Sponsor

Novartis

Generic Drug Name

[^{11}C]ABP688

Therapeutic Area of Trial

Neuroscience

Approved Indication

Investigational

Protocol Number

ABP688A2102

Title

A multi-center, open-label study in elderly healthy volunteers and elderly patients with major depressive disorder to characterize the regional distribution of [^{11}C]ABP688 in brain by positron emission tomography (PET)

Phase of Development

Phase I

Study Start/End Dates

First Patient first visit (FPFV): 28 Aug 2008

Last patient last visit (LPLV): 7 May 2010

Trial terminated early due to low enrollment of elderly patients with major depressive disorder (MDD).

Study Design/Methodology

This was an open-label, multi-center study to evaluate the regional distribution and brain-kinetics of [11C]ABP688 in the brains of elderly healthy volunteers (HV) and elderly patients with unipolar or major depressive disorder (MDD).

[^{11}C]ABP688 was administered as a single slow bolus i.v. injection, followed by a PET scan. The targeted administration of radioactivity was 300 MBq (allowed range: 150 – 400 MBq) with high specific activity corresponding to a dose of ≤ 6 μg.

The PET examination consisted of a 10 minute transmission and a 60 minute emission scan of the brain. Radioactivity concentration was measured in a set of predefined brain regions on the PET images. Time activity curves (TACs) for each region of interest (ROI) were generated by overlaying the subject's MRI with the co-registered PET image. Whenever possible, arterial input function based compartmental modeling was used to quantify [11C]ABP688 binding in brain, and obtain the following parameters: rate constants (K1-k4), total volume of distribution (DVtot), normalized total volume of distribution (DVnorm) and binding potentials (BPP, BPND). A reference tissue based quantification method was also implemented for all subjects to obtain binding potential (BPND) and ratio of distribution volumes (DVR'). The reference tissue based method was validated against the arterial blood sampling based method. Additionally, results of the ROI-based approach were confirmed using a voxel-based method (SPM5).
A total of 44 subjects (22 healthy volunteers, 22 patients with MDD) were planned to complete the study. Twenty-two healthy subjects and 20 patients with MDD were recruited, completed, and analyzed for the study.

Centers

2 centers in United States

Publication

None

Test Product (s), Dose(s), and Mode(s) of Administration

[^{11}C]ABP688 was administered as a single slow bolus i.v. injection, followed by a PET scan. The targeted administration of radioactivity was 300 MBq (allowed range: 150 – 400 MBq) with high specific activity corresponding to a dose of ≤ 6 µg.

Statistical Methods

All clinical data including background and demographic information, physical examinations, drug administration records, vital signs/body measurements, ECG evaluations, clinical laboratory evaluations as well as adverse events have been listed by subject. Descriptive statistics have been presented for demography, vital signs, clinical laboratory evaluations and adverse events.

A predefined algorithm was used to select the primary endpoint from among DV_{norm}, DV_{tot} and DVR'. A linear mixed model was used to compare the primary endpoint between healthy volunteers and the patient group. The model included the fixed effects of center, cohort, brain region, side (left, right), and center-by-cohort, region-by-cohort, side-by-cohort, region-by-side-by-cohort, and center-by-side-by-cohort interactions, and the random effect of subject.

The relationship between the primary endpoint and the psychiatric scales was explored using scatter plots and Spearman's correlation coefficient.

A supportive voxel-wise comparison of mGlu5 receptor availability between the two cohorts was also performed using SPM5.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria for healthy volunteers: subjects in good health as determined by past medical history, physical examination, vital signs, electrocardiogram (ECG), and laboratory tests at screening; no family history of movement disorders, no significant clinical neurological findings, minimum weight of 50 kg.

Inclusion criteria for patients with MDD (only acutely ill patients):

Presence of either major depressive disorder, single episode or recurrent according to DSM-IV criteria and confirmed by the Structured Clinical Interview for DSM-IV (SCID).

Patients had to show the following levels of symptomatology:

- HAM-D (17-item scale) ≥ 16
- CGI ≥ 4 (moderately ill)

Exclusion criteria specific for MDD patients:

Presence and/or history of a clinically significant major neurological or psychiatric disorder other than MDD or Generalized Anxiety Disorder.

Axis I co-morbidity was excluded except anxiety spectrum disorders.

Exclusion criteria for both volunteers and MDD patients: subjects with significant neurological or psychiatric disease or significant illness within the two weeks prior to dosing; other clinically significant abnormality on physical, neurological, or laboratory examination or on electrocardiogram (ECG) that, in the opinion of the Investigator precludes the patient from the study; current clinically significant systemic illness or symptoms (e.g., respiratory or cardiovascular disease); history of myocardial infarction or history of clinically significant cancer within the last 5 years; history of clinically significant drug allergy; history of atopic allergy (asthma, urticaria, eczematous dermatitis); history of allergic disease or anaphylactic shock; smokers (use of tobacco products in the previous 3 months and/or urine cotinine greater than 500 ng/mL), evidence suggestive of liver or renal disease (Creatinine ≥ 150 μmol/L; Bilirubin ≥ 27 μmol/L or 1.6 mg/dL); MRI scan that shows evidence of stroke, infarct, or other space-occupying lesion or structural abnormality.

