Revision Author	Comments
1.0	05Jan2018	[redacted]	

SIGNATURE PAGE

[redacted]

Table of Contents

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

A	amyloid-
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive
AE	adverse event
ANART	American National Adult Reading Test
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BNT	Boston Naming Test
C	Celsius
cm	centimeters
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
DBP	diastolic blood pressure
DSST	digit symbol substitution test
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
eCRF	electronic case report form
FAQ	Pfeffer Functional Activities Questionnaire
FDG	^{18}F- flurodeoxyglucose
H	high
hCG	human chorionic gonadotropin
IND	investigational new drug
IV	intravenous
JOLO	Benton Judgment of Line Orientation Test
K_d	dissociation constant
kg	kilograms
L	low
LOC	loss of consciousness
LS	least squares
max	maximum
MBq	megabecquerel
mCi	millicuries
MCI	mild cognitive impairment

MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MMRM	mixed model repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
mSv	millisievert
n	number of subjects
N	normal
nM	nanomolar
OSU TBI-ID	Ohio State University Traumatic Brain Injury Identification Method
PET	positron emission tomography
ROI	region of interest
RR	respiration rate
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SUVr	standardized uptake value ratio
TBI	Traumatic Brain Injury
TEAE	treatment-emergent adverse event
TEMP	temperature
WHO	World Health Organization

2 INTRODUCTION

Molecular imaging biomarkers have the potential to aid in the diagnosis of patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) (Dubois, 2010; McKhann, 2011). Positron emission tomography (PET) ligands such as florbetapir F 18 (Wong, 2010) may provide a minimally invasive estimate of cortical beta amyloid- (A) neuritic plaque deposition, a hallmark pathology, and a required element for the evaluation of AD neuropathologic diagnosis (Hyman, 2012). Multiple studies comparing amyloid PET scans to histopathologic assessment of amyloid burden, in subjects for whom biopsy samples were available or who came to autopsy after receiving a PET amyloid scan, support the relationship between PET amyloid imaging results and cortical neuritic plaque density (Clark, 2011, 2012; Leinonen, 2008; Sojkova, 2011; Kantarci, 2011; Burack, 2010). The largest of these studies (Clark, 2012) demonstrated a high sensitivity and specificity for florbetapir PET to discriminate subjects with subsequent autopsy findings of no or sparse neuritic plaques (amyloid negative) from those with moderate to frequent plaques (amyloid positive).

The ability to image brain amyloid with compounds such as florbetapir is an important advance for diagnosis of neurological disease. An amyloid negative florbetapir PET scan indicates the absence of a hallmark pathology and is inconsistent with a diagnosis of AD. However, because amyloid is believed to accumulate very early in the disease process (Jack et al., 2010) and may be present in other diseases or in clinically normal elderly subjects (Sperling et al. 2011; Price and Morris, 1999), the density or distribution of amyloid in subjects with a positive scan is not associated with Alzheimer's disease severity, has not been established to predict rate of future deterioration and has not been established as a tool to predict or monitor response to therapy.

In contrast to A neuritic plaques, the density and distribution of phosphorylated tau, aggregated in neurofibrillary tangles, increases with AD-related cognitive impairment and correlates with neurodegeneration (Dickson et al., 1997; Duyckaerts et a., 1987). Thus, a PET imaging agent that binds to phosphorylated tau has potential application as a biomarker for disease severity/neurodegeneration and may be useful both for selecting patients for therapy and for monitoring disease progression in therapeutic trials.

Flortaucipir F 18 (originally named [F-18]T807 by Siemens Molecular Imaging Biomarker Research group) has been developed as a positron emitting radiopharmaceutical for *in vivo* imaging of tau protein aggregates (Xia et al., 2013). Autoradiography results using tissue sections from human brains showed a strong signal in the grey matter of cortical slices from tau positive brains but weak or no binding in tau negative, A positive, or tau and A negative tissue.

The overarching goal of this protocol is to further investigate the spectrum of PET imaging results with flortaucipir in patients with cognitive decline and healthy controls. To accomplish this goal, the protocol will investigate flortaucipir results in younger and older controls and patients with cognitive complaints ranging from mild cognitive impairment (MCI) to mild and moderate Alzheimer's disease (AD). Additionally, this protocol will investigate correlations between 18F-AV1451 PET imaging and other biomarkers associated with AD and will test the relationship between flortaucipir PET imaging and cognitive decline over the 18 month study period.

3 STUDY OBJECTIVES

The A05 study will be conducted in two phases, an exploratory phase and a confirmatory phase. This statistical analysis plan (SAP) is for the confirmatory phase of this study.

3.1 Confirmatory Phase, Longitudinal Objectives

The confirmatory (second) phase of the study is designed to provide independent validation of the relationships observed in the exploratory analyses of the first phase. In particular, the goal of the second phase is to confirm the relationship between flortaucipir uptake in the brain as measured by PET and the subsequent rate of cognitive decline observed over longitudinal follow up.

The primary objective of the confirmatory (second) phase longitudinal component is:

- To assess whether or not the baseline tau positivity according to a flortaucipir scan visual read predicts a higher risk of subjects' clinically meaningful cognitive and functional deterioration within 18 months of scan, as measured by the Clinical Dementia Rating Scale Sum of Box (CDR-SB) change from baseline

The secondary objective of the confirmatory (second) phase longitudinal component is:

- To assess the diagnostic performance of baseline tau positivity according to a flortaucipir scan visual read, for predicting subjects' clinically meaningful cognitive and functional deterioration within 18 months of scan, as measured by the CDR-SB scales

The exploratory objectives of the confirmatory (second) phase longitudinal component are:

- To evaluate whether or not the baseline brain tau level assessed by flortaucipir scan predicts subjects' cognitive and functional deterioration including the measurements from these tests: MMSE, ADAS Cog-11, FAQ, CDR-SB, CDR global, and Neuropsychological tests (DSST, logical memory). Analyses will also include the exploration of associations between flortaucipir and biomarkers of neurodegeneration

and neurological disease such as amyloid level according to florbetapir scan; brain atrophy assessed by volumetric magnetic resonance imaging (MRI).

- To expand the flortaucipir safety database

4 STUDY DESIGN

4.1 General Design

This study is an open label, multicenter Phase II/III study. This study is conducted in two phases, an exploratory (first) phase (phase II part) and confirmatory (second) phase (phase III part).

The confirmatory (second) phase, for which this SAP is designed, will enroll subjects ≥ 50 years of age with cognitive impairment (MCI or demented subjects with a suspected neurodegenerative cause (AD)) and an MMSE ≥ 20 and ≤ 27. For the purposes of ensuring a distribution of disease severity, a target of at least 1/3 of the enrolled subjects will have dementia. Approximately 150 subjects will be enrolled in the confirmatory (second) phase of the study.

All subjects will provide informed consent before starting any study procedures.

Screening assessments may take place over several days and will include demographic information, cognitive testing, safety assessment, and MRI, including both volumetric and standard clinical sequences. Subjects who qualify for the study will undergo both a florbetapir F 18 PET imaging session and a flortaucipir PET imaging session. The imaging sessions must be performed at least 48 hours apart, but not more than 60 days apart. The order of the scans is interchangeable.

Subjects will return for follow-up visits at 9 (+/-2) and 18 (+/-2) months following the initial flortaucipir scan. Cognitive assessments and updates to concomitant medications and medical history will be collected at each follow-up visit.

Florbetapir F 18 PET Imaging Session:

For the florbetapir F 18 PET imaging session, an intravenous (IV) catheter will be placed for administration of the florbetapir F 18 injection. Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of florbetapir F 18 injection followed by a saline flush. At approximately 50 minutes following the injection, a continuous 10-minute brain scan (2 acquisitions of 5 minute duration) will begin.

Adverse events will be continuously monitored during the florbetapir F 18 PET imaging session. A physician or physician designee must evaluate the subject for AEs prior to injection and prior to discharge from the imaging center. Subjects who experience an AE will not be discharged from the imaging center until the event has resolved or stabilized.

A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days of the post-injection of florbetapir F 18, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.

Flortaucipir PET Imaging Session:

For the flortaucipir PET imaging session, an IV catheter will be placed for administration of flortaucipir injection. Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of flortaucipir injection followed by a saline flush. At approximately 80 minutes post dose, a continuous 20-minute brain scan (4 acquisitions of 5-minute duration) will be obtained. If at any point during the imaging session it is determined that the subject is not able to continue, or that it is not in the best interest of the subject to continue, imaging will be discontinued. The image data that has been collected up to that point will be analyzed. Clinical laboratory tests will be obtained prior to injection and upon completion of each imaging session. Adverse events will be monitored continuously during the imaging session. Subjects who experience any AE during an imaging session will not be discharged until the event has resolved or stabilized.

A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.

4.2 Discussion of Study Design

This trial is designed to evaluate the brain tau protein imaging properties and safety of flortaucipir to be used in subjects with cognitive impairment (first and second phases) and healthy volunteers (first phase only). Another goal of this protocol is to establish a relationship between flortaucipir imaging results and cognitive assessments. Allowing all subjects to complete various cognitive assessments, with MMSE being the primary assessment for the second phase, will provide evidence whether greater degrees of cognitive impairment will be correlated with higher levels of flortaucipir uptake. This relationship is

important in this protocol in order to determine the utility and predictive power of flortaucipir on the severity of cognitive impairment.

4.3 Method of Assignment of Subjects to Treatment Groups

Florbetapir F 18:
All subjects will receive a single IV bolus administration target dose of 370 MBq (10 mCi) of florbetapir F 18 injection.

