18F-AV-1451-A23 SAP v1.0

A Multicenter Screening Study With Flortaucipir F 18 in Patients With Early Symptomatic AD

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A MULTICENTER SCREENING STUDY WITH FLORTAUCIPIR F 18 IN PATIENTS WITH EARLY SYMPTOMATIC AD

Statistical Analysis Plan

Prepared for:
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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

Aβ	amyloid-ß
AD	Alzheimer's disease
AE	adverse event
ATC	Anatomical therapeutic chemical classification
BMI	body mass index
CIP	Clinical investigational plan
cm	centimeters
CRO	contract research organization
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
IND	investigational new drug
IV	Intravenous
K_d	dissociation constant
kg	Kilograms
max	Maximum
MBq	Megabecquerel
mCi	Millicuries
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
MMSE	Mini-Mental State Examination
mSv	Millisievert
MUBADA	Multiblock barycentric discriminant analysis
n	number of subjects
nM	Nanomolar
PET	positron emission tomography
SAE	Serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SUVr	standardized uptake value ratio
TEAE	treatment-emergent adverse event
WHO	World Health Organization

2 INTRODUCTION

Flortaucipir F 18 ($_{18}$F-AV-1451) (originally named [F-18]T807 by Siemens Molecular Imaging Biomarker Research group) is a positron emitting radiopharmaceutical developed for in vivo imaging of tau protein aggregates (Xia et al., 2013). Image assessment showed tracer deposition on brain PET scans to be consistent with that expected for a tracer of aggregated tau protein. Flortaucipir ($_{18}$F) initially entered the brain and was subsequently eliminated from the brain in clinically normal and amyloid negative cognitively impaired subjects, yielding only a diffuse pattern of background activity, whereas a regionally distinct gray matter distribution of increased tracer retention was observed in amyloid positive cognitively impaired subjects (Pontecorvo et al., 2017). Preliminary analyses of our Phase II longitudinal study (A05, exploratory cohort) also indicate a relationship between the level and pattern of flortaucipir uptake at baseline, and the rate of decline on cognitive tests over an 18-month period (Mintun, AAIC 2017). These results suggest that it may be possible to use flortaucipir PET scans to enrich clinical studies for subjects with a desired level of AD pathology and a more homogeneous rate of cognitive decline, thus increasing power to detect a treatment effect. Specifically, Lilly and Avid desire to conduct treatment trials at the earliest stage of AD neuropathology to maximize potential patient benefit.

I5T-MC-AACG is a proposed anti-amyloid trial that intends to target subjects with a certain distribution and density of tau neurofibrillary tangles that are hypothesized to be appropriate for such a trial. It is thought that patients with no tau will progress so slowly that a clinical treatment effect could not be discerned, and those with a large tau burden may not be responsive to anti-amyloid therapy as their cognitive impairment is driven primarily by tau pathology. The overarching goal of AV-1451-A23 is to test this hypothesis by pre-screening subjects with flortaucipir F 18 who have been diagnosed with suspected Alzheimer's disease and have indicated their interest to consider participation in trials such as the AACG Lilly therapeutic clinical trial.

3 STUDY OBJECTIVES

The primary objective is to pre-screen subjects via a flortaucipir scan, who have objectively verified cognitive impairment and etiology diagnosed or suspected to be due to Alzheimer's disease, and have indicated their interest in participating in Lilly sponsored trials that require tau imaging for inclusion such as AACG.

The secondary objective of the study is to expand the flortaucipir F 18 safety database.

4 STUDY DESIGN

4.1 General Design

Study ^{18}F-AV-1451-A23 is a multicenter screening study in subjects with early symptomatic AD (where early symptomatic AD refers to the combination of 2 stages: prodromal AD [MCI-AD] and mild AD dementia).

All subjects will provide informed consent before starting any study procedures. This prescreening study targets subjects who are interested in participating in AD therapeutic clinical trials and have expressed a preliminary interest in a trial like the AACG trial, and who are not known to have met any of the exclusion criteria for trials like AACG based on medical history and clinical examination. However, consent for this protocol does not constitute consent for the AACG trial or any other trials, and subjects who qualify for this protocol may still fail to qualify for trials like AACG or other trials based on the results of this protocol or based on additional testing performed in those subsequent trials.

