18F-AV-1451-A05 SAP Confirmatory Addendum 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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Protocol No. 18F-Flortaucipir-A05

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

Confirmatory (Second Phase)
Addendum to Statistical Analysis Plan

Prepared for:
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SIGNATURE PAGE

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

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

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

2 INTRODUCTION

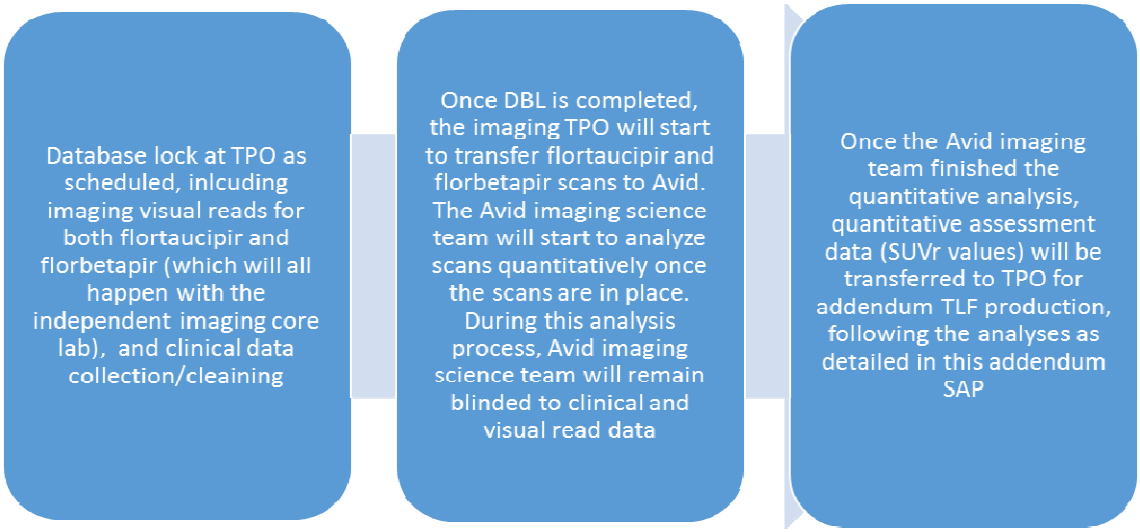
The quantitative assessment of Flortaucipir scan (standard uptake value ratio, SUVr) is important in helping to better understanding how brain tau load (as measured by flortaucipir scans) correlates with cognitive function progress. However quantitative analysis of tau PET imaging is a rapidly evolving field and not yet routine in Core laboratories. Therefore, Avid's imaging science team will assume the role for this part of imaging analysis, and the results (SUVr values) will be used in exploratory analyses in this study, and will be reported in CSR with other analysis results. To keep Avid staff blinded to the key information, the quantitative scan analysis process will be happening post main study database lock, which including the lock of both clinical and tau/amyloid imaging scan qualitative assessments (visual reads) results. Therefore this addendum SAP is created to describe the relative steps, and the planned analyses that will include imaging quantitative assessments.

3 STUDY OBJECTIVE

This SAP will detail the exploratory analyses that involve flortaucipir and florbetapir quantitative assessments. All the analyses included here are for exploratory purpose.

4 STUDY DESIGN

The process of imaging quantitative analysis (including both flortaucipir and florbetapir imaging) will be following the steps as below:



The details of this process is documented in A05 study blinding document.

4.1 Blinding

Avid imaging science team will assume the role of quantitative imaging analyses, including both flortaucipir scans, and florbetapir scans. Therefore the team will be blinded to any other study data, including both clinical and imaging qualitative assessments until the analyses results are sent to TPO for addendum TFL production, and addendum lock memo signed.

5 EFFICACY VARIABLES

5.1.1 Quantitative Imaging Assessment of Flortaucipir Scan

For the flortaucipir image, standardized uptake value ratios (SUVr) will be calculated using a subject specific white matter based parametrically derived reference region (parametric estimate of reference signal intensity, PERSI[1]). The global cortical target ROI will *c*onsist of a weighted average of voxels found, through multi-block barycentric discriminant analysis (MUBADA) to best sepaparate the amyloid positive AD/MCI and amyloid negative CN subjects, from the A05 exploratory cohort. In addition, cortical region ROI SUVr based on modified AAL regions will also be calculated. The details are documented in imaging analysis plan.

5.1.2 Quantitative Imaging Assessment of Florbetapir Scan

For the Florebetapir 18 F image, standardized uptake values (SUV) for target areas such as the frontal cortex, temporal cortex, parietal cortex, posterior cingulate cortex, anterior cingulate cortex and the precuneus will be calculated from each image. Standardized uptake value ratios (SUVr) will be calculated for target areas by calculating the ratio of the specific SUV to the entire cerebellum SUV. The global cortical average SUVr will be calculated as the average across these six target brain regions.

5.1.3 Cognitive and Functional Assessments

Cognitive and functional assessments as detailed in section 6.4.2.2 of A05 confirmatory SAP, include MMSE, ADAS, FAQ, and CDR.

5.1.4 Volumetric MRI Assessments

Volumetric MRI assessments are detailed in section 6.4.2.6 of A05 confirmatory SAP.

6 STATISTICAL METHODS

6.1 General Methodology

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

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

6.2 Adjustments for Covariates

None.

7 STATISTICAL ANALYSIS

7.1 Disposition of Subjects

Flortaucipir and florbetapir images that are not quantifiable due to reasons such as technical issues and etc. will be documented in details in a note to file (NTF). The number of subjects with imaging received by Avid imaging science team, number of subjects with imaging quantitative analysis completed, and number of subjects with imaging scans fail to complete quantitation will be presented in a table, along with reasons of why quantitation failed. A listing will also be provided.

7.2 Analysis Populations

7.2.5 Efficacy Population

The efficacy population for the analyses covered in this addendum SAP will include all subjects with a valid flortaucipir quantitative scan analysis result (SUVr value).

7.3 Analysis of Efficacy Parameters

7.3.1 Relationship between Quantitative Tau Load and Baseline Cognitive/Functional Measurement

To evaluate the relationships between brain tau load as measured by flortaucipir SUVr value and the cognitive and functional assessments, scatter plots between MUBADA SUVr and each of the baseline cognitive and functional assessments as detailed in section 5.1.3 will be generated. Pearson correlation analyses will be conducted for each of these pairs, and the correlation coefficient will be provided along with the 95% confidence intervals (CI), and the associated p-values.

7.3.2 Relationship between Quantitative Tau Load and Cognitive/Functional Change at 18 Months Visit

Similar analyses will be conducted as detailed in section 7.3.1, by changing baseline cognitive/function measurements to cognitive/functional measurements change from baseline at 18 months.

7.3.3 Relationship between Quantitative Tau Load and Other Biomarkers

Similar analyses will be conducted as detailed in section 7.3.1, by changing baseline cognitive/function measurements to the biomarkers such as below:

1. Amyloid level as assessed by florbetapir SUVr;
2. MRI volumetric assessments as detailed in A05 confirmatory SAP section 6.4.2.6.

8 COMPUTER SOFTWARE

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

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

9 REFERENCES

1. Southekal S, Devous MD, Kennedy I, Navitsky M, Lu M, Joshi AD, Pontecorvo MJ, Mintun MA. Flortaucipir F 18 Quantitation using a Parametric Estimate of Reference Signal Intensity (PERSI). Journal of Nuclear Medicine (submitted).