Flortaucipir:
All subjects will receive a single IV bolus administration target dose of 370 MBq (10 mCi) of flortaucipir injection.

4.4 Blinding

A blinded design was not used for this trial, because all subjects will receive the same medication.

Raters administering the cognitive testing will be blinded to the flortaucipir scans information.

For the confirmatory (second) phase, Avid personnel will be blinded to all clinical assessments data, including cognitive assessments. Avid personnel will also remain blinded to the PET scans (both florbetapir and flortaucipir) performed on subjects enrolled in the confirmatory (second) phase with the exception of periodic quality assurance (QA) assessment of a random subset of image data (not to exceed 20% unless issues identified that warrant additional review). Avid staff performing the PET scan QA assessment will not be aware of diagnostic group or cognitive test scores for the subjects/images being reviewed. Database will be locked as scheduled when all clinical assessments and both flortaucipir and florbetapir scan visual reading process are done. Avid will remain blinded to all clinical data and scan results until this time. After database is formally locked, flortaucipir scans will be transferred to Avid to allow for a quantitative analysis conducted by Avid's imaging science group. The quantitative analysis results (SUVR values) of flortaucipir scans will be included to exploratory analyses, which are detailed in addendum of this SAP, and the outputs will be included in clinical study report (CSR) for this study.

4.5 Determination of Sample Size

The primary objective of the confirmatory (second) phase is to assess the hazard ratio of subjects with flortaucipir scan rated as likely to progress (i.e., AD++) vs. subjects with scan rated as non-AD++ (i.e., patterns other than likely to progress) in progressing to a clinically

meaningful event (CDR-SB with 1 point or more increase) within 18 months of scan. According to A05 exploratory data, 75% (15/20) AD++ subjects had an event and 27% (7/26) non-AD++ subjects experienced an event. Assuming a similar AD++ rate, and a similar event rate will be observed in this confirmatory cohort, a sample of 120 subjects in total will give a close to 90% power to detect a risk ratio of at least 2, under a two sided type I error rate of 5%.

The key secondary objective is to validate the accuracy of flortaucipir scans to predict clinically significant disease progression within 18 months from scan (e.g., cognitive function deterioration as measured by endpoints based on Exploratory Phase results at the time of protocol finalization). For the purpose of sample size calculation, we assumed that the target success criteria would be at least 70% sensitivity and at least 70% specificity for flortaucipir scans to detect this deterioration, with the lower bound of 95% confidence intervals (CI) above 50% for both sensitivity and specificity. Preliminary analysis of the exploratory phase data showed that clinical assessments may have a relatively large variance. It is important to ensure that enough subjects will be in each group for sensitivity and specificity calculation (i.e., the subjects with or without a significant disease progression). To that end, we assumed at least 20% of the subjects will be in each group at the 18 month follow up. With this assumption, a 5% two-sided type I error rate, and that 95% CI will be calculated using Wilson score method, a sample of 115 subjects will provide an over 90% probability to observe lower bound of 95% CI above 50%, for both sensitivity and specificity. Also assuming an approximate 20% drop out rate over the 18 months follow up, this study will aim to enroll 150 subjects in total for the confirmatory (second) phase.

The exploratory cohort (first phase) data showed that for AD/MCI subjects with a baseline MMSE between 20-27, those who had flortaucipir scans classified as AD++ had an average of 4.4 point decrease in MMSE (SD=3.8), while those classified as non-AD++ had an average of 0.7 points decrease in MMSE (SD =2.5). The ratio of AD++ vs. non-AD++ was 2:3. Assuming the same ratio of AD++ ends up in this confirmatory cohort, with similar values of SD for mean changes, a total of 100 completers will give an over 90% power to detect a 2.5 points or larger difference in MMSE change from baseline values between the AD++ and non-AD++ groups, under a 5% two sided type I error rate.

A subgroup of subjects from A05 confirmatory cohort will be selected and their flortaucipir scans will be read twice in a random sequence, for the intra-reader reliability evaluation of scan interpretation. According to A05 exploratory cohort data, the AD++ rate is 47% among AD/MCI subjects with baseline MMSE 20-27. Assuming this will be the rate of AD++ from confirmatory cohort, a simulation showed that a sample size with 20 random selected cases will have an approximately 95% probability to have the AD++ rate in the range from 30% to

70% for the selected cases. This relative balance AD++ rate will ensure a meaningful kappa statistics calculation for assessing the intra-reader reliability assessment.

5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

5.1 Changes in the Conduct of the Study

There were no changes in the conduct of the study at the time of preparing this SAP.

5.2 Changes from the Analyses Planned in the Protocol/CIP

The protocol was amended (version 07 August 2015, Amendment 2). In this amendment the study was divided into two phases, exploratory (first) phase and confirmatory (second) phase. Currently, this SAP provides the planned analyses for the confirmatory (second) phase of the study.

6 BASELINE, EFFICACY AND SAFETY EVALUATIONS

6.1 Schedule of Evaluations

Exploratory (First) Phase and Confirmatory (Second) Phase:

Evaluations	Screening Visit[a]	Florbetapir F 18 Imaging Visit[b]	End of Florbetapir F 18 Imaging (prior to discharge)	Follow-up Phone Call	^{18}F-AV-1451 Imaging Visit[b]	End of ^{18}F-AV-1451 Imaging (prior to discharge)	Follow-up Phone Call
Signed Consent	X						
Demographics	X						
Medical History/Neurologic Disease History	X						
Concomitant Meds	X	X			X		
Physical Exam/ Neurological Exam	X						
ECG	X				X[c]	X	
Vital Signs	X[d]	X[e]			X[f]	X[g]	
Safety Labs	X				X[h]	X	
Serum beta-hCG[i]	X						
Urine Pregnancy test[j]		X			X		
OSU TBI-ID	X						
MMSE	X						
ADAS-Cog 11	X						
Neuropsych battery[k]	X						
MRI of the brain	X						
PET Brain Scan		X			X		
ApoE					X		
Genetic sample					X		
Optional CSF	X[l]						
Evaluation by a physician	X	X[m]	X[m]		X	X	
Adverse Events	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X

a. Screening may take place over several days. All assessments must be performed within 30 days of the first ^{18}F-AV-1451 imaging session (with the exception of the MRI if previously performed).
b. The ^{18}F-AV-1451 and florbetapir F 18 imaging sessions must be performed at least 48 hours apart, but the order of the scans is interchangeable.
c. Two ECGs will be taken approximately 5 minutes apart immediately prior to (within approximately 10 minutes) ^{18}F-AV-1451 Injection administration. One will be taken within 5 minutes after completion of injection.
d. Screening vital signs include pulse rate, respiratory rate, supine blood pressure, height and weight
e. Vital signs (pulse rate, respiratory rate, supine blood pressure, weight) will be taken immediately prior to injection of florbetapir F 18.
f. Pulse, respiratory rate, supine blood pressure, temperature and weight will be taken immediately prior to administration of ^{18}F-AV-1451. Pulse, respiratory rate, and supine blood pressure within 5 minutes after completion of injection of ^{18}F-AV-1451 Injection.
g. Pulse, respiratory rate, supine blood pressure, temperature
h. Blood and urine samples will be collected prior to administration of ^{18}F-AV-1451 Injection.
i. Serum beta-hCG pregnancy test at screening (for females of childbearing potential defined as pre-menopausal or less than 2 years post-menopausal and not surgically sterile.
j. For women of childbearing potential, a negative urine pregnancy test must be obtained within 24 hours prior to florbetapir F 18 injection and within 24 hours prior to ^{18}F-AV-1451 injection.
k. Including CDR for subjects tin the Confirmatory Cohort.
l. CSF collection may occur after the subject has passed screening procedures for subjects in the Exploratory Cohort only
m. A physician or physician designee

Confirmatory (Second) Phase Only:

Evaluations	5 Month Follow-up Phone Call	9 (+/-2) Months, First Longitudinal Follow-up Visit	14 Month Follow-up Phone Call	18 (+/-2) Months, Second Longitudinal Follow-up Visit
Updated Medical History	X	X	X	X
Updated Concomitant Meds	X	X	X	X
MMSE		X		X
ADAS-Cog 11		X		X
Neuropsych battery, including CDR		X		X

6.2 Time Point Algorithms

6.2.1 Relative Day

The date of first dose of study drug (flortaucipir) will be considered relative day 1, and the day before the first dose of study drug will be relative day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

For days on or after the first dose of study drug:
Date of Assessment – Date of First Dose of Study Drug + 1.

For days before the first dose of study drug:
Date of Assessment – Date of First Dose of Study Drug.

6.2.2 Windows

For all analyses, results will be summarized at the planned study visit they were obtained (screening/baseline, or 9 or 18 months post baseline).

6.3 Screening and Baseline Assessments

Screening may take place over several days. All screening assessments should be performed within 30 days of the initial flortaucipir PET imaging session. Screening assessments will include:

- Informed consent;
- Demographics (age, gender, race, ethnicity, education, alcohol, drug use, and smoking);
- Medical history, physical and neurological exams, concomitant medications;
- Disease history (date/months since symptom onset, date/months since diagnosis, family history of neurologic disease) for cognitively impaired subjects;
- Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID);
- Mini Mental State Exam (MMSE);
- Safety assessments: Vital signs (pulse rate, respiratory rate, supine blood pressure, height and weight), ECG, safety labs (hematology, chemistry, and urinalysis);
- Serum beta human chorionic gonadotropin (hCG) test (for females of childbearing potential defined as pre-menopausal or less than 2 years post-menopausal and not surgically sterile);
- MRI imaging including standard clinical sequences and volumetric MRI;
- A physician will see the patient during the screening visit.