Screening assessments may take place over several days and will be performed within 30 days prior to flortaucipir F 18 injection. Screening assessments will include demographic information, cognitive testing, disease history, concomitant medications, vital signs, ECG and medical history. Subjects who are deemed eligible to continue will complete a flortaucipir PET scan.

A physician or a licensed/credentialed medial professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to administration of flortaucipir F 18 injection to determine if they are still suitable to undergo the scan.

All subjects will receive a single IV bolus administration target dose of 370 MBq (10 mCi) of flortaucipir F 18 injection followed by saline flush. At approximately 75 minutes following injection, a continuous 30-minute brain scan will be performed.

The injection site will be observed for excessive inflammation or damage to the surrounding tissue at the injection site. Adverse events will be continuously monitored during the flortaucipir PET imaging visit. 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 informant where applicable, will be conducted within 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect any new adverse events.

A physician or a licensed/credentialed medial professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge.

Subjects who meet eligibility criteria will participate in this protocol until they complete their flortaucipir PET scan, or they discontinue, withdraw consent, or if the sponsor decides to end this protocol early.

4.2 Discussion of Study Design

This trial is designed to pre-screen subjects via a flortaucipir scan, who have objectively verified cognitive impairment and etiology diagnosed or suspected to be Alzheimer's disease, and have indicated their interest in participating in Lilly sponsored trials that require tau imaging for inclusion, such as AACG.

4.3 Method of Assignment of Subjects to Treatment Groups

Flortaucipir F 18:
All subjects will receive a single IV bolus administration target dose of 370 MBq (10 mCi) of flortaucipir F 18 Injection.

4.4 Blinding

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

4.5 Determination of Sample Size

This is a pre-screening study that targets subjects who are interested in participating in AD therapeutic clinical trials and have expressed a preliminary interest in a trial like the AACG trial. Therefore, approximately 500 subjects will be enrolled in this study.

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

There were no changes in the analyses planned in the Protocol/CIP at the time of preparing this statistical analysis plan.

6 BASELINE, EFFICACY AND SAFETY EVALUATIONS

6.1 Schedule of Evaluations

Evaluations/Procedures	Screening Visit[a]	Flortaucipir F 18 Imaging Visit	End of Flortaucipir F 18 Imaging (prior to discharge)	Follow-up Phone Call
Signed Consent	X			
Demographics	X			
Medical History/Neurologic Disease History	X			
Concomitant Meds	X	X		
Vital Signs[b]	X			
ECG	X			
MMSE	X			
Serum beta-hCG [c]	X			
Urine Pregnancy Test[d]		X		
flortaucipir F 18 scan		X		
Evaluation by a physician[e]	X	X	X	
Adverse Events	X	X	X	X
Serious Adverse Events	X	X	X	X

a. Screening may take place over several days. All assessments must be performed within 30 days of the ^{18}F-AV-1451 imaging session.
b. Vital signs (pulse, respiratory rate, supine blood pressure). Weight will be taken at the imaging visit.
c. Serum beta-hCG pregnancy test at screening for females of childbearing potential.
d. For women of childbearing potential, a negative urine pregnancy test must be obtained within 24 hours prior to the flortaucipir F 18 injection.
e. A physician or physician designee

6.2 Time Point Algorithms

6.2.1 Relative Day

The date of first dose of study drug (flortaucipir F 18) 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 Assessments

Screening may take place over several days. All screening assessments will be performed within 30 days prior to flortaucipir F 18 injection. Screening assessments will include:

- Informed consent for subject;
- Demographics (age, gender, years of education, race, ethnicity); weight;
- Medical history, concomitant medications;
- Vital Signs (pulse, respiration rate, supine blood pressure)
- A resting 12 lead ECG will be performed to assess the subject's cardiac status. If an ECG was performed within the last 12 months of the flortaucipir (^{18}F) PET Imaging Visit and is available for review, the ECG does not need to be repeated.
- ApoE status, if available;
- Disease history (date/months since symptom onset, date/months since diagnosis, family history of relevant neurologic disease);
- Cognitive status interview, including MMSE;
- A physician will see the subject during the screening visit.
- For women of childbearing potential, a negative serum pregnancy test must be obtained at the screening visit

Weight will be displayed in kilograms (kg), height will be displayed in centimeters (cm). Weights and heights 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).

