A Placebo-controlled, Double-blind, Parallel-group, Bayesian Adaptive Randomization Design and Dose Regimen-finding Study to Evaluate Safety, Tolerability, and Efficacy of BAN2401 in Subjects With Early Alzheimer*s Disease

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Objectives:Primary Objectives:1. To evaluate the efficacy of BAN2401 compared to placebo by establishing the ED90 (as defined in theprotocol) for BAN2401 on the derived Composite Clinical Score at 12 months of treatment in subjects withEarly...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mental impairment disorders
Study type	Interventional

Summary

ID

NL-OMON40054

Source
ToetsingOnline

Brief title
Eisai Alzheimer disease ABBA

Condition

- Mental impairment disorders

Synonym
Alzheimer's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Industry: Eisai

Intervention

Keyword: Alzheimer Disease, BAN2401

Outcome measures

Primary outcome

Analysis for the Primary Endpoint

The primary analysis will be based on subjects from the Full Analysis Set with

the prespecified censoring rules

applied. . The primary endpoint is the change from baseline to 12 months in the

derived Composite Clinical Score.

The dose-response of the primary endpoint is modeled with a two-dimensional

first-order normal dynamic linear

model, where Normal and Inverse-Gamma priors are used. The primary efficacy

analysis will calculate the

Bayesian posterior probability that the dose identified is the most likely ED90

dose that achieves the CSD compared

to the placebo arm. At each interim analysis and the final analysis, three

Bayesian probabilities will be

summarized for each active dose: the probability of being the ED90 dose, the

probability of being statistically

superior to placebo and the probability of being statistically superior to

placebo by the CSD. The study will be
considered a success in the final analysis (full randomization and all subjects reach 12 months of treatment) if there
is at least an 80% probability that the ED90 achieves the CSD from placebo.
For the clinical efficacy data (i.e., derived Clinical Composite Score, MMSE, CDR-SB, ADAS-cog, and FAQ),
subjects will be censored at the time of initiation of new AChEIs or memantine treatment regimens if they were not
on AChEIs or memantine at randomization, and will be censored at the time of dose adjustment of AChEIs or
memantine if they were already on stable treatment of AChEIs or memantine at randomization. Subjects with poor
compliance (proportion of doses taken <60%) at each interim or final analysis will be censored at the last visit time
that the subject is in good compliance (proportion of doses taken 60%). The compliance at each interim analysis or
at the final analysis is cumulative. The value of the primary endpoint for censored subjects will be imputed using
data up to the censoring time and Bayesian imputation methods.
After unblinding, the primary endpoint will be analyzed using the Bayesian methods described above as well as
conventional statistical methods. The following additional Bayesian analyses will be conducted:

* The primary endpoint will be analyzed regardless of compliance using the same

Bayesian analysis method

as in the primary analysis.

* The primary endpoint will be analyzed regardless of initiation or dose

adjustment of new AChEIs or

memantine using the same Bayesian method as in the primary analysis

* The primary endpoint will be analyzed regardless of initiation or dose

adjustment of new AChEIs or

memantine and regardless of compliance using the same Bayesian analysis method

as primary analysis.

This is an intent-to-treat analysis without any censoring.

* In case of early success, the primary analysis as well as sensitivity

analyses will be repeated after all

subjects have completed 12 months of followup or have been lost to followup.

Statistical methods for the final conventional analyses will use a mixed

effects model with repeated measures on the

change from baseline in the derived Composite Clinical Score at 12 months. The

model will include randomization

stratification variables; clinical subgroup (MCI due to AD, mild AD), the

presence or absence of ongoing AD

treatment (i.e., AChEIs and/or memantine), APOE status (positive, negative) and

baseline Composite Clinical Score

as covariates. These analyses will be performed on the full analysis set as

well as the per protocol set based on the

ITT principle.

