18F-AV-1451-A05 SAP Exploratory 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

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Exploratory (First Phase)
Statistical Analysis Plan

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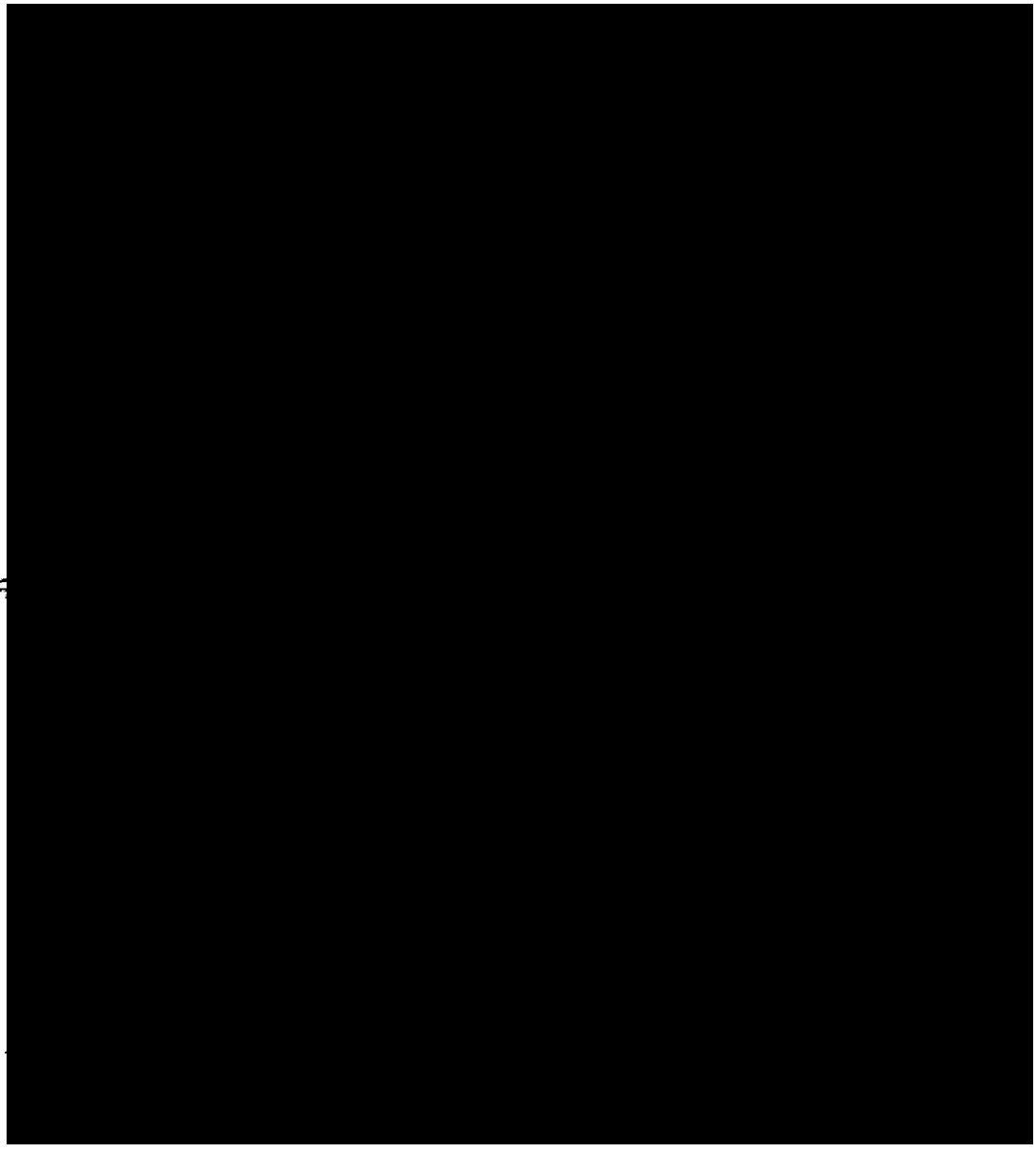
SIGNATURE



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1 1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

AAL VOI	automatic anatomical labeling volume of interest
AB	amyloid-ß
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
CDR	Clinical Dementia Rating
cm	centimeters
CN	cognitively normal
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	flurodeoxyglucose
H	high
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
LP	lumbar puncture
LS	least squares
max	maximum
MBq	megabecquerel
mCi	millicuries

MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
mSv	millisievert
n	number of subjects
N	normal
nM	nanomolar
OCN	old cognitively normal
OSU TBI-ID	Ohio State University Traumatic Brain Injury Identification Method
PET	positron emission tomography
ROI	region of interest
rsf	resting state functional
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
YCN	young cognitively normal

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 (AB) 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 AB 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 (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, AB positive, or tau and AB negative tissue. Scatchard analysis based on this heterogeneous autoradiography assay

yielded an estimated dissociation constant (K_d) of 15nM. A saturation binding experiment using purified Paired Helical Fragment Tau isolated brains of AD patients yielded a K_d value of 0.7 nanomolars (nM).