History of immunocompromise, including a positive HIV (ELISA and Western blot) test result, a positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.

Use of any prescription drug or over-the-counter (OTC) medication within 2 weeks prior to dosing, history of drug or alcohol abuse within the 12 months prior to dosing, current use of anticonvulsant, anticoagulant or narcotic medications,; evidence from an Allen test of incomplete communication between the radial and ulnar artery, in either hand.

Significant radiation exposure, especially in the last quarter (either x-ray or nuclear medicine studies). Any earlier nuclear medicine studies. Presence of contraindications to PET scan or MRI investigations. Participation in any clinical investigation within 4 weeks prior to dosing or ever participated in a research study with an amyloid lowering objective. Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing.

Participant Flow

	MDD Patient N=20 n (%)	Healthy Volunteers N=22 n (%)	Total N=42 n (%)
Patients			
Completed	20 (100.0)	22 (100.0)	42 (100.0)
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)
Main cause of discontinuation			
Adverse event(s)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Subject withdrew consent	0 (0.0)	0 (0.0)	0 (0.0)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)

Baseline Characteristics

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		MDD Patient N=20	Healthy Volunteers N=22	Total N=42
Age (years)	Mean (SD)	63.0 (6.33)	66.4 (7.30)	64.8 (6.98)
	Median	61.0	68.0	62.5
	Range	55 - 80	55 - 78	55 - 80
Gender - n (%)	Female	15 (75.0)	13 (59.1)	28 (66.7)
	Male	5 (25.0)	9 (40.9)	14 (33.3)
Race - n (%)	Caucasian	13 (65.0)	17 (77.3)	30 (71.4)
	Black	6 (30.0)	4 (18.2)	10 (23.8)
	Asia	1 (5.0)	0 (0.0)	1 (2.4)
	Other	0 (0.0)	1 (4.5)	1 (2.4)
Weight (kg)	Mean (SD)	83.18 (17.908)	81.02 (14.052)	82.05 (15.841)
	Median	83.75	79.15	79.15
	Range	61.6 - 122.9	62.5 - 116.6	61.6 - 122.9
Height (cm)	Mean (SD)	166.7 (9.64)	168.6 (8.09)	167.7 (8.81)
	Median	167.5	168.0	168.0
	Range	149 - 180	156 - 180	149 - 180

Safety Results

ABP688 was safe and well tolerated following a single dose administration in elderly healthy volunteers and elderly MDD patients. There were no clinically relevant changes in the Laboratory assessments, vital signs, or ECG during the trial. There were only a few AEs noted during the trial. All AEs were mild in nature and not considered to be clinically significant in either treatment group.

Adverse Events by System Organ Class

	MDD Patient N=20 n (%)	Health Volunteers N=22 n (%)	Total N=42 n (%)
Patients with AE(s)	2 (10.0)	1 (4.5)	3 (7.1)
System organ class			
Gastrointestinal disorders	1 (5.0)	0 (0.0)	1 (2.4)
General disorders and administration site conditions	1 (5.0)	0 (0.0)	1 (2.4)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (4.5)	1 (2.4)
Nervous system disorders	2 (10.0)	0 (0.0)	2 (4.8)
Skin and subcutaneous tissue disorders	1 (5.0)	0 (0.0)	1 (2.4)

Reported AEs Overall by Preferred Term n (%)

	MDD Patient N=20 n (%)	Health Volunteers N=22 n (%)	Total N=42 n (%)
Patients with AE(s)	2 (10.0)	1 (4.5)	3 (7.1)
Preferred term			
Nausea	1 (5.0)	0 (0.0)	1 (2.4)
Fatigue	1 (5.0)	0 (0.0)	1 (2.4)
Injection site erythema	1 (5.0)	0 (0.0)	1 (2.4)
Edema peripheral	1 (5.0)	0 (0.0)	1 (2.4)
Bone pain	0 (0.0)	1 (4.5)	1 (2.4)
Headache	1 (5.0)	0 (0.0)	1 (2.4)
Migraine	1 (5.0)	0 (0.0)	1 (2.4)
Hyperhidrosis	1 (5.0)	0 (0.0)	1 (2.4)

Serious Adverse Events and Deaths

None

Other Relevant Findings

PET imaging results

In the present study, there was no detectable difference in mGlu5 receptor availability in the brain of elderly patients with MDD compared to elderly healthy volunteers. The binding of [^{11}C]ABP688 was also similar between MDD patients with early and late onset depression.

Date of Clinical Trial Report

18 Aug 2011

Date Inclusion on Novartis Clinical Trial Results Database

03 Feb 2012

Date of Latest Update

27 Jan 2012