Baseline assessments may be performed at the screening visit or +/- 30 days of the initial flortaucipir Imaging Visit. Raters administering the MMSE and baseline assessments described below will be blinded to the flortaucipir scans for subjects in the confirmatory (second) phase.
Baseline assessments will include:

- Alzheimer's Disease Assessment Scale- Cognitive subscale (ADAS-Cog11);
- Neuropsychological test battery (Digit Symbol Substitution Test (DSST), Digit span forward and backward, Trail Making A and B, Logical Memory Test, Immediate and Delayed Recall Story A, Animal list generation, Boston Naming Test (BNT) (30 item), American National Adult Reading Test (ANART), Clock Drawing Test, Benton Judgment of Line Orientation test);
- Clinical Dementia Rating (CDR) Sum of Boxes Scale;
- Pfeffer Functional Activities Questionnaire (FAQ).

Tau pathology can be associated with Traumatic Brain Injury (TBI), therefore the OSU TBI-ID (Corrigan and Bogner 2007) short version will be used to screen for a history of traumatic brain injury. It is the briefest version that still provides several summary indices on which the original version was validated. To shorten the instrument, TBIs resulting in loss of consciousness (LOC) are emphasized over less severe injuries. Classifying worst injury based on the OSU TBI-ID will all be displayed. The following classifies worst injury:

- 1= Improbable TBI- if interview data reports all questions numbered 1-5 are all 'no' or if response to question 6, interview data reports never having LOC, being dazed or having memory lapses.
- 2= Possible Mild TBI without LOC- if in response to question 6, interview data reports being dazed or having memory lapse.
- 3= Mild TBI with LOC- if in response to question 6, interview data reports LOC does not exceed 30 minutes for any injury.
- 4= Moderate TBI- if in response to question 6 , interview data reports LOC for one injury is between 30 minutes and 24 hours.
- 5= Severe TBI- if in response to question 6, interview data reports LOC for any one injury exceeds 24 hours.

Weight will be displayed in kilograms (kg), height will be displayed in centimeters (cm), and temperature will be displayed in Celsius (C). Weights, heights, or temperatures recorded in alternate units will be converted to the units being displayed using standard conversion formulas. Body mass index (BMI) will be calculated as weight (kg) divided by height squared (cm^2).

Each subject's age (years) will be calculated based on his/her date of informed consent and will be truncated to a whole number. Because only year of birth is collected, January 1 will be imputed for the month and day of birth. To calculate age, count the number of

months between the date of informed consent and the imputed birthdate. Divide the result by 12 and round down to the nearest integer to get the age of the subject.

The number of years of education for a subject will be calculated for individuals who have specified the level of schooling he/she has obtained. The years of education will be calculated as follows: elementary school = 6 years, middle school = 8 years, high school = 12 years, college/university = 16 years, graduate/master's degree = 18 years, PhD/multiple graduate degrees/medical degree = 20 years. Otherwise, if a subject specified the number of years of education, then this number will be used.

For efficacy measurements, baseline is defined as the assessments recorded at screening visit. Baseline for safety assessments, including vital signs and labs are defined as last assessments prior to flortaucipir injection. For ECG safety assessments during the flortaucipir scan session, baseline value will be calculated as the average of the two ECGs administered prior to flortaucipir administration. If only one ECG was administered prior to flortaucipir administration, the baseline will be defined as the singular ECG administered prior to flortaucipir administration.

6.4 Efficacy Variables

6.4.1 Primary Efficacy Variable(s)

6.4.1.1 Tau Status Based on flortaucipir

Flortaucipir images will be assessed by 5 independent readers blinded to any clinical information of the subjects. The images will be classified as either AD++ (AD pattern, likely to progress), AD + (AD pattern, but unlikely to progress; tau limited to temporal/occipital lobe) or AD- (Inconsistent with an AD pattern) by each reader, following the pre-specified reading method (see imaging reading manual for details). The majority reading results derived from the 5 readers will be used to determine the tau status for each subject for primary objective analysis. For the purposes of study analyses images will be considered positive for progression if they are rated AD ++ and negative for progression if they are rated non-AD++ (AD- or AD+ but not AD++).

6.4.1.2 Clinical Dementia Rating (CDR) Scale (Berg, 1988)

The CDR examines 6 categories of cognitive functioning domains. Each domain is scored on a scale ranging from 0 to 3 (including 0.5). A global rating of dementia can be generated from the domain scores. A CDR Sum of Boxes (CDR-SB) will be generated as the sum of the values in each of the six domains. The CDR-SB sum scores ranges from 0-18, where higher scores indicate greater cognitive impairment. CDR will be performed at screening or baseline, 9 months, and 18 months post-baseline. CDR-SB will be used as a continuous scale in exploratory objective analysis, when assessing the average change from baseline by tau status.

The detailed derivation of CDR global score is defined in Appendix 1 of this SAP.

For primary and secondary analysis, the CDR-SB score change from baseline will be dichotomized in two groups: CDR-SB score change 1 point or more at 18 months, or otherwise.

6.4.2 Additional Efficacy Variables

6.4.2.1 Amyloid Beta Status Based on Florbetapir

Florbetapir F 18 images will be assessed by an expert reader blinded to all clinical related information for the subjects. The images will then be classified as either AB+ (amyloid positive) or AB- (amyloid negative).

6.4.2.2 Cognitive Assessments

Cognitive assessments will be performed at screening or baseline. Some of the cognitive assessments will be evaluated at follow-up visits (9 (+/- 2) months, and 18 (+/- 2) months) during the study. These cognitive assessments include the following:

Mini-Mental State Examination (MMSE)

The MMSE (Folstein et al., 1975) is a brief instrument used to assess cognitive function in elderly patients. The range for the total MMSE score is 0 to 30, the sum of each correct answer, with higher scores indicating better cognition. MMSE will be performed at screening or baseline, 9 months, and 18 months post-baseline. The score on a continuous scale will be used for primary objective analysis, when assessing the average change from baseline by tau status.

Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog11)

The ADAS (ADAS-Cog; Rosen et al. 1984) was designed to assess the severity of the dysfunction in the cognitive and noncognitive behaviors characteristic of persons with AD. The cognitive subscale of the ADAS, the ADAS-Cog11, consists of 11 items assessing areas of function most typically impaired in AD: orientation, verbal memory,

language, and praxis. The overall score for ADAS-Cog11 ranges from 0 to 70, with higher scores indicating greater disease severity, and is calculated as the sum of all 11 individual component scores. ADAS total score will be used as a continuous variable for the exploratory analysis, to assess the average change from baseline by tau status.

Pfeffer Functional Activities Questionnaire (FAQ), (Pfeffer et al. 1982)

Functional status is conceptualized as the "ability to perform self-care, self-maintenance and physical activities." The FAQ was developed to assess instrumental activities of daily living involving higher level functional skills such as shopping alone, writing checks, remembering appointments, etc. The FAQ asks the informant to rate the patient's ability using the following scoring system: Dependent = 3; Requires assistance = 2; Has difficulty but does by self = 1; Normal = 0; Never did [the activity] but could do now = 0; Never did and would have difficulty now = 1. The sum scores ranges from 0-30, where higher scores indicate greater functional impairment. FAQ will be performed at screening or baseline, 9 months, and 18 months post-baseline. FAQ sum score will be used as a continuous variable in secondary objective analysis, when assessing the average change from baseline by tau status.

Digit Symbol Substitution Test (DSST)

The DSST (Wechsler Adult Intelligence Scale F Revised, 1981) is a paper test of psychomotor performance in which the subject is given a key of numbers and matching symbols and a test section with numbers and empty boxes. Under each number the subject should write down the corresponding symbol as fast as possible. The score is the number of correct number-symbol matches made within the allowed time (90 seconds). The strategy to solve the DSST consists of sequential encoding and retrieval of numbers and corresponding symbols. Incidental memory, visuo-motor coordination, perceptual organization, and selective attention are key factors that determine the final score (Wechsler Adult Intelligence Scale Revised, 1981). The ability to sort out irrelevant information (e.g., symbols that may look alike) also impacts performance. This test has high test–retest reliability (Matarazzo and Herman, 1984). One point is given for each symbol correctly drawn during the ninety seconds, with the maximum score of 93. Greater totals denote lower disease severity. DSST total score will be used as a continuous variable for the exploratory analysis, to assess the average change from baseline by tau status.

Digit span forward and backward (from Wechsler Memory Scale-Revised (WMS-R))

Digit Span is composed of two tasks administered independently of each other: Digits Forward and Digits Backward. On both tasks, the examiner reads a series of number sequences to the subject. For each Digits Forward item, the subject is required to repeat the number sequence in the same order as presented. For Digits Backward, the subject is

required to repeat the number sequence in the reverse order. The score ranges from 0-24, a maximum score of 12 for digit span forward and a maximum score of 12 for digit span backward, with lower scores indicating greater disease severity. Total score from this test will be used as a continuous variable for the exploratory analysis, to assess the average change from baseline by tau status.

Trail Making A and B

The trail making test (Reitan and Wolfson, 1985) is a test of executive function. Part A consists of 25 circles numbered 1 through 25 distributed over a sheet of paper. The subject is instructed to connect the circles by drawing a line as quickly as possible in ascending numerical order. Part B consists of 25 circles containing either numbers (1 through 13) or letters (A-L). The subject is instructed to connect the circles while alternating between numbers and letters in ascending order. The subject is timed. The total score is the time to complete Part A, with a maximum of 150 seconds and Part B with a maximum of 300 seconds. Timing is not stopped while correcting errors. Testing is stopped if the maximum time is reached. The total score is the number of seconds to complete both trails, where higher scores indicate greater disease severity. Total score will be used as a continuous variable for the exploratory analysis, to assess the average change from baseline by tau status.