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 AD. Additionally, this protocol will investigate correlations between Flortaucipir 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

This study will be conducted in two phases, an exploratory phase and a confirmatory phase. This statistical analysis plan is for the exploratory phase of this study. The exploratory phase of this study will be comprised of a cross-sectional component and a longitudinal component.

3.1 Exploratory Phase, Cross-sectional Objectives

The primary objective of the cross-sectional component is:

- To compare Flortaucipir imaging results in subjects with AD to subjects with MCI and cognitively healthy older individuals

The secondary objective of the cross-sectional component is:

- To establish a database of cognitively healthy individuals to show the spectrum of Flortaucipir imaging results in cognitively healthy individuals across a range of age strata

Exploratory objectives of the cross-sectional component are:

- To determine whether greater degrees of cognitive impairment correlate with higher Flortaucipir uptake in subjects with an amyloid positive status
- To explore whether tests of specific cognitive domains correlate with regional Flortaucipir uptake
- To explore the relationships between Flortaucipir uptake and biomarkers of neurodegeneration and neurological disease (cerebrospinal fluid (CSF) markers including tau, phospho-tau and beta-amyloid (AB), genetic markers, PET amyloid imaging, and brain atrophy assessed by volumetric magnetic resonance imaging (MRI))
- To expand the Flortaucipir safety database

3.2 Exploratory Phase, Longitudinal Objectives

The primary objective of the longitudinal component is:

- To assess the rate of change of tau deposition as measured by Flortaucipir uptake over time

The exploratory objectives of the longitudinal component are:

- To explore associations between changes in Flortaucipir uptake in the brain and clinical and functional measures, as well as, biomarkers of neurodegeneration and neurological disease (CSF markers including tau, phospho-tau and beta-amyloid (AB), genetic markers, PET amyloid imaging, and brain atrophy assessed by volumetric MRI)
- To expand the Flortaucipir safety database

4 STUDY DESIGN

4.1 General Design

This study is an open label, multicenter Phase 2 study. This study is conducted in two phases, an exploratory (first) phase and complimentary (second) phase. The study will enroll cognitively healthy volunteers, subjects with mild cognitive impairment (MCI) and subjects with Alzheimer's disease. Approximately 230 subjects will be enrolled in the study: 80 cognitively healthy volunteers (20 subjects who will be ≥20 to ≤40 years of age, and 60 subjects who will be ≥ 50 years of age), 80 subjects with MCI, 70 subjects with AD (60 subjects with a Mini-Mental State Examination (MMSE) ≥20, and 10 subjects with an MMSE > 10 and < 20). For the 60 cognitively healthy volunteers ≥ 50 years of age, these subjects will be distributed across age deciles (50-59, 60-69, 70-79 and >80).

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. Some subjects, who are ≥ 50 years of age, will have the option to also participate in cerebrospinal fluid (CSF) collection by lumbar puncture (LP).

Subjects who are ≥ 50 years of age will return for have a follow-up visits at 9 (+/-2) months 18 (+/-2) following the initial Flortaucipir scan. Cognitive assessments and updates to concomitant medications and medical history will be collected at each follow-up visit. Subjects will also have follow-up Flortaucipir scans and MRI, including both volumetric and

standard clinical sequences. A sub-set of subjects may have the option to have an additional resting state functional (rsf) MRI sequence scan in addition to the volumetric and standard clinical sequences at both the screening MRI and follow-up MRIs. Subjects or their designated decision maker will be contacted by phone at 5 and 14 months following the initial Flortaucipir scan to collect updated concomitant medications and medical history.

Florbetapir F 18 PET Imaging Session:

For the florbetapir F 18 PET imaging session, an intravenous (IV) catheter will be placed for administration of 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 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 adverse events prior to injection and prior to discharge from the imaging center. Subjects who experience an adverse event 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(s):

For the Flortaucipir PET imaging session(s), 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 adverse event 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). Subjects will be categorized into groups of AD, MCI, and cognitively normal (CN). Comparing the mean standardized uptake value ratios (SUVr) from each category will support the primary objective of detecting a significant difference of Flortaucipir imaging results among diagnostic groups. CN subjects will also be further stratified by age. This stratification will establish a database of imaging results to collect data on the accumulation of brain tau protein across age ranges. 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 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 except for young cognitive normal (YCN) subjects will receive a single IV bolus administration target dose of 370 MBq (10 mCi) of Flortaucipir injection at each of the baseline, 9 months, and 18 months visits. YCN subjects will only receive a single IV bolus administration of Flortaucipir injection with a target dose of 370 MBQ (10 mCi) at baseline visit.

4.4 Blinding

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

For the exploratory (first) phase, Avid personnel will not be blinded to longitudinal cognitive data nor to the PET scans (both florbetapir and Flortaucipir). The blinding of imaging and/or clinical information at confirmatory phase will be discussed at confirmatory SAP.