Secondary outcome

Analysis for the Secondary Endpoints

A mixed-effects model with repeated measures will be used to analyze the

secondary endpoints:

* Change from baseline in the derived Composite Clinical Score at 18 months

* Change from baseline in total hippocampal volume at 12 ad 18 months

* Change from baseline in amyloid PET at 12 and 18 months

Comparisons between each treatment group and placebo will be performed.

Study description

Background summary

The main purpose of this research study is to find out how well a possible new drug called BAN2401 works in people who have early Alzheimer*s disease (Mild Cognitive Impairment due to Alzheimer*s disease or mild Alzheimer*s dementia). People with Alzheimer*s disease have a build-up of abnormal protein known as amyloid in their brains. BAN2401 is thought to reduce the amount of this abnormal protein. The purpose of this research is to find out if the study drug has a benefit on a person*s cognitive status via a series of specialised cognitive tests.

The purpose of this research is also to find out if this study drug is safe and well-tolerated in people with early Alzheimer*s disease. The study drug will be given by injecting it into a vein and the research will also find out how much of the study drug is in the blood at different times after the injection.

Study objective

Objectives:
Primary Objectives:
1. To evaluate the efficacy of BAN2401 compared to placebo by establishing the ED90 (as defined in the
protocol) for BAN2401 on the derived Composite Clinical Score at 12 months of treatment in subjects with

Early Alzheimer*s Disease (EAD), defined as mild cognitive impairment (MCI) due to Alzheimer*s
disease (AD) - intermediate likelihood or mild Alzheimer*s dementia
2. To assess the safety and tolerability of 3 doses and 2 dose regimens of BAN2401 in subjects with EAD
Secondary Objectives:
1. To evaluate the effect of BAN2401 compared to placebo on the derived Composite Clinical Score
following 18 months of treatment in subjects with EAD
2. To evaluate the potential disease-modifying effects of BAN2401 compared to placebo on total
hippocampal atrophy at 6, 12, and 18 months of treatment in subjects with EAD as measured by total
hippocampal volume using volumetric magnetic resonance imaging (vMRI)
3. To evaluate the potential disease-modifying effects of BAN2401 compared to placebo on brain amyloid
levels at 12 and 18 months of treatment in subjects with EAD as measured by amyloid positron emission
tomography (PET)

Study design

Study Design:
This will be a multinational, multicenter, double-blind, placebo-controlled, parallel group study, using a Bayesian
design with response adaptive randomization (RAR) across placebo or 5 active arms of BAN2401 to determine
clinical efficacy and to explore the dose response of BAN2401 using a composite clinical score.
BAN2401-G000-201 is an 18-month study with 5 dose regimens, which comprise 3 dose levels given biweekly
(once every 2 weeks) and 2 dose levels given monthly (once every 4 weeks). The dose levels are 2.5, 5 and 10
mg/kg biweekly and 5 and 10 mg/kg monthly.
Frequent interim analyses will be conducted to continually update randomization allocation on the basis of the
primary clinical endpoint, which is the change from baseline in the derived composite score at 12 months of
treatment. This approach allows for ongoing assessment of drug futility or evidence for early success and for
continued changes in randomization that favor efficacious treatment arms. Thus, the Bayesian approach not only
limits exposure of subjects to non-efficacous treatment arms but can also mitigate the risks associated with larger
and longer trials required to demonstrate clinical efficacy by leading to more efficient project termination or early
advancement to a successful Phase 3 program. After the 12-month assessments

have been completed, treatment
will continue to 18 months to follow the time course of any treatment effects observed at 12 months, and to evaluate
biomarker and neuroimaging effects that may be consistent with potential disease modification.
Subjects will be from two clinical subgroups, collectively designated as EAD for the purposes of this protocol:
(a) MCI due to AD - intermediate likelihood and (b) mild Alzheimer*s dementia.
At study entry, subjects will be
stratified according to clinical subgroup, apolipoprotein E (APOE) status (i.e., APOE4 positive and negative) and
the presence or absence of ongoing AD treatment (i.e., acetylcholinesterase inhibitors [AChEIs] and/or memantine).
Randomization into the two clinical subgroups will be reasonably balanced whereby at least 60% of the total
number of subjects will have MCI due to AD - intermediate likelihood and at least 30% will have mild Alzheimer*s
dementia. The first 196 subjects will be randomized according to a fixed schedule (4:2:2:2:2:2; Placebo [4] to each
of the active arms [2 each]). After 196 subjects have been randomized into the study, an interim analysis (IA) will
be conducted and the RAR will guide subsequent randomization into dose groups.
Interim analyses and RAR will
be repeated after 250 subjects have been randomized and again after each additional 50 subjects are randomized up
to a maximum of 800 subjects, and will then be repeated at 3-month intervals until all subjects complete 12 months
of treatment.