Logical Memory Test, Immediate and Delayed Recall, Story A (WMS-R)

The logical memory test (Wechsler D. 1987) assesses the ability to recall a short story. Subjects are read a story and asked to recall the story immediately and after a delay. The maximum score is 25, and each point is obtained based on how much of the story is correct. Higher scores indicate better cognition. The immediate recall total as well as delayed recall total score will be used as continuous variables for the exploratory analysis, to assess the average change from baseline by tau status.

Animal List Generation

The animal list generation (Morris et al. 1989) is used to measure verbal fluency. The subject is asked to name as many animals as possible in 60 seconds. The total score is the count of all admissible words, where lower scores denote greater cognitive impairment. The total score will be used as a continuous variable for the exploratory analysis, to assess the average change from baseline by tau status.

Boston Naming Test (BNT) (30 item)

The 30 item Boston Naming Test (Kaplan, et al. 1983) is a measure of the ability to orally label 30 line drawings of objects. The objects are presented to the subject in order of frequency, from most frequent to least frequent. The maximum score is 30, where

higher scores indicate better cognition, obtained from the number of spontaneously given correct responses in addition to the number of correct responses following a stimulus cue. The total score will be used as a continuous variable for the exploratory analysis, to assess the average change from baseline by tau status.

American National Adult Reading Test (ANART)

ANART (Grober and Sliwinski 1991) is a measure for estimating premorbid verbal intelligence. The subject is presented with a word list and asked to pronounce the words. One point is given for each correctly pronounced word, with a maximum score of 45, where lower scores indicate greater disease severity. As an indicator of cognition reserve, baseline ANART score will be used as an adjusting variable in all the multivariate models.

Clock Drawing Test

The clock drawing test (Goodglass and Kaplan 1983) has two components: a command condition and a copy condition. In the command condition, the subject draws a clock according to verbal instructions. In the copy condition, the subjects copy a model clock drawn at the top of a form. The score ranges from 0-5 where a point is obtained for approximately circular face, symmetry of number placement, correctness of numbers, presence of two hands, and presence of two hands set to the correct time. Higher scores suggest better cognition. The total score will be used as a continuous variable for the exploratory analysis, to assess the average change from baseline by tau status.

Benton Judgment of Line Orientation Test (JOLO)

The JOLO (Benton 1978) is a non-motor measure of visual perceptual ability where there is no time demand. The task asks subjects to match two lines by their angle of orientation to a test set of lines presented below the stimulus lines. Each correct response is given one point and the maximum score is 30, where higher scores denote lesser disease severity. . The total score will be used as a continuous variable for the exploratory analysis, to assess the average change from baseline by tau status.

6.4.2.3 Clinically Meaningful Progress

The following cognitive/functional assessments will be dichotomized or categorized, to allow for the assessment of risk to progress to a clinically significant change. Subjects within each diagnostic group will be categorized to these groups by the criteria accordingly.

MMSE: clinically significant progress is defined as MMSE has a 3 points or more decrease from baseline.

FAQ: clinically significant progress is defined as FAQ has a 3 points or more increase from baseline.

ADAS Cog-11: clinically significant progress is defined as ADAS Cog-11 has a 4 points or more increase from baseline.

CDR Global: CDR global change from baseline will be categorized into 3 groups such as >0, = 0 and <0.

6.4.2.4 ApoE Genotyping

ApoE genotyping will be performed at the initial flortaucipir imaging session for those subjects whose ApoE is unknown. For analysis purposes, subjects will be categorized as ApoE 4 positive (4+) if at least one allele is an 4 allele and ApoE 4 negative (4-) if neither allele is an 4 allele.

6.4.2.5 Genetic Samples

A one-time blood collection (10 mL, blood) will be performed on the day of the initial flortaucipir imaging session for genetic analysis. Where local regulations allow, samples will be stored and analysis may be performed on genetic variants thought to play a role in dementia or related diseases. Samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis. No prospective analyses will be performed using this data.

6.4.2.6 MRI Scan of the Brain

MRI, including both volumetric and standard clinical sequences, will be conducted during Screening. A MRI will be performed on the whole brain, ventricle, and hippocampus. Normalized volumetric measurements, including whole brain, total gray region, ventricle, and hippocampal volumes will be conducted, and used for correlation analysis with cognition changes or corresponding flortaucipir imaging uptake values.

6.5 Drug Concentration Measurements and Pharmacokinetic Parameters

6.5.1 Handling of Pharmacokinetic Parameter Outliers

No pharmacokinetic parameters or drug concentration measurements will be collected during this study.

6.6 Safety Assessments

6.6.1 Extent of Exposure and Compliance to Study Treatment

During the florbetapir F 18 imaging session, subjects will receive a single IV bolus administration target dose of 370 MBq (10 mCi) of florbetapir F 18 injection followed by a 10 minute PET brain scan (2 acquisitions of 5 minute duration) at 50 minutes post injection. During the flortaucipir imaging session, all subjects will receive a single IV bolus administration target dose of 370 MBq (10 mCi) of flortaucipir injection. At approximately 80 minutes post dose, scanning will begin. Four 5-minute acquisitions will be taken. Exposure to study drug will be summarized as the total administered dose for both florbetapir F 18 injection and for flortaucipir exposures.

6.6.2 Adverse Events

The investigator's verbatim term of both serious and non-AEs will be mapped to system organ class (SOC) and preferred terms using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent AEs (TEAEs) are undesirable experiences, signs, or symptoms that begin or worsen in intensity or frequency at the time of or after the administration of study drug, and prior to 48 hours post dose injection of each scan sessions. Trial-emergent AEs are undesirable experiences, signs or symptoms between enrollment and any of the baseline scan sessions, or between the baseline florbetapir and baseline flortaucipir scan sessions but not within the 48 hours window post dose injection of each scan session. These events will be recorded on the AE page of the electronic case report form (eCRF). During the trial, any events happening outside the TEAE or trial-emergent AE window as defined above will be collected in medical history form, unless the site physicians consider it a study drug related event.

Serious AEs (SAEs) are events that result in one of the following outcomes or constitute one of the following events:

- Death
- Initial or prolonged hospitalization (other than that required by protocol; "social hospitalization" or any hospitalization for non-medical reasons does not constitute an SAE)
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason

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

For the summarization of TEAEs by seriousness, events recorded with missing seriousness will be summarized as serious.

Investigators will be instructed to report their assessment of the potential relatedness of each AE to protocol procedure, concomitant medication, and/or investigational product. The assessment of the relationship of an AE to the administration of the investigational product is a clinical decision based on all available information at the time of the completion of the eCRF. For the summarization of TEAEs by relationship to study drug or protocol procedure, events recorded with missing relationship will be summarized as Related.

In addition to assessing the relationship of the administration of the investigational product to AEs, an assessment is required of the severity of the event. The following classifications should be used:

Mild:
A mild AE is an AE, usually transient in nature and generally not interfering with normal activities.

Moderate:
A moderate AE is an AE that is sufficiently discomforting to interfere with normal activities.

Severe:
A severe AE is an AE that incapacitates the subject and prevents normal activities. Note that a severe event is not necessarily a serious event. Nor must a serious event necessarily be severe.

For the summarization of TEAEs by intensity, events recorded with missing intensity will be summarized as Severe.

6.6.3 Clinical Laboratory Evaluations

Clinical laboratory evaluation will be performed at screening, prior to administration of flortaucipir injection, and after completion of flortaucipir imaging. Tests will include:

- Hematology (5 mL EDTA): hemoglobin, hematocrit, RBC, WBC, MCH, MCHC, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelets, morphology, MCV, and RBC morphology.

- Chemistry (6 mL blood): total bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), urea nitrogen, creatinine, glucose, uric acid, calcium, phosphorus, total protein, albumin, total cholesterol, triglycerides, sodium, potassium, bicarbonate, chloride, magnesium, globulin, GGT.
- Urinalysis (10 mL, urine): Samples will be used to assess glucose, RBC, WBC, specific gravity, pH, protein, ketones, urobilinogen, blood, nitrite, microscopic, color, bilirubin, casts, epithelial cells, leukocyte, esterase, and bacteria.
- Serum beta hCG, qualitative: performed at screening for females of childbearing potential who are not surgically sterile. A serum pregnancy test may also be obtained prior to injection at the Imaging Visit if required by the local site.
- Urine beta hCG: performed at the imaging visit(s) prior to injection for females of childbearing potential (defined as pre-menopausal, less than 2 years post-menopausal or not surgically sterile).
- ApoE Genotyping (10mL, blood): will be performed at the initial flortaucipir imaging session for those subjects whose ApoE results are unknown.

Baseline for clinical laboratory evaluations will be calculated as described in section 6.3. Change from baseline for continuous post-baseline assessments will be calculated as the result at the visit minus the baseline value. For applicable laboratory tests, laboratory values will be defined as low, normal, or high relative to the normal reference ranges for each subject's age and sex. Criteria for potentially clinically significant laboratory results are defined in Appendix 2 of the SAP. A result will be considered potentially clinically significant if the result occurs post-baseline and no test results at or prior to baseline for the parameter in question meet the same criteria for potential clinical significance.