4.5 Determination of Sample Size

A total of 230 subjects (80 cognitively healthy volunteers, 80 MCI and 70 AD) will be enrolled in the Exploratory Phase of this study. To explore the Flortaucipir SUVr values across age strata among cognitively healthy subjects, these subjects will be divided into 5 age groups as 20-40 years old, 50-59 years old, 60-69 years old, 70-79 years old and 80 years old or above. There will be 15 subjects in each of the 50 or older age groups and about 20 subjects from age group 20-40 years old. From a preliminary analysis of study T807000, the standard deviation (SD) of SUVr from combination region of interest (ROI) was 0.06 for subjects with low probability of AD. Therefore assuming a 0.06 SD, a sample of 15 subjects will give an approximately 90% probability to observe a 95% confidence interval as accurate as +/-0.04 around the point estimation.

From previous studies, the amyloid positive rate is approximately 50% among MCI patients and approximately 80% from AD subjects. Therefore 80 MCIs and 70 ADs will likely result in 40 amyloid positive MCIs and 56 amyloid positive ADs. Also from study T807000, the combination ROI SUVr difference between CN and AD was 0.39, with a pooled SD of 0.27. Assume a pooled SD of 0.30, a sample of 60 CNs and 56 amyloid positive ADs will give a 90% power to detect a 0.18 difference between the CN and AD groups.

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 statistical analysis plan.

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 exploratory (first) 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

Longitudinal Component
Exploratory (First) 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
ECG		X[n]		X[n]
Vital Signs		X[o]		X[o]
Safety Labs		X[p]		X[p]
Urine Pregnancy test[q]		X		X
MMSE		X		X
ADAS-Cog 11[r]		X		X
Neuropsych battery, including CDR[r]		X		X
MRI of the brain[r]		X		X
PET Brain Scan		X		X
Follow-up Phone Call[s]		X		X
Evaluation by a physician		X		X
Adverse Events		X		X
Serious Adverse Events		X		X

The First and Second Longitudinal Follow-up Visits will be performed over several days.

n. 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. One will be obtained at the end of imaging day

o. Vital signs include pulse rate, respiratory rate, supine blood pressure, temperature and weight

p. Blood and urine samples will be collected prior to administration of ^{18}F-AV-1451 Injection and at the end of the imaging day.

q. For women of childbearing potential, a negative urine pregnancy test must be obtained within 24 hours prior to ^{18}F-AV-1451 injection.

r. ADAS-Cog 11, Neuropsych battery, and MRI can be performed +/- 30 days of the ^{18}F-AV-1451 scan and within 30 days of each other. Assessments should be performed within the specified window of 9 (+/-2) months or 18 (+/-2) months.

s. Between 2 or 3 business days of the imaging day

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

No window algorithm is being used for this study.

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 (with the exception of the MRI if previously performed). 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), electrocardiogram (ECG), safety labs (hematology, chemistry, and urinalysis);
- Serum beta-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;
- Optional CSF collection by LP
- A physician will see the patient during the screening visit.

For efficacy analyses, baseline assessments may be performed at the screening visit or +/- 30 days of the initial Flortaucipir Imaging Visit.

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);
- Pfeffer Functional Activities Questionnaire (FAQ). For the MCI and AD groups only.

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

addition, age will be categorized into 5 groups: 20-40 years, 50-59 years, 60-59 years, 70-79 years, and 80 years or older.

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 safety analyses (vital signs, lab and ECG), baseline will be defined as the last assessment recorded on or prior to the start of Flortaucipir.

Baseline for ECGs will be calculated as the average of the two ECGs administered on the imaging day 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 Quantitative assessment of images for Flortaucipir (SUVr based)

For the Flortaucipir image, standard uptake value ratios (SUVr) will be calculated to estimate tau load globally and for each individual region. For global assessment, a target region derived statistically with a Multiblock Barycentric Discriminant Analysis (MUBADA) method will be used; at individual region level, VOIs determined in the AAL atlas masked to exclude white matter and CSF for parietal, temporal, occipital, anterior hippocampal parahippocampal and fusiform gyri will be applied. For all SUVr value calculations, a selected white matter region derived using a parametric estimated signal reference intensity (PERSI) method will be used as reference region.

6.4.1.2 Qualitative assessment for Flortaucipir and Diagnostic Performance

At the exploratory phase, the baseline flortaucipir scan images will be visually interpreted by Avid's imaging experts. The scans will be classified as either

- AD pattern (AD+)
- AD pattern and likely to progress (AD++)
- Not consistent with an AD pattern (AD-)

AD++ also is referenced as Tau+ in the SAP, and the rest is referenced as Tau-.

6.4.2 Secondary Efficacy Variables

6.4.2.1 Amyloid Beta Status Based on Florbetapir

Florbetapir F 18 images will be assessed by expert readers blinded to the diagnostic group for the subjects. The images will then be classified as either AB+ (amyloid positive) or AB- (amyloid negative). For images read by more than one reader, the majority or consensus read will be used for each subject.