Intervention

NA

Study burden and risks

NA

Contacts

Public
Eisai

European Knowledge Centre, Mosquito Way
Hatfield AL10 9SN

GB
Scientific
Eisai

European Knowledge Centre, Mosquito Way
Hatfield AL10 9SN
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Diagnosis
Mild Cognitive Impairment due to Alzheimer*s Disease - intermediate likelihood:
1. Subjects who meet the National Institute of Aging - Alzheimer*s Association (NIA-AA) core clinical criteria for mild cognitive impairment due to Alzheimer*s disease - intermediate likelihood
2. Subjects who have a CDR score of 0.5 and a Memory Box score of 0.5 or greater at Screening and Baseline
3. Subjects who report a history of subjective memory decline with gradual onset and slow progression over the last one year before Screening; MUST be corroborated by an informant
4. Subjects with objective impairment in episodic memory as indicated by 1-1.5 standard deviations below age-adjusted mean in the WMS-IV LMII:
a) 11-15 for age 50 to 64 years
b)9-12 for age 65 to 69 years
c) 8-11 for age 70 to 74 years
d)6-9 for age 75 to 79 years
e) 4-7 for age 80 to 90 years;Mild Alzheimer*s Dementia:
5. Subjects who meet the NIA-AA core clinical criteria for probable AD
6. Subjects who have a CDR score of 0.5-1.0 and a Memory Box score of 0.5 or greater at Screening and Baseline;Key Inclusion Criteria that must be met by ALL Subjects:
7. Positive amyloid load as indicated by PET assessment of imaging agent uptake into brain

8. Male or female subjects aged between 50 and 90 years, inclusive
9. MMSE score equal to or greater than 22, and equal to or less than 30, Screening and Baseline except for the following countries, where MMSE score must be equal to or greater than 22 and equal to or less than 28 at Screening and Baseline: United Kingdom, Spain, Germany, Sweden, France, and the Netherlands
10. Body Mass Index (BMI) < 35 at Screening
11. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative human β-chorionic gonadotropin assay [ß-hCG]. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
12. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).
13. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (e.g., total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 35 days after study drug discontinuation. If currently abstinent, the subject must agree to use a double-barrier method as de cribed above if she becomes sexually active during the study period or for 35 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 35 days after study drug discontinuation.
14. Subjects who are receiving an acetylcholine esterase inhibitor and/or memantine for AD must be on a stable dose for at least 12 weeks prior to Baseline. Treatment-naïve subjects for AD can be entered into the study. Unless otherwise stated, subjects must have been on stable doses of all other (i.e., non-AD related) permitted concomitant medications for at least 4 weeks prior to Screening.
15. Must have an identified caregiver/informant, defined as an informant or person who spends at least 8 hours per week with the subject, and who is able to support the subject for the duration of the study. The caregiver/informant must provide separate written informed consent. In addition this person must be willing and able to provide follow-up information on the subject throughout the course of the study. A permanent caregiver/informant need not be living in the same residence with the subject. For such a caregiver/informant not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver/informant readily during the times when the caregiver/informant is not with the subject. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. Caregivers/informants need only to be present at visits where clinical assessment of CDR, and FAQ takes place.
16. Provide written informed consent
17. Willing and able to comply with all aspects of the protocol