6.6.4 Other Observations Related to Safety

6.6.4.1 Vital Signs

Vital signs (pulse rate, respiratory rate, and supine blood pressure) will be taken at the following time points:

- Screening visit
- Florbetapir F18 Imaging Day
    - immediately prior to injection of florbetapir F 18
- Flortaucipir Imaging Day
    - Immediately prior to the administration of flortaucipir injection
    - Within 5 minutes after completion of injection of flortaucipir injection
    - After the completion of imaging prior to discharge

Temperature will be obtained at the following time points:

- Flortaucipir Imaging Day
    - Immediately prior to the administration of flortaucipir injection

- After the completion of imaging prior to discharge

Baseline for vital signs will be calculated as described in Section 6.3. Change from baseline for post-baseline assessments will be calculated as the result at the visit minus the baseline value. Criteria for potentially clinically significant vital sign results are defined in Appendix 3 of this SAP. A measurement will be considered potentially clinically significant if the measurement occurs post-baseline and no measurements at or prior to baseline for the parameter in question meet the same criteria for potential clinical significance.

6.6.4.2 Electrocardiogram (ECG)

A resting 12-lead electrocardiogram will be recorded at screening. At the ^{18}F-AV -1451 imaging visits the ECGs will be taken at the following time points:

- Two ECGs will be taken at approximately 5 minutes apart immediately prior (within approximately 10 minutes) to flortaucipir injection administration.
- One ECG will be taken immediately (within approximately five minutes) after completion of flortaucipir injection.
- One ECG will be taken after completion of the PET scan prior to discharge.

Baseline for ECGs will be calculated as described in section 6.3. Change from baseline for post-baseline assessments will be calculated as the result at the visit minus the baseline value. Criteria for potentially clinically significant ECG results are defined in Appendix 3 of this SAP. A result will be considered potentially clinically significant if the result occurs post-baseline and the baseline result for the parameter in question does not meet the same criteria for potential clinical significance.

6.7 Pharmacodynamics Parameters

No pharmacodynamics parameters will be collected during this study.

7 STATISTICAL METHODS

7.1 General Methodology

Frequency distributions including counts and percentages will be included for all categorical outcomes. Summary statistics including mean, standard deviation, median, minimum and maximum values will be presented for all continuous outcomes. Unless otherwise specified, hypothesis testing will be two-sided with type I error rate of 0.05.

All statistical analyses will be performed using SAS® version 9.3 or higher.

7.2 Adjustments for Covariates

For multivariate model analyses using cognitive or function assessments as dependent variables, the models will be adjusted for baseline age and baseline American national adult reading test (ANART) score.

7.3 Handling of Dropouts or Missing Data

Dropout subjects will not be replaced in this study. For situations with no rules for handling missing data the default will be no imputation.

A likelihood-based mixed effects model for repeated measures will be used to handle missing data. The model parameters are simultaneously estimated using restricted likelihood estimation incorporating all of the observed data. Estimates have been shown to be unbiased when the missing data are missing at random and when there is ignorable non-random missing data.

Repeated measures analyses will only use data from visits where the data was scheduled to be collected. When subjects discontinue from the study early, there may be efficacy data measurements at visits where the variables were not scheduled to be collected. These data will appear in listings only.

7.4 Interim Analyses and Data Monitoring

No interim analysis or data monitoring is planned for this study.

7.5 Multi-center Studies and Pooling of Centers

This study will be conducted in approximately 30 centers. The data from all centers will be pooled. The pooled data will be analyzed and presented.

7.6 Multiple Comparisons/Multiplicity

To control the overall type I error rate at 0.05, a gate keeper methodology will be employed (Marcus, et. al., 1976). Hypotheses will be tested in the following order:

1. Testing of hypothesis for primary objective analysis;
2. Testing of hypothesis for secondary objective analysis.

Hypothesis testing will begin testing (1) at the 0.05 level. If the p-value is less than or equal to 0.05, the second hypothesis will be tested. These hypotheses will be marked in the table as having passed or failed the multiple comparisons testing. All p-values will be displayed regardless of passing or failing the multiple comparisons testing.

7.7 Use of an "Efficacy Subset" of Subjects

Invalid PET images will be excluded from analysis. An image will be considered invalid if it is missing, cannot be reconstructed or is irretrievably missing key identifying information as determined by the Expert Review Process document. All scans that pass Quality Control and the Expert Review Process will be read for the purposes of the primary and secondary endpoints. The contracted independent imaging readers will be able to rate scans as evaluable or unevaluable. Regardless of reader rating of technical adequacy (i.e., evaluable vs. unevaluable), all readers will be asked to record their scan interpretation and this result will be used for study endpoints analyses. If 3 or greater of the 5 readers rate a scan as unevaluable, additional sensitivity
analyses for key primary and secondary endpoints will be conducted excluding these scans. All analyses involving flortaucipir imaging outcomes will be based on the efficacy population.

7.8 Active-Control Studies Intended to Show Equivalence

Not applicable to this study.

7.9 Examination of Subgroups

Not applicable to the confirmatory phase of this study.

8 STATISTICAL ANALYSIS

8.1 Disposition of Subjects

The number and percentage of subjects who were treated, who completed the study, and who discontinued from the study, as well as the reasons for discontinuing, will be summarized.

Data on screening failures (subjects who signed informed consent but were not entered into the trial) were not collected on the CRF, are not included in the database and will not be presented.

8.2 Protocol Deviations/Violations

Subjects who entered the study even though they did not satisfy one or more of the inclusion/exclusion criteria will be listed. Deviations/violations from the protocol will be documented, the Avid/contract research organization (CRO) monitor will then be informed and a course of action will be agreed upon.

8.3 Analysis Populations

8.3.1 Enrolled Population

The enrolled population will consist of all subjects in the clinical database. Disposition information will be summarized using the safety population.

8.3.2 Safety Population for flortaucipir

The safety population for investigational drug will consist of all subjects that received an injection of flortaucipir. All baseline, efficacy endpoints, and safety endpoints for flortaucipir will be summarized and listed using the safety population for flortaucipir.

8.3.3 Safety Population for florbetapir

The safety population for investigational drug will consist of all subjects that received an injection of florbetacipir. All safety endpoints for florbetapir will be summarized and listed using the safety population for florbetapir.

8.3.4 Safety Population for Study

The safety population for study will consist of all subjects that received an injection of flortaucipir and/or an injection of florbetapir 18 F. The disposition summary will be based on the safety population for study.

8.3.5 Efficacy Population

The efficacy population will include all subjects with a valid, interpretable PET images and at least one clinical/cognitive assessment. The primary/secondary efficacy population will include all subjects with a valid, interpretable PET images and the relevant clinical/cognitive assessment post flortaucipir scan.

8.4 Demographic and Other Baseline Characteristics

All baseline summaries will be based on the safety population.

Frequency distributions and summary statistics for demographic and baseline variables will be presented by enrolling diagnosis groups, and for all subjects combined. Key demographic and baseline characteristics to be summarized include: age, gender, race, ethnicity, height, weight, BMI, education, alcohol history, recreational drug use history, smoking history, medical history, family disease history, cognitive assessments, worst brain injury history, physical examination, and neurological examination.

All demographic and baseline characteristics data will be presented in listings.

8.5 Prior and Concomitant Therapy

A current version of the World Health Organization (WHO) Drug Dictionary will be used to classify medications by preferred term and WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients. ATC classification level 3 will be used. If level 3 is missing, then level 2 will be used. If level 2 is missing, then level 1 will be used. Any medication given before the day of administration of study drug is considered a *prior* medication. Any medication given on or after the day of administration of study drug is considered a *concomitant* medication. A medication can be considered both prior and concomitant. The most conservative algorithms will be implemented in case a medication has partial start/stop date information.

Descriptive statistics, such as frequency counts and percentages will be provided to summarize the use of medications other than the study drug reported throughout the study. The number and percentage of subjects who received other treatment will be shown by WHO classification of ingredients and by preferred term. No statistical tests will be performed on prior and concomitant medications. All prior and concomitant medications data will be presented in listings.

8.6 Analysis of Efficacy Parameters

8.6.1 *Confirmatory Phase, Longitudinal Analysis*

8.6.1.1 Analysis of Primary Efficacy Variable

8.6.1.1.1 Hazard Ratio of AD++ vs. Non-AD++ Subjects in Progression to Clinically Meaningful Changes Evaluated by CDR-SB

As described in section 6.4.1.2, the primary efficacy variable will be the dichotomized CDR-SB score change from baseline (1 point or more increase vs. otherwise). Time to first occurrence of this clinically meaningful event will be modeled using a Cox proportional hazard model by baseline tau status as determined by majority flortaucipir scan visual reading results from the 5 independent imaging physicians, and the hazard ratio of AD++ rated subjects progressing to the event over non-AD++ rated subjects along with the 95% confidence interval will be provided. The Cox proportional hazard model will be adjusted for baseline age, ANART, and baseline CDR-SB score.

The specific hypothesis for testing is that the hazard of progressing to this clinically meaningful event as determined by CDR-SB value change within 18 months will be significantly greater for subjects with flortaucipir scans rated as AD++, as comparing to those with scans rated as non-AD++ (otherwise, including AD- and AD+ but not AD++ reading).

8.6.1.2 Analysis of Secondary Efficacy Variable

8.6.1.2.1 Diagnostic Performance of Baseline Tau Status in Predicting Clinically Meaningful Changes Evaluated by CDR-SB

This Analysis will use dichotomized CDR-SB Change (1 point or more increase vs. otherwise) as a truth standard (TS) to assess the diagnostic performance of baseline tau status as determined by flortaucipir scan. The assessments will be conducted for each of the 5 independent imaging readers. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-) will be calculated, with details as below:

	Clinically Meaningful Change	
	Change +	Change-
AD++	A	B
Non-AD++	C	D

Sensitivity = A/*(A+C)*

Specificity = *D/(B+D)*

Accuracy = *(A+D)/(A+B+C+D)*

PPV=*A/(A+B)*

NPV = *D/(C+D)*

LR+ = *Sensitivity/ (1-Specificity)*

LR- = *(1-Sensitivity) /Specificity*

The confidence intervals around sensitivity, specificity, accuracy, NPV, and PPV will be calculated by Wilson score method.