6.4.2.2 Quantitative Imaging for Florbetapir (SUVr based)

For the Florebetapir 18 F image, the global cortical average SUVr will be calculated as the average across these six target brain regions: the medial frontal cortex, temporal cortex, parietal cortex, posterior cingulate cortex, anterior cingulate cortex and the precuneus with entire cerebellum as a reference region.

6.4.2.3 Cognitive and Functional Assessments

Except for Clinical Dementia Rating (CDR) scale, cognitive assessments will be performed at screening or baseline, at follow-up visits (9 (+/- 2) months, and 18 (+/- 2) months) during the study. CDR scales will be performed at 9 months and 18 months visits only. 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 instrument is divided into 2 sections. The first section measures orientation, memory, and attention. The maximum score for the first section is 21. The second section tests the ability of the patient to name objects, follow verbal and written commands, write a sentence, and copy figures. The maximum score for the second section is 9. The range for the total MMSE score is 0 to 30, the sum of each correct answer, with higher scores indicating better cognition.

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.

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.

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.

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 a 150 seconds and Part B with a maximum of is a 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.

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 obtained based on how much of the story is correct. Higher scores indicate better cognition.

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.

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.

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.

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 from 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.

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 angel 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.

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 informant to rate 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 cognitive impairment.

6.4.2.3.1 Clinical Meaningful Changes

Clinically meaningful changes will be defined by categorizing the change in psychometric scores, as follows:

1. a 3 point or more drop in MMSE relative to baseline;
2. a 4 point or more increase in ADAS Cog 11 relative to baseline;
3. a 3 point or more increase in FAQ relative to baseline ;
4. a 1 point or more increase in CDR SB relative to 9 month ;
5. a 12 point or more increase in ADAS+FAQ composite relative to baseline
6. CDR global score will be categorized as decreasing; stay the same; increasing from 9 month.

6.4.3 Additional Efficacy Variables

6.4.3.1 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.

6.4.3.2 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.

6.4.3.3 MRI Scan of the Brain

MRI, including both volumetric and standard clinical sequences, will be conducted at each tau scan visit. Volumetric measurements, including the whole brain, grey matter, ventricle, and hippocampus will be performed. The brain volumes will be normalized for analysis purpose.

6.4.3.4 Optional Cerebrospinal fluid (CSF) collection by Lumbar Puncture (LP)

Some subjects (depending on site participation) who are □50 years of age who qualify for the study will be offered to consent for optional CSF collection by LP. The LP should be performed at least 48 hours apart from the PET imaging sessions and should be performed within +/- 60 days of the initial Flortaucipir Imaging Visit. Each LP will be done by a qualified physician who is experienced in performing the procedure. Subjects, or their designated decision maker, will call the investigator to report any adverse events associated with the LP procedure. The CSF will be assessed for biomarkers of neurodegeneration and neurological disease (tau, phosphor-tau and beta-amyloid (AB)).

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 using the total administered dose at each scan visit for Flortaucipir and Florbetapir F 18 injection respectively.

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 the end of observation windows defined as following: the TEAE window for Flortaucipir will be from injection of Flortaucipir until 48 hours post Flortaucipir injection. For florbetapir F 18, the TEAE window will be from injection of florbetapir F 18 until 48 hours post florbetapir injection. The injection of florbatapir and flortaucipir dosages will be at least 48 hours apart. Trial-emergent AEs are undesirable experiences, signs or symptoms happened after subjects' enrollment to this trial but before the exploratory phase imaging sessions, or between the florbetapir and flortaucipir sessions but outside the 48 hour windows following the administrating of Flortaucipir or Florbetapir F 18 injection. These will be recorded on the AE page of the electronic case report form (eCRF). Any event happens during study visits will be captured in medical history form, unless the site physicians consider they are related to the study drugs.

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, are 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 for each of the scan sessions, including the makeup scan session if the original planned scan session fail. 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 1 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 2 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 ECG will be recorded at screening. At the Flortaucipir 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 2 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

All values will be summarized by the four diagnostic groups: young cognitively normal (YCN) subjects (healthy volunteers >=20 years of age and <= 40 years of age), old cognitively normal (OCN) subjects (healthy volunteers >=50 years of age), patients with AD, patients with MCI, and overall. 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

Not applicable for the primary analyses.

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 longitudinal follow up cognitive measurements, or flortaucipir SUVr 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

For the exploratory (first) phase analysis, no adjustment for multiplicity will be performed when analyzing the differences among diagnostic groups.

7.7 Active-Control Studies Intended to Show Equivalence

Not applicable to this study.

7.8 Examination of Subgroups

Flortaucipir SUVr values will be further investigated stratified by age group (>=75 vs. <75).

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. Subjects will be considered to have completed the study if they have completed all three flortaucipir imaging sessions and clinical visits.

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 who signed inform consent and have data captured in the clinical database. Disposition information will be summarized using the enrolled population.