APOE4 Positive is any subject with at least one of their two APOE alleles as an E4 allele.

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. Age will be calculated as the number of months between the date of informed consent and the imputed birthdate, divided by 12. Age will be rounded to the nearest integer.

The MMSE (Folstein et al., 1975) is a brief instrument used to assess cognitive function in elderly subjects. 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 subject 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.

6.4 Efficacy Variables

6.4.1 Qualitative assessment for Flortaucipir and Diagnostic Performance

The flortaucipir scan image will be visually interpreted. The scans will be classified as either

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

6.4.2 Quantitative assessment of images for Flortaucipir (SUVr based)

For the flortaucipir image, standard uptake value ratios (SUVr) will be calculated to estimate tau globally. SUVr will be calculated after the visual read and only on scans that were τAD+ or τAD++. For global assessment, a target region derived statistically with a Multiblock Barycentric Discriminant Analysis (MUBADA) method will be used.

6.4.3 Increased neocortical Flortaucipir activity

The hemisphere and region of increased neocortical flortaucipir activity will be identified.

The hemisphere will be classified as either left or right and the region is classified as

- Anterior Lateral Temporal
- Posterior Lateral Temporal
- Occipital
- Parietal
- Precuneus
- Frontal

6.5 Drug Concentration Measurements and Pharmacokinetic Parameters

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 flortaucipir imaging session, subjects will receive a single IV bolus administration target dose of 370 MBq (10 mCi) of flortaucipir F 18 injection followed by a saline flush. At approximately 75 minutes following injection, a continuous 30-minute brain scan will begin. Exposure to study drug will be summarized using the total administered dose at the scan visit for flortaucipir F 18 injection.

6.6.2 Adverse Events

The investigator's verbatim term of adverse events 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 at the imaging visit, and prior to the end of observation windows defined as following: the TEAE window will be from injection of flortaucipir F 18 until 48 hours post flortaucipir F 18 injection. These will be recorded on the AE page of the electronic case report form (eCRF).

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 or study drug. 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 Other Observations Related to Safety

6.6.3.1 Vital Signs

Vital signs (pulse rate, respiratory rate, and supine blood pressure) will be taken at the screening visit. Weight will be measured, lightly clothed during the imaging visit.

6.6.3.2 Electrocardiogram (ECG)

A resting 12-lead electrocardiogram will be recorded as part of the screening visit, unless an ECG was performed within twelve months of the flortaucipir PET Imaging Visit and is available for review.

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 as a single group, early symptomatic AD. Frequency distributions including counts and percentages will be reported for all categorical outcomes. Summary statistics including number of subjects [N], mean, standard deviation [SD], median, quartiles, minimum and maximum values will be presented for all continuous outcomes.

All statistical analyses will be performed using SAS® version 9.3 or higher. Patient listings of all data form the eCRF as well as any derived variables will be presented.

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.

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 15 centers. The data from all centers will be pooled. The pooled data will be analyzed and presented.

7.6 Multiple Comparisons/Multiplicity

No adjustment for multiplicity will be performed in this study.

7.7 Active-Control Studies Intended to Show Equivalence

Not applicable to this study.

7.8 Examination of Subgroups

No subgroup analysis will be performed.

8 STATISTICAL ANALYSIS

8.1 Analysis Populations

8.1.1 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.

8.1.2 Safety Population

The safety analysis population will include all eligible subjects who enroll in ^{18}F-AV-1451-A23 (A23) and have received at lease on dose of flortaucipir F 18 injection.