The hypothesis for testing is that, of the 5 independent imaging physicians, at least the same 3 will have the lower bounds of two-sided 95% CIs 50%, for both sensitivity and specificity.

8.6.1.3 Exploratory Analysis

8.6.1.3.1 CDR Clinically Meaningful Deterioration

The CDR global score change from baseline will be categorized into 3 groups: <0, = 0 and >0.
A Cochran-Armitage trend test will be applied to compare the groups of CDR global score change from baseline by baseline tau scan groups at 9 months and 18 months respectively.

8.6.1.3.2 Mixed Model Repeated Measures for Comparison of MMSE over time as a function of Tau scan visual interpretation

Descriptive summary statistics for the MMSE cognitive scale at baseline, 9 months, and 18 months will be provided by all subjects. The change from baseline to 9 months and 18 months will be summarized in the same corresponding table.

The objective of this analysis is to test the hypothesis that baseline tau status as determined by the flortaucipir scan will predict subjects' cognitive deterioration. This exploratory analysis will test that hypothesis using change from baseline MMSE as the indicator of cognitive deterioration. The flortaucipir scans will be visually interpreted by 5 imaging physicians independently, and the majority classification from their interpretations will be used to decide if the scan is AD++ (predicts cognition likely to progress) or non-AD++ (not likely to progress over 18 months). The specific hypothesis for testing is that the MMSE change (worsening) from baseline to month 18 will be significantly larger for AD++ group, as comparing to non-AD++ group. The hypothesis will be tested using an MMRM analysis method. MMSE change from baseline (at 9 and 18 months visit) will be used as a dependent variable, and the model will include the fixed effects of tau status (AD++ or non-AD++), visit (categorical covariate), tau status-by-visit interaction, baseline MMSE score, baseline age, and baseline ANART score as continuous covariates. The null hypothesis is that the least squared mean contrast between AD++ and non-AD++ groups at month 18 visit equals zero. An unstructured covariance matrix will be used to model the within-subject variance-covariance. If the unstructured covariance structure matrix results in a lack of convergence, the following tests will be used in sequence: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, and compound symmetry covariance

structure. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

LS Mean change will also be graphed as the change in MMSE score across time by AD++ and non-AD++ groups.

8.6.1.3.3 Mixed Model Repeated Measures for Comparison of CDR-SB over time as a function of Tau scan visual interpretation

The same analyses will be performed as described in Section 8.6.1.3.2 with the substitution of CDR-SB for MMSE.

8.6.1.3.4 Mixed Model Repeated Measures for Comparison of FAQ over time as a function of Tau scan visual interpretation

The same analyses will be performed as described in Section 8.6.1.3.2 with the substitution of FAQ for MMSE.

8.6.1.3.5 Mixed Model Repeated Measures for Comparison of ADAS Cog-11 Score over time as a function of Tau scan visual interpretation

The same analyses will be performed as described in Section 8.6.1.3.2 with the substitution of ADAS Cog-11 for MMSE.

8.6.1.3.6 Mixed Model Repeated Measures for Comparison of DSST over time as a function of Tau scan visual interpretation

The same analyses will be performed as described in Section 8.6.1.3.2 with the substitution of Digital Symbol Substitute Test (DSST) for MMSE.

8.6.1.3.7 Mixed Model Repeated Measures for Comparison of Logical Memory Test-Delayed Recall over time as a function of Tau scan visual interpretation

The same analyses will be performed as described in Section 8.6.1.3.2 with the substitution of logical memory test-delayed recall score for MMSE.

8.6.1.3.8 Mixed Model Repeated Measures for Comparison of Logical Memory Test-Immediate Recall over time as a function of Tau scan visual interpretation

The same analyses will be performed as described in Section 8.6.1.3.2 with the substitution of logical memory test-immediate recall score for MMSE.

8.6.1.3.9 MMSE Clinically Meaningful Changes

A 3 point drop in MMSE at follow up visits will be considered as clinically meaningful change for this analysis. Time to first occurrence of this clinically meaningful event will be modeled using a Cox proportional hazard model by tau status as determined by flortaucipir scan, and the hazard ratio of AD++ rated subjects progressing to the event over non-AD++ rated subjects along with the 95% confidence interval will be provided. The Cox proportional hazard model will be adjusted for baseline age, ANART, and baseline MMSE score.

8.6.1.3.10 FAQ Clinically Meaningful Deterioration

The same analysis will be performed as described in Section 8.6.1.3.9 for FAQ. However, a change from baseline in FAQ score >= 3 will be used instead of the MMSE evaluation.

8.6.1.3.11 ADAS Clinically Meaningful Deterioration

The same analysis will be performed as described in Section 8.6.1.3.9 for ADAS Cog-11. However, a change from baseline in ADAS Cog-11 total score >= 4 will be used instead of the MMSE evaluation.

8.6.1.3.12 Prognostic Value of the Classification According to Amyloid and Tau Scans

Subjects will be sorted to these 3 groups, according to their flortaucipir and florbetapir scan visual reading results: AB+ AD++, AB+ AD+ (but not AD++) or AB+ AD-, and AB-. Then analyses as described in section 8.6.1.3.2 to 8.6.1.3.5 will be repeated, by replacing flortaucipir scan reading results with this 3-level group variable.

8.6.1.3.13 Relationship of Amnestic MCI and Tau among MCI Subjects

MCI subjects will be classified as amnestic MCI vs. non-amnestic MCI according to their logical memory delayed recall score: MCI subjects with baseline logical memory delayed recall score 8 or less (approximately 1 SD below mean value at baseline according to the exploratory cohort data) will be classified as amnestic MCI, otherwise will be classified as non-amnestic MCI. An MMRM model will be applied to explore the relationship of amnestic MCI and tau among MCI subjects, on the global cognitive and functional assessments including MMSE, CDR-SB, ADAS Cog-11 and FAQ. The model will have change from baseline in cognitive/functional assessments as dependent variable, and the model will include the fixed effects of tau status (AD++ vs. non-AD++), amnestic status

(amnestic + or amnestic -), visit (categorical covariate), amnestic-by-tau status interaction, amnestic-by-tau status-by-visit interaction, baseline assessment score, baseline age, and baseline ANART score as continuous covariates. The model building will follow details as described in section 8.6.1.3.2. The contrast will be set up to compare the MMSE change at 18 months between AD++, amnestic + vs. AD++, amnestic -; between AD++, amnestic + vs. non-AD++, amnestic +; between –non-AD++, amnestic + vs. –non-AD++, amnestic -; between AD++, amnestic - vs. –non-AD++, amnestic -.

LS Mean change will also be graphed as the change in MMSE score across time by these 4 groups (AD++amnestic+, AD++amnestic-, non-AD++amnestic+, and non-AD++ amnestic-).

8.6.1.3.14 Prognostic Value of Baseline Clinical Evaluations versus Tau Scan

Relevant baseline clinical and demographic information that are commonly used in clinical practice for patient's clinical stage assessment, including diagnosis (MCI or dementia), MMSE, age, education, and APOE E4 allele carrying status will be included in the following analyses to evaluate the prognostic values of these information in regards to the progression in CDR-SB values. Two sets of analyses will be performed:

8.6.1.3.14.1 Multivariate Regression Model

For this analysis, the CDR-SB change from baseline at 18 months will be used as dependent variable, and the baseline clinical/demographic information (diagnosis, MMSE, age, years of education, and E4 carrying vs. not) will be included as predictors. The partial R-squares from each predictor, associated F and P-value will be reported.

A separate model will be run by including majority tau scan visual reads (AD++ vs. non-AD++, as described in section 6.4.1.1), in addition to all those baseline clinical/demographic information. An identical analysis as above will be performed to assess the contribution of the majority tau scan visual reads, in addition to the baseline information.

8.6.1.3.14.2 Receiver Operating Characteristic Analysis

For this analysis, CDR-SB change at 18 months will be dichotomized as CDR-SB change 1 point or more vs. otherwise (described in section 6.4.1.2), and will be used as a dependent variable in a logistic regression model. Baseline clinical/demographic information as described in section 8.6.1.14.1 will be included in this logistic regression as predictors, along with the majority tau scan visual reads. Two receiver operating characteristic (ROC) curves will be generated from this model, and will be displayed in the same figure: ROC curve for model including all baseline clinical/demographic

information; ROC curve for model including both baseline clinical/demographic information and majority tau scan visual reads. Area under curve (AUC) values from both models will be contrasted, and the associated p-value for comparison will be reported. In addition, the sensitivity and specificity of majority tau scan visual reads alone will be determined, and its relative data point (sensitivity, 1-specificity) will be displayed along with the other two ROC curves in the same figure.

8.6.1.4 Additional Efficacy Analysis

8.6.1.4.1 Inter-rater Agreement

A Fleiss' kappa will also be calculated to assess the overall inter-reader agreement across all 5 readers for visual classification of flortaucipir scans. The Cohen's kappa coefficients to show pair-wise agreement between readers will also be calculated.
The P value testing will be presented if a nonzero correlation is observed.