8.3.2 Safety Population

The safety population will consist of all subjects that received either an injection of flortaucipir or florbetapir dosage. The summary of safety will be defined according to the study drugs subjects received: for the safety summary of flortaucipir scans, the safety population consist of all subjects that received an injection of Flortaucipir;for the safety summary of florbetapir scan, the safety population is defined as all subjects that received and injection of Florbetapir injection.

All baseline and safety endpoints will be summarized and efficacy endpoints listed using the safety population.

8.3.3 Efficacy Population

The efficacy population will include all subjects from safety population that received an injection of Flortaucipir plus valid flortaucipir imaging data available (either visual reads or SUVr).

All analyses involving amyloid imaging outcomes will be based on the efficacy population. For flortaucipir SUVr related analyses, any scans deemed to be unquantifiable due to technical reasons will be excluded from analyses.

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 diagnostic 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 *Exploratory Phase, Cross-sectional Analysis*

8.6.1.1 Analysis of Primary Efficacy Variable

Quantitative Assessment of Images

A one-way ANOVA will be used to compare the mean flortaucipir SUVr values between diagnostic groups (AD, MCI, and OCN). The F test in the corresponding ANOVA model

will used to test for the difference in SUVr values among all diagnostic groups while contrasts within the ANOVA model will be used to perform pairwise comparisons between diagnostic groups.

This analysis will be performed on the global cortical average SUVr (ie, MUBADA SUVr) as well as the SUVr for each brain region.

Due to the obvious age difference, YCN group will not be included in the analysis as described above. A two sample t-test between OCN and YCN will be performed instead, to evaluate the differences between OCN and YCN subjects.

An analysis of covariance (ANCOVA) will be used to compare the mean SUVr values between diagnostic groups (AD, MCI, and OCN) by amyloid beta status (AB+, AB-), and compare mean SUVr values between amyloid beta status by diagnosis groups while adjusting for age as a continuous covariate. The least square mean estimates will be provided, and proper contrast will be set to compare the LS mean differences within the ANCOVA models. This analysis will be performed on the global cortical average SUVr (MUBADA SUVr) as well as the SUVr for each brain region.

Descriptive statistics for overall SUVr values for each brain region will be displayed for each diagnostic group as well as by Amyloid beta status (AB+, AB-).

Scatter plots will be generated for Flortaucipir SUVr versus diagnostic groups (AD, MCI, OCN, and YCN) and Amyloid Beta status (AB+/AB-) across all subjects.

Qualitative Assessment of Images

Flortaucipir scan visual interpretation results, as explained in section 6.4.1.2 will be summarized by clinical diagnosis and by amyloid status as decided by visual interpretation of florbetapir scans. Except for YCN, the overall association of frequency by diagnosis groups and by amyloid status will be tested with a Mantel-Haenszel test. Pearson's Chi-squared test, or Fisher's exact test when appropriate, will be used to test for the general association of tau scan interpretation results by amyloid status, and tau scan interpretation results by clinical diagnosis respectively.

8.6.1.2 Analysis of Second Efficacy Variable

Age correlation with SUVr

Pearson's correlation coefficient will be used to determine the correlation of age with mean SUVr from cognitively healthy individuals.

Descriptive statistics will be performed according to cognitively healthy subject category and by the age groups. Subjects are divided to the age group of: YCN 20-40, OCN 50-59, OCN 60-69, OCN 70-79, and OCN >=80.

Box plot (including individual data points plotted) for overall SUVr will be generated for all cognitively healthy subject categories by age group: YCN 20-40, OCN 50-59, OCN 60-69, OCN 70-79, and OCN >=80.

8.6.1.3 Exploratory Analyses

8.6.1.3.1 Correlations between Flortaucipir uptake and cognitive impairment

This analysis will be limited to the subjects with an amyloid beta positive (AB+) status. Partial Pearson's correlation analysis adjusted for age will be conducted.

The correlation analyses will be conducted between these measurements: baseline MUBADA SUVr versus baseline ADAS total, MMSE, and FAQ scores.

To visually explore the cognitive domain relationship with flortaucipir uptake, scatter plots will be generated between the variables as described above.

8.6.1.3.2 Correlations between Flortaucipir SUVr uptake and Biomarkers of neurodegeneration and neurological disease.

Correlations analysis will be used to evaluate the association between baseline flortaucipir MUBADA SUVr results and florbetapir SUVr, with Pearson's correlation. Correlations will be completed using all subjects except for YCN.

Scatter plot between MUBADA SUVr and florbetapir SUVr will be created to visually display the relationship, with diagnosis shape coded.

Correlations will be used to evaluate the association between flortaucipir SUVr results and the atrophy assessed by volumetric MRI (whole brain, volume, total ventricle size, total gray volume). Correlations will be completed for AD/MCI subjects.