Exclusion criteria

1. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject*s AD
2. History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of Screening
3. Any psychiatric diagnosis or symptoms, (e.g., hallucinations, major depression, or delusions) that could interfere with study procedures in the subject
4. GDS score >= 8 at Screening
5. Contraindications to MRI scanning, including cardiac pacemaker/ defibrillator, ferromagnetic metal implants, e,g., in skull and cardiac devices other than those approved as safe for use in MR scanners
6. Evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening. All MRIs will be acquired using a standardized procedure that will be outlined in the Imaging Charter and Imaging Acquisition Guidelines (IAG) and will be read by an approved centralized reader.
7. Other significant pathological findings on brain MRI at Screening, including but not limited to: more than 4 micro-hemorrhages (defined as 10 mm or less at the greatest diameter); a single macro-hemorrhage greater than 10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions (e.g., arachnoid cysts); or brain tumors (e.g., meningioma)
8. Hypersensitivity to BAN2401 or any of the excipients, or to any monoclonal antibody treatment
9. Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study
10. Subjects with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or INR >1.5)
11. For subjects not taking thyroid hormone, free triiodothyronine (T3), free thyroxine (T4), or thyroid stimulating hormone (TSH) outside the normal range. For subjects taking thyroid hormone, free T3 or free T4 outside the normal range, or TSH above the upper limit of normal (ULN) at Screening
12. Abnormally low serum Vitamin B12 levels for the testing laboratory (if subject is taking Vitamin B12 injections, level should be at or above the lower limit of normal [LLN] for the testing laboratory).
13. A prolonged QT/QTc interval (QTc > 450 ms) as demonstrated by a repeated electrocardiogram (ECG)
14. Known to be human immunodeficiency virus (HIV) positive
15. Any other clinically significant abnormalities in physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the principal investigator (PI), require further investigation or treatment or which may interfere with study procedures or safety
16. Uncontrolled Type 1 or Type 2 diabetes mellitus. Evidence of uncontrolled diabetes mellitus includes hemoglobulin A1c (HbA1c) > 9%.
17. Uncontrolled hypertension with a history of blood pressure consistently above 165/100

mm Hg at Screening
18. History of uncontrolled cardiovascular disease within 6 months of Screening, including acute coronary syndrome, clinically significant valvular heart disease, uncompensated heart failure (New York Heart Association [NYHA] Class III and Class IV), or uncontrolled arrhythmia
19. Subjects with malignant neoplasms within 3 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects). Subjects who had malignant neoplasms but who have had at least 3 years of documented uninterrupted remission before Screening need not be excluded.
20. Has a *yes* answer to Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation type 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
21. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening or a positive urine drug test at Screening. Subjects who test positive for benzodiazepines or opioids in urine drug testing need not be excluded if in the clinical opinion of the investigator, this is due to the subject taking prior/concomitant medications containing benzodiazepines or opioids for a medical condition and not due to drug abuse.
22. Any other medical conditions (e.g., cardiac, respiratory, gastrointestinal, renal disease) which are not stably controlled, or which in the opinion of the investigator(s) could affect the subject*s safety or interfere with the study assessments
23. Subjects who are taking prohibited medications
24. Participation in a clinical study involving any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 1 year before Screening
25. Participation in a clinical study involving any new chemical entities for AD within 6 months prior to Screening unless it can be documented that the subject was in a placebo treatment arm
26. Participation in any other investigational medication or device study in the 8 weeks or 5 half-lives (whichever is longer) of the medication before randomization unless it can be documented that the subject was in a placebo treatment arm
27. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the principal investigator this operation does not interfere with study procedures and subject safety.
28. Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

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):	17-06-2014
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Amyvid
Generic name:	Florbetapir (18F)
Product type:	Medicine
Brand name:	BAN2401
Generic name:	BAN2401
Product type:	Medicine
Brand name:	flutemetamol
Generic name:	flutemetamol

Ethics review

Approved WMO Date:	22-10-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-02-2014
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-08-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2012-002843-11-NL
Other	IND number 105081
CCMO	NL42652.056.13