All demographic, baseline and safety endpoints will be using the safety population.

8.1.3 Efficacy Population

Efficacy analysis population will include all subjects in safety population, with a valid flortaucipir scan assessment [SUVr (quantitative) and/or visual reads (qualitative)].

For flortaucipir SUVr related analyses, any scans deemed to be unquantifiable due to technical reasons will be excluded from analyses.

All analyses involving imaging outcomes will be based on the efficacy population.

8.2 Disposition of Subjects

The enrolled population will be represented in the disposition table. The disposition table will include a summary of the analysis populations, number of completed and discontinued subjects, and the reasons for discontinuation. All percentages will be based on the safety population.

Disposition data will be presented in a listing.

8.3 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.

8.4 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 across all subjects. Key demographic and baseline characteristics to be summarized include: age, gender, race, ethnicity, height, weight, BMI, highest level of education, alcohol history, recreational drug use history, smoking history, MMSE, and ApoE Genetic testing.

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

8.5 Relevant Family History

Data from Family History CRF will be summarized in a table with counts and percentages and presented in a listing for the safety population.

8.6 Disease History

Months since symptom onset and diagnosis will be summarized in a table using descriptive statistics and presented in a listing for the safety population.

For subjects with dates of diagnosis or symptom onset, months will be calculated as the difference of symptom onset/diagnosis date and the date of their flortaucipir injection.

For partial symptom onset/diagnosis date, if only the day is missing, then impute the day as the first day of the month; if both the day and month are missing, then imputed it as 01 January of the year.

8.7 Pregnancy Test

Data from Pregnancy Test CRF will be presented in a listing for the safety population.

8.8 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.

All concomitant medications data will be presented in listings for the safety population.

8.9 Medical and Surgical History

Medical and Surgical History will be coded using MedDRA Version 21.1. Medical and surgical history will be presented in a listing for the safety population.

8.10 Analysis of Efficacy Parameters

All efficacy information as well as related data (flortaucipir PET scan information and flortaucipir PET results) will be presented in the listings.

8.10.1 Qualitative Assessment of Images

The visual read results will be categorized as τAD+, τAD++ and τAD-. The visual read results will be summarized by frequency distribution (count and percentage) for the efficacy population by subject eligibility and overall.

8.10.2 Quantitative Assessment of Images

The Screening MUBADA SUVr will be summarized using descriptive statistics [n, mean, SD, median, minimum and maximum values, and quartiles (25th and 75th percentile)] by visual read results (τAD+, τAD++ subject eligibility and overall.

8.10.3 Other Efficacy Variables

8.10.3.1 Increased Neocortical Activity

Increased neocortical flortaucipir activity by hemisphere and region will be presented in a listing.

8.11 Analysis of Safety

8.11.1 Extent of Exposure and Compliance to Study Treatment

The total dose administered (MBq) of Flortaucipir F 18 will be summarized using descriptive statistics. All exposure data captured on the CRF will be presented in listings for the safety population.

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

8.11.1.1 Unit Conversion and Volume Calculation

All exposure tables will display volume in MBq. Radioactive dose collected in millicuries (mCi) will be converted to MBq as follows:

$$MBq = 37 \times mCi$$

8.11.2 Adverse Events

TEAEs will be summarized by descending frequency, then 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
6. All Serious TEAEs by system organ class (SOC) and preferred term;
7. All TEAE leading to study termination by system organ class (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.

All AE will be presented in the listings.

8.11.3 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse, respiration rate) will be summarized using descriptive statistics.

All vital signs data will be presented in the listings.

8.11.4 Electrocardiogram (ECG)

Electrocardiogram (ECG) Results (Normal, Abnormal – Not Clinically Significant, Abnormal – Clinically Significant) will be summarized using counts and percentage.

All ECG data will be presented in the listings.

8.12 Pharmacodynamics

No pharmacodynamics analyses are planned for this study.

9 COMPUTER SOFTWARE

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

The standard operating procedures (SOPs) of Chiltern will be followed in the creation and quality control of all data displays and analyses.