The relationship between genetic markers including ApoE and MAPT will be assessed using ANCOVA models. The analysis will include all subjects except for YCN. For the ANCOVA model, MUBADA SUVr values will be used as dependent variable, and independent variables include ApoE E4 status (carriers vs. non-carries), Amyloid status (AB+ vs. AB-), interaction of ApoE E4 status and amyloid status, and age. LS means of

AB+, AB-, E4 carriers, non E4 carriers, AB+ E4 carriers, AB+ non E4 carriers, AB- E4 carriers, AB- non E4 carriers will be calculated through proper contrast set up, along with the 95% CI.

Scatter plot of MUBADA SUVr values, overlay with box plots by MAPT genotypes (H1/H1, H1/H2 and H2/H2) will be used to display the tau load level by MAPT genotypes. If there are notable differences across MAPT genotypes, further analyses will be carry out accordingly, which will not be detailed in this SAP.

8.6.1.3.3 Muti-variate models to explore possible factors for cognitive impairments

To further explore the possible factors for cognitive impairment, multivariate models will be conducted. The following variables will be used as dependent variables for each of these models: ADAS Cog 11, MMSE, and FAQ. Each of these models will include these variables as independent variables: baseline age, ANART, MUBADA SUVr, florbetapir SUVr, whole brain volume, and ApoE E4 status. Stepwise selection technique will be used to build the most parsimonious model, with entry and stay selection p-value set at 0.2. The analyses will be run separately with all subjects except for YCN, and with AB+ subjects only.

8.6.2 Exploratory Phase, Longitudinal Analysis

8.6.2.1 Analysis of Primary Efficacy Variable

Mixed Model Repeated Measures for Evaluation of Flortaucipir SUVr over time

Descriptive summary statistics for Flortaucipir SUVr will be provided by amyloid beta status (AB+, AB-) at baseline, 9 month, and 18 month across all subjects.

Change from baseline for Flortaucipir SUVr will be estimated using repeated measures models for all subjects except for YCN subjects (who do not have follow-up flortaucipir scans at 9 months and 18 month). Due to the concern of unequal variance for flortaucipir SUVr changes by amyloid status, the model will be run for AB+ subjects only, and for AB- subjects only separately. For this analysis, time will be considered to be categorical variable. A mixed model will be run with MUBADA SUVr change from baseline as dependent variable, baseline MUBADA SUVr and age, and visit as independent variables. In order to appropriately model the within subject covariance, the covariance structure must be pre-specified. Each model should be fit using the unstructured covariance structure. If this structure does not converge, covariance structure in the order as auto-regressive, Toeplitz structures and the compound symmetry will be used.

The LS means of MUBADA SUVr change at each visit from the model will be displayed along with the corresponding 95% confidence intervals. In addition, p-values will be

provided for testing that whether or not the LS means at each visit is significantly different than zero.

Spaghetti plots will be generated to display the relationship of Flortaucipir SUVr change across the follow up visits, by each subject. The plot will use MUBADA SUVr as y-axis, subjects' age at each visit as x-axis, and color code according to amyloid status.

Explore Factors Associated with Flortaucipir SUVr Change using Multivariate Analysis

The analysis will be completed for AB+ subjects. A multivariate step wise selection regression model will be used to explore factors associated with the change in Flortaucipir SUVr (MUBADA). The dependent variable will be Flortaucipir SUVr (MUBADA) change at 18 months. The independent variables include baseline information such as age, cognitive assessments (MMSE), APOE4 status (carrier or non-carrier), florbetapir SUVr, and flortaucipir MUBADA SUVr. The significance level of entry and stay in the model will be both set as 0.2. For each variable in the final model, the parameter estimate, SE, 95% CI and associated p-value will be reported.

8.6.2.2 Analysis of Second Efficacy Variable

Not applicable for this section to this study.

8.6.2.3 Analysis of additional Efficacy Variable

Not applicable to longitudinal part of this study.

8.6.2.4 Exploratory Analyses

8.6.2.4.1 Mixed Model Repeated Measures for Comparison of Psychometric Assessment over time between diagnostic groups

Descriptive summary statistics for each cognitive scale (ADAS, MMSE, FAQ, and ADAS+FAQ composite) at baseline, 9 month, and 18 month will be summarized by subjects' tau and/or amyloid status of interest (details below). The change from baseline to 9 month and 18 month will be summarized in the same corresponding table.

Change from baseline for each psychometric assessment will be analyzed using mixed model with repeated measures (MMRM) for subjects who have follow-up information for 18 months (baseline, 9 months, and/or 18 month).

The MMRM model will be run to include MCI/AD subjects with these tau and/or amyloid status classified as below respectively:

1: Tau visual reads as AD++ vs. non-AD++ ;
2: Three level categorical variable by combining tau and amyloid status:
   a. AB+ AD++ (AB+ and tau pattern likely to progress)
   b. AB+ non-AD++ (AB+ and tau AD pattern but not likely to progress, i.e., AB+ AD+ subjects but not AD++, or AB+ AD-)
   c. AB-

For this analysis, time will be considered to be Categorical variable. A mixed model will be used with psychometric score change at each visit as dependent variable. Independent variables include categorical variable baseline tau (AD++ vs non-AD++) and/or amyloid status by visual interpretation (category a, b, c defined above in this section), visit and interaction of tau status and visit, and baseline age, ANART score and psychometric score as continuous covariates. In order to appropriately model the within subject covariance, the covariance structure must be pre-specified. Each model should be fit using the unstructured covariance structure. If this structure does not converge, then covariance structure in the order of the auto-regressive, and toeplitz structures and the compound symmetry will be used.

