STATISTICAL ANALYSIS PLAN

DATE OF PLAN:

01 May 2018

BASED ON:

^{18}F-AV-45-A14 Protocol, 17-Feb-2013 (Amendment 3)

STUDY DRUG:

Florbetapir ^{18}F (18F-AV-45)

PROTOCOL NUMBER:

^{18}F-AV-45-A14

STUDY TITLE:

Clinical Evaluation of Florbetapir F 18 (18F-AV-45)

SPONSOR:

Avid Radiopharmaceuticals, Inc.

3711 Market Street

Philadelphia, PA 19104

215-298-0700

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

NCT01518374

SIGNATURE PAGE

This document has been prepared by:

Ming Lu, M.S., M.P.H, M.D. Lead Statistician	Signature For Ming Lu	08 MAY 2018 Date

This document has been reviewed and accepted by:

Michael Pontecorvo, Ph.D. Vice President in Clinical Development	Signature	09 May 2018 Date
Anupa Arora, M.D. Medical Director	Signature	08 MAY 2018 Date

TABLE OF CONTENTS

LIST OF TABLES

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Aß	**Amyloid-ß**
Aß+	**Amyloid positive, AD-like**
Aß-	**Amyloid negative, not AD**
AD	**Alzheimer's disease**
CERAD	**Consortium to Establish a Registry for Alzheimer's Disease**
CN	**Cognitively Normal**
CRF	**Case report form**
PET	**Positron emission tomography**
SD	**Standard deviation**
SE	**Standard error**
SUVR	**Ratio of standardized uptake values**

2. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, affecting more than 4 million people in the United States alone. However, diagnosis and treatment of the disease have been hampered by the absence of reliable non-invasive markers for the underlying pathology.

Florbetapir F 18 is well-tolerated imaging tracer, that has an acceptable radiation dosimetry profile at the proposed injected dose level of 370Mq (10mCi) and can distinguish patients with AD from normal subjects, and may be useful for the detection of amyloid plaque pathology in the brains of living subjects. This protocol has been developed to allow non-Avid investigator initiated studies to incorporate florbetapir F 18 in their protocol. The purpose of this statistical analysis plan (SAP) is to describe the statistical methods used in safety evaluation of subjects who exposed to florbetapir injection under this protocol. This SAP should be read in conjunction with protocol.

3. STUDY OBJECTIVES

The specific objectives of this protocol were to expand the safety database of florbetapir F 18 PET imaging safety, amyloid binding, and long-term outcome, and to provide standardized conditions for florbetapir F 18 use, data collection, and analysis in other studies (companion protocols). This SAP will only assess the safety of florbetapir. Imaging assessments for the study population were scientifically interesting at the time the study was initiated, but are no longer relevant to the field, as the efficacy of the companion studies, as well as other efficacy studies, have been extensively published in the academic literature.

4. STUDY DURATION AND VISIT SCHEDULE

The following flow chart describes the study duration and visit schedule:

Evaluations	Screen	Pre-dose	Dose	Injection Circulation (0 – 50 minutes)[3]	Continuous PET Imaging 10 minutes	End of Imaging	24-72 hours post injection
Signed Consent	X						
Medical / Disease History	X						
Concomitant Meds	X	X					
MMSE	X						
Physician Visit	X	X[1]				X[1]	
Vital Signs		X					
Urine Pregnancy Test	X	X					
Florbetapir F 18 Administration			X				
PET Imaging[2]					**Continuous 10 minute scan - 50 minutes after dose injection**		
Follow-up Phone Call							X
Adverse Event Assessment	X	X	X	X	X	X	X[3]

5. CLINICAL ASSESSMENTS

5.1. Screening and Baseline Assessments

There are many clinical assessments data collected in companion protocols. For the safety evaluation purpose of this protocol, the following screening and baseline assessments will be included:

1). Subjects' birth year, sex, race, ethnicity, and education;

5.2. Image visit Assessments

AE, and/or SAE; vital signs: immediate prior to injection, and at the end of study visit, prior to discharge (approximately 50 minutes after florbetapir F 18 administration).

5.3. Follow up

A follow-up phone call to the subject (or the caregiver as appropriate) will be conducted approximately 24-48 hours after the imaging session to confirm their well-being and query them about any new adverse events.

6. GENERAL CONSIDERATIONS

Study day is calculated as assessment date minus date of study drug (florbetapir) administration + 1. Date of florbetapir administration is defined as study day 1.

Individual data will be displayed in listings sorted by subject identification number. The subject identification number is a combination of the site number and the subject number.

Continuous data will be summarized using the following descriptive statistics: number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Categorical data will be summarized using the number (n) and percentage (%) of subjects for each category. When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. The denominator for all percentages will be the number of subjects in that treatment group within the population of interest unless otherwise specified.

All analyses will be conducted using SAS® Version 8.2 or higher.

6.1. Analysis Populations

6.1.1. Enrolled Population

Not all subjects enrolled in companion protocol would receive a florbetapir scan. The purpose of this protocol is to evaluate the safety of florbetapir, therefore the enrolled population will not be defined in this SAP. The disposition table will summarize the study subjects based on safety population.

