A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, Pharmacodynamic and Pharmacokinetic Effects of BMS-708163 in the Treatment of Patients with Prodromal Alzheimer's Disease

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON33225

Source
ToetsingOnline

Brief title
CN156-018

Condition

- Other condition
- Dementia and amnestic conditions

Synonym
Prodromal Alzheimer's Disease

Health condition

Milde geheugenstoornissen, amnestische stoornissen, prodromale stoornissen ziekte van Alzheimer

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharma Industry

Intervention

Keyword: BMS-708163, Phase 2, Prodromal Alzheimer's Disease

Outcome measures

Primary outcome

The primary outcome of the study is to evaluate if BMS-708163 is safe and well

tolerated.

Secondary outcome

The secondary outcomes of the study are to assess if BMS-708163 lowers Aβ40 and

Aβ42 in CSF and plasma and if it slows clinical progression.

Study description

Background summary

This is the second multiple-dose clinical trial experience with BMS-708163, a GammaSecretase Inhibitor, in patients with AD. The first multiple dose study in mild to moderate AD is ongoing. This study will evaluate and compare BMS-708163 125 mg/day versus placebo with regard to safety, tolerability, pharmacodynamic and pharmacokinetic effects. The information from this study will be used primarily to provide safety and tolerability data but will also serve to verify biomarker inclusion criteria, assist in dose selection and inform sample size estimates for a Phase 3 prodromal AD program using BMS-708163.
Dose selection for this study is based on the strategy of safely delivering sufficient gamma secretase inhibition (reduction of brain Aβ concentrations) while minimizing Notch inhibition. Since there is no clinical data to suggest

the minimum level of gamma-secretase inhibition that is necessary for clinical efficacy, the upper range dose of 125 mg/day selected in this Phase 2 study is based on safety. That is, the 125 mg/day dose of BMS-708163 yields a target exposure that was associated with acceptable tolerability and safety in Phase 1 studies with an approximately > 50% reduction in CSF Aβ.

Study objective

The primary objective of the study is to assess the safety and tolerability of BMS-708163 in patients with prodromal Alzheimer*s disease.

Study design

The study is a multi-center, randomized, double-blind, 2-arm, placebo-controlled, 176 week, parallel-group study in patients with prodromal Alzheimer*s disease to evaluate safety, tolerability, pharmacodynamic and pharmacokinetic effects of once daily dosing of BMS-708163.
All patients will be randomly assigned in a double-blind manner to one of the following treatment groups: placebo or 125 mg BMS-708163 once daily. All patients will initially be treated with 50 mg for 2 weeks and then increased to 125 mg for the remainder of the treatment period.
Subjects who do not meet the CSF inclusion criteria (CSF Aβ42 < 200 pg/mL or Total tau/Aβ42 ratio >= 0.39) but otherwise fulfill the study inclusion criteria may continue to be followed for rating scale visits but will not be randomized to any treatment arm. Approximately 100 patients will enter the non-randomized observational group. Subjects in this non-randomized observational cohort will serve to provide prospectively collected comparison data regarding CSF cutoff values and progression to dementia rates. Once subjects in this observation cohort progress to a diagnosis of dementia they will be discontinued from the study and receive standard of care treatment.

Intervention

BMS-708163 is an investigational product in this study. All patients who meet the study entry criteria will receive placebo or 125 mg BMS-708163 once daily.

Study burden and risks

Burden: study procedures (physical exams, blood sampling, MRI scan, lumbar puncture, completing questionnaires) and regular attendance for hospital visits during the treatment phase

Risks: possible adverse events of BMS-708163

Benefit: possibility that BMS-708163 slows down disease progression

Group relatedness: knowledge gain from this study may also help other patients in the future

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

a) Patient meets prodromal Alzheimer*s disease criteria as defined by:
i) Memory complaint by subject or study partner that is verified by a study partner.
ii) Abnormal memory function documented by at least 1 of the 2 following criteria: scoring below the education adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale - Revised (the maximum score is 25):
- less than or equal to 8 for 16 or more years of education.
- less than or equal to 4 for 8 - 15 years of education.
- less than or equal to 2 for 0 - 7 years of education OR Free and Cued Selective Reminding

Test (FCSRT) Total score of <=39.
b) CSF Aβ42 levels below 200 pg/mL or Total Tau/Aβ42 ratio of >= 0.39. Additionally, patients who meet all other inclusion/exclusion criteria with the exception of the CSF criteria above, may be eligible to be followed in a non-randomized, observational cohort to assess progression rates
c) Mini-Mental State Exam score between 24 and 30 (inclusive)
d) Clinical Dementia Rating global score must be = 0.5 at screening and baseline and the Memory Box score must be at least 0.5 at both screening and baseline;
e) If patients have had either CT or MRI imaging of the brain within 12 months prior to baseline, the results should either be normal or demonstrate atrophy consistent with an Alzheimer*s disease diagnosis;
f) Patient has a score of less or equal than 4 on the Modified Hachinski Scale (MHIS) at screening
g) Women who are postmenopausal and men, ages 45 to 90.

Exclusion criteria

a) Patient*s diagnosed with Dementia per DSM-IV criteria;
b) Patients with a history of gastrointestinal illnesses
c) Patients taking memantine or ginko biloba
d) Patients that have taken an agent with a primary mechanism of action related to Aβ levels or function (eg, gamma-secretase inhibitors, Aβ antibodies or vaccines targeting beta-amyloid) within 12 months prior to baseline.
e) Patients that required medications for agitation or psychotic features within 3 months prior to baseline (including all antipsychotic medications).
f) Patients that have received a new anxiolytic or sleep medication not taken at a stable dose within 30 days prior to baseline. Low dose anxiolytics pre-medications prior to diagnostic testing (e.g. neuroimaging, lumbar puncture, etc.) is allowed.
g) Pg-p substrates with narrow therapeutic index, Digoxin
h) Patients who have been treated for or have had a diagnosis of schizophrenia or Bipolar Disorder within 3 years, prior to screening
i) Patients who have had an active depressive episode within six months prior to screening
j) Patients with a history of neurosyphilis (indicated by a positive RPR test and confirmed by a positive FTA-ABS test)
k) Patients having a history of drug or alcohol abuse within 12 months prior to screening as defined by DSM-IV-TR criteria

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-10-2009
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	gamma-secretase inhibitor

Ethics review

Approved WMO Date:	08-06-2009
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-05-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-04-2013

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-010067-16-NL
ClinicalTrials.gov	NCT00890890
CCMO	NL28084.028.09