The least squares (LS) mean from the model will be displayed separately for each Tau status and/ amyloid status by visual interpretation with the corresponding 95% confidence intervals and p-values testing that the LS mean is significantly different between any of the two categories.

In addition, LS means difference between any of the two categories will be presented with the 95% confidence interval and p-value testing that the difference is significantly different than zero. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The LS means at each visit from the models described above will be displayed by line graphs, by the tau and/or amyloid status.

CDR-SB scales were only collected at 9 and 18 months. Thus an ANCOVA model will be applied to explore the relationship between CDR-SB change and baseline tau/amyloid status. The model will use CDR-SB change from 9 month as dependent variable, and independent variable will include categorical variable baseline tau and/or amyloid status by visual interpretation (as described above), and continuous covariates including baseline age, ANART score and psychometric score. LS means and difference in LS means for the tau/amyloid status will be calculated through proper contrast.

To visually display the change of cognition/function assessments by subjects' tau status, the follow plots will be made: cumulative frequency of each score change at 18 months as y-axis, score change at 18 months as x-axis. The data points should be connected, and

displayed according to tau status (AD++ vs. non-AD++, or AB+AD++, AB+ non-AD++, and AB-). The plots will be completed for ADAS-Cog 11, MMSE, FAQ, ADAS+FAQ and CDR.

8.6.2.4.2 Rate Ratio of Clinically Meaningful Changes by Baseline Tau Scan Status

The analyses for clinically meaningful changes will be restricted to AD/MCI subjects only.

Clinically meaningful changes assessed by psychometric scores are defined in section 6.4.2.3.1

For each of the categorized clinically meaningful changes (event) except for CDR global score change, a Poisson regression model will be applied. The model will have these defined event as dependent variable respectively, and the independent variables will include tau status at baseline (AD++ vs. non-AD++), visit and the interaction of tau status and visit as a categorical variable, and continuous covariates that include baseline psychometric score, age, and ANART.

At each visit, person-year will be calculated for each subjects, as time from baseline to first event, or time from baseline to visit date or end of study if no event for the subject.

General estimating equation (GEE) technique will be used to adjust for the intra subject correlation. The variance-covariance matrix is pre-specified: each model should be fit using the unstructured covariance structure. If this structure does not converge, the exchangeable, auto-regressive, and m-dependent structures will be fit and the model with the lowest BIC value will be selected to use. The rate ratio estimated at 18 month visit will be reported along with 95% confidence interval.

8.6.2.4.3 Association of CDR Global Change at 18 Months with Tau Status

The association of change in CDR global score at 18 months by tau status (AD++ vs. non-AD++) will be assessed using a Cochran-Armitage trend test. The analysis will be performed with MCI/AD subjects. Frequency table, along with p-values for the trend test will be provided.

8.6.2.4.4 Diagnostic Performance of Baseline Tau Status in Predicting Clinical Meaningful Changes at 18 Months

This analyses will be restricted to AD/MCI subjects only.

For each cognitive assessment of cognitive impairment and TAU status, a 2x2 table will be generated and the appropriated diagnostic performance parameters determined.

CMC+ is defined as the clinically meaningful changes assessed by psychometric scores are defined in section 6.4.2.3.1. CMC- are those patient with related data but not meet the CMC+ definition.

	Clinical meaningful changes	
	CMC+	CMC-
AD++	A	B
Non-AD++	C	D

Sensitivity is defined as the number of Tau+ subjects who are cognitively impaired divided by the total number of subject with cognitive impairment.: *A/(A+C)*

Specificity is defined as the number of Tau- subjects who are not cognitively impaired divided by the total number of subjects without cognitive impairment. *: D/(B+D)*

Accuracy is defined as the number of subjects with cognitive impairment who are Tau+ and the number of subjects without cognitive impairment who are Tau- divided by the total number of patients. : *(A+D)/(A+B+C+D)*

Positive predictive Value is defined as the number of Tau+ subjects who are cognitively impaired divided by the total number of subjects who tested Tau+*: A/(A+B)*

Negative predictive value is defined as the number of Tau- subjects who are cognitively not impaired divided by the total number of subjects who test Tau-: *D /(C+D)*

Positive Likelihood Ratio (LR+) for positive result shows the odds of the cognitive impairment increases when TAU+: *Sensitivity/ (1-Specificity)*

Negative Likelihood Ratio (LR-) for negative result shows the odds of the cognitive impairment decreases when TAU- : *(1-Sensitivity) /Specificity*

Relative risk: (A/(A+B))/(C/(C+D))

The analyses from 8.6.4.2.1 – 8.6.2.4.2, and 8.6.2.4.4 will be repeated with subjects with AD/MCI diagnosis and baseline MMSE 20 -27, which is similar to the target enrolled population in confirmatory cohort.