6.1.2. Efficacy Population

No efficacy analyses will be performed, hence no efficacy population is defined for this safety report.

6.1.3. Safety Population

The safety population will consist of all subjects who received at least one injection of florbetapir ^{18}F. All safety endpoints will be summarized using the safety population.

7. SUBJECT DISPOSITION AND ELIGIBLITY CRITERIA

Disposition of subjects including the number and percentage of subjects will be displayed based on Safety population. Since there no efficacy analysis planned for this protocol, the efficacy population will not be included in the disposition table.

A listing will present subject disposition data.

8. BASELINE PATIENT DATA

8.1. Baseline Demographic and Physical Characteristics

Frequency distributions and summary statistics for demographic and baseline characteristics will be presented all subjects in the Safety population.

Demographics and baseline characteristics will be also presented in listings.

8.2. Concomitant Medications

Due to the consideration that this protocol is focus on safety evaluation of florbetapir F18, the concomitant medications are not be presented. If concomitant medications are needed to explain safety findings, tables and listings will be generated post hoc.

9. EFFICACY

This SAP will only assess the safety of florbetapir F18 by examining reported adverse events for the study. Imaging assessments for the study population were scientifically interesting at the time the study was initiated, but are no longer relevant to the field, as the efficacy of the companion studies have been extensively published in the academic literature.

10. SAFETY AND TOLERABILITY

All safety analyses will be conducted using the safety population.

10.1. Adverse Event Preferred Term and Body/Organ System Summary Tables

In this study, an Adverse Event (AE) is defined as any undesirable experience occurring to a subject after an injection of florbetapir F 18, whether or not it is considered as related to the investigational product. Laboratory test abnormalities considered by the Investigator to be clinically relevant should be reported as AEs. For this protocol, treatment-emergent AEs (TEAE) are considered as any 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 within 48 hours since study drug injection. These will be recorded on the AE pages.

The incidence of AEs will be presented overall by system organ class (SOC) and by preferred term. Incidence of AEs by severity and relationship to study medication will also be presented. Adverse events resulting in discontinuation from the study and the incidence of serious adverse events (SAE) will be summarized.

Pre-existing conditions (i.e., undesirable experiences, signs, or symptoms that begin prior to the Screening Visit) will be recorded on the medical history and/or physical exam pages and will not be summarized in this study.

10.1.1. Summaries of Adverse Event Incidence Rates for All Patients

All treatment-emergent AEs will be presented in a summary table, by SOC and preferred term. At each level of summarization, a subject will only be counted once per SOC or preferred term. For example, if a subject reports multiple TEAEs with the same SOC, then that SOC will only be incremented by one. As with the SOC, if a subject reports multiple AEs with the same preferred term, then that preferred term will only be incremented by one since subject counts will be presented. AEs will be presented in descending order of frequency. An additional table will present TEAEs is descending frequency by preferred term only. TEAEs will also be summarized by relationship to study drug, and by severity.

All AEs will also be presented in a listing.

10.1.2. Missing and Partial AE Onset Dates

In the event that only a partial end date (month/year) is available, and month/year occurs before that of study drug injection date, the adverse event will be considered as non-treatment-emergent. However, if the onset date is a partial date (month/year) and month/year occurs on or after that of study drug injection date, the following cases will be considered:

- If month/year of the onset date is greater than the month/year of study drug injection date, the adverse event will be considered treatment-emergent;
- If month/year of the onset date is equal to the month/year of study drug injection date, and the end date is present, the end date will be used to determine when the adverse event

resolved. If the end date is on or after study drug injection date, the adverse event will be considered treatment-emergent; otherwise, if the adverse event stopped before study drug injection date, then it will not be treatment-emergent;

- If month/year of the onset date is equal to the month/year of study drug injection date, and the end date is a partial date, the adverse event will be considered treatment-emergent.

10.1.3. Summaries of Adverse Incidence Rates for Serious Adverse Events (SAE), Adverse Event Dropouts, and Death

A serious adverse event (SAE) is an AE that is fatal or life-threatening, or results in hospitalization, prolongation of hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. A life-threatening AE is an AE that, in the view of the investigator, places the subject at immediate risk of death from the reaction as it occurred. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may requie medical or surgical intervention to prevent one of the outcomes listed in this definition.

If there are any SAE, they will be presented by system organ class and preferred term in a table and a listing. All AEs collected with an outcome of "Fatal" will be presented in a listing.

10.2. Concomitant and Other Medications

Concomitant medication information will not be summarized in this study.

10.3. Routine Laboratory Data

Not done for this study.

10.4. Vital Signs

Vital signs (blood pressure, pulse, respiratory rate, and body temperature) will not be summarized in this study. The safety profile of florbetapir F 18 is well-characterized and no safety issues related to vital signs are expected. Should safety analyses from this study indicate that vital sign data should be examined more carefully, post hoc tables and listing will be generated.

10.5. Study Termination Status

For this protocol, the end of study is defined as the completion of 24-48 hours follow up phone call post 18F-florbetapir scan. The reason for study termination will also be summarized in disposition table. The primary reasons for study termination include: completed study, lost to

follow-up, consent withdrawn, administrative decision, and others.

11. INTERIM ANALYSES

Interim analysis is not planned for this study.