8.6.1.4.2 Intra-rater Agreement

Twenty scans from the confirmatory cohort will be randomly selected for the evaluation of intra-rater agreement. These 20 scans will be assigned with two unique randomization codes each, and randomized into the reading sequence along with all other scans in order to be read twice by the same readers in a random sequence. To assess the intra-rater agreement, a Cohen's kappa statistics will be applied. A point estimation along with 95% CI will be reported for each reader.

8.6.1.5 Subgroup Analyses

8.6.1.5.1 Age group: Subjects will be grouped as age <=75 years or >75 years.

Primary and secondary analyses as described in section 8.6.1.1.1 and 8.6.1.2.1 will be repeated according to the age groups.

8.6.1.5.2 Sex

Primary and secondary analyses as described in section 8.6.1.1.1 and 8.6.1.2.1 will be repeated according to sex.

8.6.1.5.3 Diagnosis

Primary and secondary analyses as described in section 8.6.1.1.1 and 8.6.1.2.1 will be repeated according to enrollment diagnosis, that is, demented or MCI.

8.6.1.5.4 CDR Global Score Group

Subjects will be grouped to two groups according to baseline CDR global score: CDR global score $\geq$ 1, and otherwise. Primary and secondary analyses as described in section 8.6.1.1.1 and 8.6.1.2.1 will be repeated according to this baseline CDR global score group.

8.7 Analysis of Safety

8.7.1 Extent of Exposure and Compliance to Study Treatment

The total dose administered (mCi) of flortaucipir and florbetapir F 18 will be summarized using descriptive statistics (n, mean, SD, median, min, max, 25th, and 75th pct). All exposure data will be presented in listings.

Because this is a study with only one bolus of study medication per imaging agent, compliance will not be summarized.

8.7.2 Adverse Events

All AE summaries will be based on the set of TEAEs only. TEAEs will be summarized alphabetically by SOC and preferred term; a subject will only be counted once per SOC and once per preferred term. Subject counts and percentages will be presented for the following summaries:

1. All TEAEs by system organ class (SOC) and preferred term;
2. All TEAEs by preferred term (in order of descending frequency);
3. All TEAEs by relationship to study drug, SOC, and preferred term;
4. All TEAEs by relationship to protocol procedure, SOC and preferred term;
5. All TEAEs by severity, SOC and preferred term

For the summary of TEAEs by severity, if a subject has multiple events occurring in the same SOC or same preferred term, the event with the highest severity will be counted.

TEAEs by relationship to study drug and protocol procedure will be summarized as Related vs. Not Related. If a subject has multiple events occurring in the same SOC or same preferred term, the related event will be summarized.

Listings will be presented by subject for all TEAEs as well as for Serious TEAEs, TEAEs associated with death, and TEAEs associated with study discontinuation. Listings will

also present adverse events relative to the first dose and relative to the flortaucipir injection.

8.7.3 Clinical Laboratory Evaluations

Laboratory test values from the flortaucipir imaging session at each time point and for change from baseline to end of study will be displayed using summary statistics (n, mean, SD, median, min, max, 25th pct, and 75th pct). This will be calculated within each diagnostic group and on all subjects. Potentially clinically significant laboratory results will be displayed using frequency and percentage of subjects with the result.

All clinical laboratory data will be presented in listings. Within each listing, laboratory values outside the normal ranges will be flagged as either high (H) or low (L). In addition, shift tables will be presented to display the shift in the normal range categories (L, normal (N), H) from baseline to the final evaluation. Baseline is defined in section 6.3.

8.7.4 Other Observations Related to Safety

8.7.4.1 Vital Signs

Observed vital sign measurements as well as changes from baseline will be summarized using descriptive statistics (n, mean, SD, median, min, max, 25th pct, and 75th pct) for each time point across all subjects and by diagnostic group. At each post-baseline assessment, a paired t-test will be used to test the hypothesis that the change from baseline is not statistically different than zero, for all subjects summary only. Clinically significant vital signs will be highlighted.

All vital signs data will be presented in listings. Baseline is defined in section 6.3.

8.7.4.2 Electrocardiogram

The ECG measures (QTc-B, QTc-F, QT, RR, PR, and QRS) from the flortaucipir imaging session will be listed and summarized with descriptive statistics (n, mean, SD, median, min, max, 25th pct, 75th pct) at each time point by diagnostic group. At each post-baseline assessment, a paired t-test will be used to test the hypothesis that the change from baseline is not statistically different than zero. This will be calculated within each diagnostic group and on all subjects. Potentially clinically significant ECG results will be displayed using frequency and percentage of subjects with the result.

The number and percentage of subjects with normal and abnormal ECG results, as judged by the investigator, will be displayed and ECG changes from screening will be calculated.

8.8 Pharmacodynamics

No pharmacodynamics analyses are planned for this study.

9 COMPUTER SOFTWARE

All analyses will be performed by Chiltern International Inc. using Version 9.3 or later of SAS® software. All summary tables and data listings will be prepared utilizing SAS® software.

For continuous variables, descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, maximum, 25th pct, and 75th pct) will be generated. The standard operating procedures (SOPs) of Chiltern International Inc. will be followed in the creation and quality control of all data displays and analyses.

10 REFERENCES

Albert, M. S., DeKosky, S. T., Dickson, D., et al. "The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and Alzheimer's Association workgroup." The Alzheimer's Association. Alzheimer's and Dementia, 1-10, 2011.

Burack, M.A., Hartlein, J., Flores, H.P., Taylor-Reinwald, L., Perlmutter, J.S., Cairns, N.J. "In vivo amyloid imaging in autopsy-confirmed Parkinson disease with dementia". Neurology. 2010;74(1):77-84.

Chien, D.T., Bahri, S., Szardenings, A.K., Walsh, J.C., Mu, F., Su, M.Y., Shankle, W.R., Elizarov, A., Kolb, H.C., "Early clinical PET imaging results with the novel PHF-tau radioligand [18F]-T807." J Alzheimers Dis, 2013 Jan 1l34(2):467-68

Clark, C.M., Pontecorvo, M.J., Beach, T.G., Bedell, B.J., Coleman, R.E., Doraiswamty, P.M., Fleisher, A.S., Reiman, P.E.M., Sabbagh, M.N., Sadowsky, C.H., Schneider, J.A., Arora, A., Carpenter, A.P., Flitter. M.L., Joshi, A.D., Krautkramer, M.J., Lu, M., Mintun, M.A., Skovronsky, D.M. "Florbetapir PET for Detection of Amyloid Neuritic Plaques, Comparison to Neuropathology at Autopsy: A Prospective Cohort Study." The Lancet Neurology, 2012; 11: 669–78.

Clark, C.M., Schneider, J.A., Bedell, B.J., et al. "Use of florbetapir-PET for imaging beta-amyloid pathology". JAMA. 2011;305(3):275-283.

Dickson, T.C., Saunder, H.L., Vickers, J.C. "Relationship between apolipoprotein E and the amyloid deposits and dystrophic neuritis of Alzheimer's disease." Neuropathol Appl Neurobiol. 1997; (23):483-491.

Dubois, B., Feldman, H.H., Jacova, C., et al. “Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS-ADRDA criteria.” Lancet Neurol. 6:734-46 Review, 2007.

Dubois B., Feldman H.H., Jacova C., et al. “Revising the definition of Alzheimer's disease: a new lexicon”. Lancet Neurol. 2010;9(11):1118-1127.

Duyckaerts, C., Brion, J.P., Hauw, J.J., Flament-Durand, J. “Quantitative assessment of the density of neurofibrillary tangles and senile plaques in senile dementia of the Alzheimer type. Comparison of immunocytochemistry with a specific antibody and Bodian’s protargol method.” Acta Neuropathol. 1987;(7):129-135.

Folstein, M.R., Folstein, S.E., and McHugh, P.R. “Mini Mental State: A practical method for grading the cognitive status of patients for the clinician.” Journal of Psychiatric Research, 12: 189-198, 1975.

Hyman, B.T., Phelps, C.H., Beach, T.G., et al. “National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease”. Alzheimers Dement. 2012;8(1):1-13.

Jack, C.R., Knopman, D.S., Jagust, W.J., Shaw, L.M., Aisen, P.S., Weiner, M.W., Petersen, R.C., Trojanowski, J.Q. “Hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade.” Lancet Neurol 9:119-128, 2010.

Kantarci, K., Lowe, V.J., Boeve, B.F., Weigand, S.D., Senjem, M.L., Przybelski, S.A., et al. “Multimodality imaging characteristics of dementia with Lewy bodies”. Neurobiol Aging 2011: Oct 20. [Epub ahead of print].

Leinonen, V., Alafuzoff, I., Aalto S., Suotunen, T., Savolainen, S., Nagren, K., et al. “Assessment of beta-amyloid in a frontal cortical brain biopsy specimen and by positron emission tomography with carbon 11-labeled Pittsburgh Compound B”. Arch Neurol 2008; 65(10):1304–1309.

McKhann, G.M., Knopman, D.S., Chertkow, H., et al. “The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease”. Alzheimers Dement. May 2011;7(3):263-269.

Price, J.L., Morris, J.C. ”Tangles and plaques in nondemented aging and “preclinical” Alzheimer’s disease.” Ann Neurol 45:358–368, 1999.

Sojkova J., Driscoll I., Iacono D., Zhou Y., Codispoti K., Kraut M., et al. “In vivo fibrillar beta-amyloid detected using [11C] PiB positron emission tomography and neuropathologic assessment in older adults”. Arch Neurol 2011;68(2):232–240.

Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., Iwatsubo, T., Jack, C.R., Jr., Kaye, J., Montine, T.J., Park, D.C., Reiman, E.M., Rowe, C.C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M.C., Thies, B., Morrison-Bogorad, M., Wagster, M.V., Phelps, C.H. 2011. “Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease”. Alzheimers Dement 7(3), 280-92.

Wechsler Adult Intelligence ScaleFRevised. San Antonio, TX: Psychological Corporation, 1981.

Wong, D.F., Rosenberg, P.B., Zhou, Y., et al. “In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (florbetapir [corrected] F 18)”. J Nucl Med. 2010;51(6):913-920.

Xia, C.F., et al. “[18F]T807, a novel tau positron emission tomography imaging agent for Alzheimer’s disease,” Alzheimers Dement. 2013, 1-11

11 APPENDICES

11.1 Appendix 1 - Derivation of Clinical Dementia Rating Score

The global CDR was derived from the scores in each of 6 categories ("box scores"). Memory (M) was considered the primary category and all others were secondary.

- CDR = M if at least 3 secondary categories were given the same score as M.
- Whenever 3 or more secondary categories were given a score greater or less than M, CDR equaled the score of the majority of secondary categories on whichever side of M had the greater number of secondary categories.
- When 3 secondary categories were scored on one side of M and 2 secondary categories were scored on the other side of M, CDR = M.
- When M = 0.5, CDR = 1 if at least 3 of the other categories were scored 1 or greater. If M = 0.5, CDR could not be 0; it could only be 0.5 or 1. If M = 0, CDR = 0, unless there was impairment (0.5 or greater) in 2 or more secondary categories, in which case CDR = 0.5.

Although applicable to most AD situations, these rules do not cover all possible scoring combinations. Unusual circumstances occur occasionally in AD and may be expected in non-Alzheimer's dementia as well. These circumstances were scored as follows:

- With ties in the secondary categories on one side of M, the tied scores closest to M for CDR were chosen (eg, M and another secondary category = 3, 2 secondary categories = 2, and 2 secondary categories = 1; CDR = 2).
- When only 1 or 2 secondary categories were given the same score as M, CDR = M as long as no more than 2 secondary categories were on either side of M.
- When M = 1 or greater, CDR could not be 0; in this circumstance, CDR = 0.5 when the majority of secondary categories were 0.

11.2 Appendix 2 – Laboratory Results – Potentially Clinically Significant Criteria

Parameter (Full Names)	Parameter (Short Names)	Reporting Unit	Low	High	SI Unit	Conversion Factor
Hematology						
Hematocrit	HCT	%	Male ≤ 37% Female ≤ 32%	NA	L/L	0.01
Hemoglobin	Hgb	g/dL	Male ≤ 11.5 Female ≤ 9.5	NA	g/L	10
White blood cell	WBC	10^3/mm3	≤2.8	≥16.0	GI/L	1
Platelets	PLT	10^3/mm3	≤ 75	≥ 700	GI/L	1
Mean corpuscular hemoglobin	MCH	pg/cell	NA	NA	pg/cell	1
Mean corpuscular hemoglobin concentration	MCHC	g/dL	NA	NA	g/L	10
Mean corpuscular volume	MCV	fl	NA	NA	fl	1
Red blood cell	RBC	10^6/mm3	≤ 3.5	NA	TI/L	1
Differential						
Bands or (Band neutrophil (stab))	BAND	%	NA	≥ 10%	%	1
Basophil (absolute)	Baso.	10^3/mm3	NA	≥ 0.4	GI/L	1
Basophil (%)	Baso.	%	NA	≥ 5%	%	1
Lymphocytes (absolute)	lymphs	10^3/mm3	≤ 0.5	≥ 4.5	GI/L	1
Lymphocytes (%)	lymphs	%	≤ 10%	≥ 80%	%	1
Monocytes (absolute)	MONO	10^3/mm3	NA	≥ 1.5	GI/L	1
Monocytes (%)	MONO	%	NA	≥ 20%	%	1
Neutrophils (absolute)	NEUT	10^3/mm3	≤ 1.0	NA	GI/L	1

Parameter (Full Names)	Parameter (Short Names)	Reporting Unit	Low	High	SI Unit	Conversion Factor	SI Low	SI High
Neutrophils (%)	NEUT	%	≤ 15%	≥ 90%	%	1	≤ 15%	≥ 90%
Eosinophils (absolute)	EOS	10^3/mm3	NA	≥0.7	GI/L	1	NA	≥0.7
Eosinophils (%)	EOS	%	NA	≥ 10%	%	1	NA	≥ 10%
Chemistry								
Heart Function								
Aspartate transaminase	AST	IU/L	NA	≥3 x ULN	U/L	1	NA	≥3 x ULN
Lactic dehydrogenase	LDH	U/L	NA	≥3 x ULN	U/L	1	NA	≥3 x ULN
Liver Function								
Alkaline Phosphatase	ALP	IU/L	NA	≥ 3 x ULN	U/L	1	NA	≥ 3 x ULN
Alanine transaminase	ALT	IU/L	NA	≥3 x ULN	U/L	1	NA	≥3 x ULN
Total Bilirubin	TBili	mg/dL	NA	≥ 2.0	umol/L	17.1	NA	≥34.2
Gamma-glutamyltransferase	GGT	IU/L	NA	≥ 3 x ULN	U/L	1	NA	≥ 3 x ULN
Total Protein	TPRO	g/dL	≤ 4.5	≥ 9.0	g/L	10	≤ 45	≥ 90
Albumin	ALB	g/dL	≤ 2.5	≥ 6.5	g/L	10	≤ 25	≥ 65
Renal Function								
Blood urea nitrogen	BUN	mg/dL	NA	≥ 30	mmol/L	0.357	NA	≥10.7
Creatinine	CREAT	mg/dL	NA	≥ 2.0	µmol/L	88.4	NA	≥176.8
Lipid Chemistry								
Total cholesterol	chol	mg/dL	NA	≥ 300	mmol/L	0.0259	NA	≥ 7.77
Triglycerides	TG	mg/dL	NA	≥ 300	mmol/L	0.0113	NA	≥3.39
Electrolytes								
Chloride	Cl	MEq/L	≤ 90	≥ 112	mmol/L	1	≤ 90	≥ 112

Parameter (Full Names)	Parameter (Short Names)	Reporting Unit	Low	High	SI Unit	Conversion Factor	SI Low	SI High
Potassium	K	MEq/L	≤ 3.0	≥ 5.8	mmol/L	1	≤ 3.0	≥ 5.8
Sodium	Na	MEq/L	≤ 130	≥ 150	mmol/L	1	≤ 130	≥ 150
Bicarbonate	Bicarb	MEq/L	NA	NA	mmol/L	1	NA	NA
Magnesium	MG	mg/dL	<1.0	>4.4	mmol/L	0.411	<0.41	>1.81
Metabolic								
Calcium	Ca	mg/dL	≤ 7.0	≥ 15.5	mmol/L	0.25	≤1.75	≥3.88
Phosphorous	P	mg/dL	<1.0	>10.0	mmol/L	0.323	<0.32	>3.23
Blood Glucose	BGL	mg/dL	≤ 50 (fasting)*	≥ 180 (fasting)*	mmol/L	0.0555	≤2.8 (fasting)*	≥10.0 (fasting)*
Uric Acid	URICA	mg/dL	NA	Male ≥ 10.5 Female ≥ 8.5	µmol/L	59.48	NA	Male ≥ 624 Female ≥ 505
Urinalysis								
(Urine) protein	UPROT	0 to 3+	NA	Change≥2	0 to 3+	1	NA	Change≥2
(Urine) glucose	UGL	0 to 3+	NA	Change≥2	0 to 3+	1	NA	Change≥2
(Urine) hemoglobin	UHgb	0 to 3+	NA	Change≥2	0 to 3+	1	NA	Change≥2
(Urine) white blood cells	UWBC	0 to 3+	NA	Change≥2	0 to 3+	1	NA	Change≥2
(Urine) white blood cells (Microscopic test)	UWBC	WBC/hpf	NA	≥20	WBC/hpf	1	NA	≥20
(Urine) red blood cells	URBC	0 to 3+	NA	Change≥2	0 to 3+	1	NA	Change≥2
(Urine) red blood cells (Microscopic test)	URBC	RBC/hpf	NA	≥10	RBC/hpf	1	NA	≥10
Specific gravity	USpG	0 to 3+	NA	NA	0 to 3+	1	NA	NA
Specific gravity (Microscopic test)	USpG		≤ 1.005	NA			≤ 1.005	NA

11.3 Appendix 3 – Vital Signs and ECGs – Potentially Clinically Significant Criteria

Parameter (Full Names)	Parameter (Short Names)	Reporting Unit	Reporting Format	Potentially Clinically Significant Criteria	
				Low	High
Vital Sign					
Systolic blood pressure	SBP	mmHg	3.0	≤ 90 and ≥ 20 decrease	≥ 180 and ≥ 20 increase
Diastolic blood pressure	DBP	mmHg	3.0	≤ 50 and ≥ 15 decrease	≥105 and ≥ 15 increase
Pulse rate	PULSE	bpm	3.0	≤ 50 and ≥ 15 decrease	≥ 120 and ≥ 15 increase
Body Temperature	TEMP	C°	3.1	NA	≥ 1.11 C° increase ≥ 2 F ° increase
Respiration rate	RESP	#/min	3.1	≤ 10	--
Weight	WEIGHT	kg	4.1	≥ 7% decrease	≥ 7% increase
QTcB					> 500 msec or CfB > 60 msec
QTcF					> 500 msec or CfB > 60 msec

Cfb=Change from Baseline