8.6.2.4.5 Muti-variate models to explore possible factors for cognitive impairments changes

The analysis will be completed for AB+ subjects. A multivariate step wise selection regression model will be used to explore factors associated with the change in psychometric score change at 18 months. The dependent variable will be each of these psychometric score change at 18 months respectively: ADAS Cog 11, MMSE, and FAQ. The independent variables include baseline information such as psychometric score (baseline ADAS Cog-11, MMSE, or FAQ), age, ANART score, APOE4 status (carrier or non-carrier), florbetapir SUVr, and flortaucipir MUBADA SUVr. The significance level of entry and stay in the model will be both set as 0.2. For each variable in the final model, the parameter estimate, SE, 95% CI and associated p-value will be reported.

Scatter plots will be generated for the following scenarios:

1. Change of ADAS score at 18 month versus Flortaucipir MUBADA SUVr score at baseline by each diagnostic groups.
2. Change of MMSE score at 18 month versus Flortaucipir MUBADA SUVr score at baseline by each diagnostic groups.
3. Change of FAQ score at 9 month or 18 month versus Flortaucipir SUVr score at baseline by each diagnostic groups.

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). Flortaucipir exposures will be summarized by each of the scans and all exposure data will be presented in listings.

Because this is a study with only one bolus of study medication per imaging visit, 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. 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 (QT_{c-B}, QT_{c-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.

8.8 Pharmacodynamics

No pharmacodynamics analyses are planned for this study.

9 COMPUTER SOFTWARE

All analyses will be performed by Chiltern 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 will be followed in the creation and quality control of all data displays and analyses.

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11 APPENDICES

11.1 Appendix 1 – Laboratory Results – Potentially Clinically Significant Criteria

Parameter (Full Names)	Parameter (Short Names)	Reporting Unit	Low	High	SI Unit	Conversion Factor	SI Low	SI High
Hematology								
Hematocrit	HCT	%	Male ≤ 37% Female ≤ 32%	NA	L/L	0.01	Male ≤ 0.37 Female ≤ 0.32	NA
Hemoglobin	Hgb	g/dL	Male ≤ 11.5 Female ≤ 9.5	NA	g/L	10	Male ≤ 115 Female ≤ 95	NA
White blood cell	WBC	10^3/mm3	≤2.8	≥16.0	GI/L	1	≤2.8	≥16.0
Platelets	PLT	10^3/mm3	≤ 75	≥ 700	GI/L	1	≤ 75	≥ 700
Mean corpuscular hemoglobin	MCH	pg/cell	NA	NA	pg/cell	1	NA	NA
Mean corpuscular hemoglobin concentration	MCHC	g/dL	NA	NA	g/L	10	NA	NA
Mean corpuscular volume	MCV	fl	NA	NA	fl	1	NA	NA
Red blood cell	RBC	10^6/mm3	≤ 3.5	NA	TI/L	1	≤ 3.5	NA
Differential								
Bands or (Band neutrophil (stab))	BAND	%	NA	≥ 10%	%	1	NA	≥ 10%
Basophil (absolute)	Baso.	10^3/mm3	NA	≥ 0.4	GI/L	1	NA	≥ 0.4
Basophil (%)	Baso.	%	NA	≥ 5%	%	1	NA	≥ 5%
Lymphocytes (absolute)	lymphs	10^3/mm3	≤ 0.5	≥ 4.5	GI/L	1	≤ 0.5	≥ 4.5
Lymphocytes (%)	lymphs	%	≤ 10%	≥ 80%	%	1	≤ 10%	≥ 80%

Parameter (Full Names)	Parameter (Short Names)	Reporting Unit	Low	High	SI Unit	Conversion Factor	SI Low	SI High
Monocytes (absolute)	MONO	10^3/mm3	NA	≥ 1.5	GI/L	1	NA	≥ 1.5
Monocytes (%)	MONO	%	NA	≥ 20%	%	1	NA	≥ 20%
Neutrophils (absolute)	NEUT	10^3/mm3	≤ 1.0	NA	GI/L	1	≤ 1.0	NA
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

Parameter (Full Names)	Parameter (Short Names)	Reporting Unit	Low	High	SI Unit	Conversion Factor	SI Low	SI High
Electrolytes								
Chloride	Cl	MEq/L	≤ 90	≥ 112	mmol/L	1	≤ 90	≥ 112
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	USpG		≤ 1.005	NA			≤ 1.005	NA

Parameter (Full Names)	Parameter (Short Names)	Reporting Unit	Low	High	SI Unit	Conversion Factor	SI Low	SI High
(Microscopic test)								

11.2 Appendix 2 – 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