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2. Synopsis

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-3328

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Clinical Trial to Characterize the Performance of MK-3328 in Subjects with Alzheimer's Disease or Mild Cognitive Impairment, and Healthy Young, and Healthy Elderly Subjects #002[redacted]

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter: 4 sites in the US

PRIMARY THERAPY PERIOD: 08-Sep-2011 to 23-Apr-2012
Frozen File Date: 31-Jan-2013

CLINICAL PHASE: Ib

DURATION OF TREATMENT:

A single IV dose of [18F]MK-3328 (~150 MBq) was administered to subjects. Following injection of [18F]MK-3328 either a dynamic PET scan was performed for approximately 90 minutes postdose, or a static PET scan for approximately 30 minutes starting 60 minutes after injection (60-90 min. time window).

The duration of participation was approximately 3 weeks per subject, including prestudy and poststudy visits.

OBJECTIVE(S):

1. To validate [18F]MK-3328 as a radiopharmaceutical tracer for quantifying amyloid plaque burden in Alzheimer's disease (AD) brain with PET.
2. Establish the neural plaque burden threshold associated with AD when using the PET scanning agent [18F]MK-3328.

STUDY STATUS: Complete

STUDY DESIGN:

This study was planned as an adaptive three-part, multi-center, open-label, parallel-group study.

Part I enrolled (healthy elderly) HE and AD subjects. Following the completion of Part I, an interim analysis was planned to be performed for futility. Futility criteria were based on inability of the MK-3328 PET signal to discriminate adequately between AD and healthy control subjects. If futility was demonstrated, the trial was to be terminated, otherwise, the study would have continued to Part II. However, Part II and the optional Part III were not conducted due to a business decision to end this program after completion of Part I.

Part II was planned to occur upon success in the Part I futility analysis, and enroll (Healthy Young) HY, HE and AD subjects to meet the primary objective of the study.

Part III was an adaptive-design and the population planned was amnestic Mild Cognitively Impaired (aMCI) subjects. Enrollment for Part III was to begin at any time per the discretion of the Sponsor. The decision to initiate Part III was dependent upon the results of Part I. If initiated, the Sponsor could have decided to terminate Part III at any time depending on the results of Part II, challenges in recruiting the aMCI population, changes in Sponsor program objectives, and/or the availability of other marketed amyloid PET tracers. An interim analysis was planned to be performed during Part III to determine whether additional subjects were needed to meet the exploratory objective of the study.

The procedures in each of the completed as well as planned parts study were to be identical as per the protocol. There were a total of 3 visits and a follow-up phone call (also referred as Visit 4) for each subject: the Pre-Screening Visit (V1), which could occur up to 28 days prior to the PET scan; the

Screening Visit (V2), which would occur after V1 and within 27 days prior to the PET scan; and the PET Scan/Treatment Visit (V3) where the radiolabeled tracer was administered and the subject would undergo a PET scan. Because no pharmacologically active agent was being tested in this study, a follow-up visit was not required. Subjects were contacted by phone approximately 72 hours and also 14 days after their PET scan to review concomitant medications and inquire about any serious adverse events that may have occurred.

SUBJECT/PATIENT DISPOSITION:

Entered: Total	**24 (55 to 82)**
Male (age range):	12 (55 to 82)
Female (age range):	12 (63 to 82)
Completed:	**20**
Discontinued:	4
Clinical adverse experience:	0
Laboratory adverse experience:	0
Other:	4†

†4 Subjects discontinued due to cancellation of program..

DOSAGE/FORMULATION NOS.:

A single IV dose of approximately 150 MBq [approximately 4.05 mCi, containing ≤20 mcg of MK-3328 (maximum amount for the precursor being <2 mcg)] was administered by bolus IV injection.

DIAGNOSIS/INCLUSION CRITERIA:

Two groups of subjects were involved in Part 1 of this study, 65 to 85 years of age with exceptions outside of this range granted as clinically acceptable to the investigator and Sponsor:

1) Mild-to-Moderate Alzheimer's Disease (AD) as determined by MMSE, Clinical Dementia Rating, and Modified Hachinski scores as well as criteria probable for AD per NINCDS-ADRDA, and MRI.
2) Healthy Elderly (HE).

EVALUATION CRITERIA:

Efficacy/Pharmacokinetic/Immunogenicity:

Efficacy measurements to investigate tracer binding capacity in all subjects were evaluated via brain PET scans and included standardized uptake value ratio (SUVR) and distribution volume ratio (DVR) in brain regions of interest (ROI) using PET imaging after [18F]MK-3328 administration. A baseline MRI was obtained for anatomical co-registration with the brain PET scan.

Safety:

Clinical evaluations, including vital sign measurements, physical examination, 12-lead electrocardiograms, and standard laboratory safety tests were performed at various times throughout the study. Subjects were assessed for adverse events during the study.

Results:

Efficacy/Pharmacokinetic/Immunogenicity:

Analysis of PET images acquired during this terminated trial has not been performed at this time due to internal resources prioritization

Safety:

All 24 subjects enrolled in this study were included in the assessment of safety and tolerability. Single doses of 18F]MK-3328 (~150 MBq) were generally well tolerated in healthy elderly males and females, as well as elderly males and females with AD. There were no serious adverse events (AEs) and no deaths occurred. Four subjects reported a total of 4 clinical adverse experiences, of which 3 were rated as mild (stinging at injection site, sinusitis, and loose stools), and 1 was rated as severe in intensity (vasovagal reaction) by the investigator. Of the clinical AEs, 1 event of "stinging at injection site" was considered to be definitely drug related by the investigator. [redacted]

No clinically significant abnormalities were noted in vital sign parameters, routine blood and urine chemistry panels, hematology, ECGs, and physical or neurological exams.

Conclusions:

MK-3328 has an overall safety profile supportive of continued clinical investigation.