A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of agitation in patients with dementia of the Alzheimer*s type.

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The primary objective is to:* Evaluate the efficacy, safety, and tolerability of AVP-786 compared to placebo for thetreatment of agitation in patients with dementia of the Alzheimer*s typeThe secondary objectives are to:* Evaluate the effects of AVP...

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

Summary

ID

NL-OMON52046

Source
ToetsingOnline

Brief title
Otsuka 307

Condition

- Mental impairment disorders
- Dementia and amnestic conditions

Synonym
Agitation, due to Alzheimer, restlessness

Research involving
Human

Sponsors and support

Primary sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Agitation, AVP-786, Dementia

Outcome measures

Primary outcome

Primary Efficacy Measure: Cohen-Mansfield Agitation Inventory (CMAI)

Secondary outcome

Key Secondary Efficacy Measure: Clinical Global Impression of Severity of

Illness for Agitation (CGIS-Agitation)

Other efficacy measures include:

* Change from baseline to each study visit in efficacy period in CMAI Total

score

* Change from baseline to each study visit in efficacy period in CGISAgitation

score

* CGIC-Agitation score at each study visit in the efficacy period

* Change from baseline to each study visit in efficacy period in NPI-AA score

* Change from baseline to each study visit in efficacy period in NPI total score

* CMAI Response Rate at each study visit in efficacy period, where response is

defined as >= 30% reduction in CMAI Total Score from baseline

* CMAI Response Rate at each study visit in efficacy period, where response is defined as >= 50% reduction in CMAI Total Score from baseline

* Change from baseline to each study visit in efficacy period in the EQ- 5D-5L total score

* Change from baseline to each study visit in efficacy period in the RUDLite

Safety: Safety and tolerability of AVP-786 will be assessed by reported adverse events (AEs), physical and neurological examinations, vital signs, clinical laboratory assessments, resting 12-lead electrocardiograms (ECGs), MMSE, the Epworth Sleepiness Scale (ESS), and the Sheehan Suicidality Tracking Scale (S-STS).

Study description

Background summary

Agitation is widely recognized by clinicians as a common and important clinical feature of Alzheimer*s disease and other forms of dementia. Agitation, aggression, depression, hallucinations, and delusions are estimated to affect up to approximately 90% of patients with Alzheimer*s disease with an increase in prevalence as the disease progresses. In a meta analyses of data from 55 studies, overall prevalence of agitation ranged from 5% to 88% across all studies, with 23 studies reporting the prevalence of at least one neuropsychiatric syndrome with a range of 40% to 100%. Agitation in patients with dementia is associated with increased functional disability, worse quality of life, earlier institutionalization, increased caregiver burden, increased healthcare costs, shorter time to severe dementia and accelerated mortality. Currently, there is no approved treatment in the US to manage agitation in patients with Alzheimer*s disease. Pharmacologic treatments for patients with agitation in Alzheimer*s disease include off-label use of atypical antipsychotics, selective serotonin reuptake inhibitors, benzodiazepines, and anticonvulsants; however, these treatments provide only modest efficacy that is

offset by relatively poor adherence, safety, and tolerability. It is widely recognized that a safe and effective treatment for patients with agitation in Alzheimer*s disease represents a significant unmet need. Such a treatment could profoundly impact patient care, potentially reduce caregiver burden, and improve overall disease prognosis. AVP-786 is a combination product of deudextromethorphan hydrobromide (d6-DM), a central nervous system (CNS)-active agent, and quinidine sulfate (Q), used as an inhibitor of d6-DM metabolism via the cytochrome P450 (CYP) liver isoenzyme 2D6 (CYP2D6). AVP-786 is being developed by Otsuka Pharmaceutical Development & Commercialization, Inc. for the treatment of neuropsychiatric conditions.
The demonstrated receptor pharmacology of d6-DM supports a potential clinical benefit for agitation in patients with dementia of the Alzheimer*s type.

Study objective

The primary objective is to:
* Evaluate the efficacy, safety, and tolerability of AVP-786 compared to placebo for the
treatment of agitation in patients with dementia of the Alzheimer*s type
The secondary objectives are to:
* Evaluate the effects of AVP-786 compared to placebo on global assessments of severity and
improvement of agitation
* Evaluate the effects of AVP-786 compared to placebo on neuropsychiatric symptoms
* Evaluate the effects of AVP-786 compared to placebo on measures of quality of life and
resource utilization

Study design

Phase 3, multicenter, randomized, double-blind, placebo-controlled study

Intervention

AVP-786 capsule will be administered orally BID up to a maximum dose of d6-DM 42.63 mg and Q 4.9 mg and matching placebo capsule (identical appearance to AVP-786 capsule) will be administered orally BID.

Study burden and risks

For this study the patients will need to visit hospital 10 times in 20 weeks. A visit lasts 1-2 hours.

they will have to undergo/complete the following:
- Physical exam and neurological exam, 2 times

- Measurement of blood pressure, body temperature, breathing rate, and heart rate, 9 times
- ECG, 5 times
- Questionnaires: NPI (9 times), MMSE (3 times), ESS (2 times), S-STS (3 times), RUD-Lite (2 times), EQ-5D-5L (2 times)
- Blood (total 262.5 ml) and urine tests, 4 and 1 times respectively
- Pregnancy tests in women of childbearing potential, 3 times
- Female patients: no breastfeeding allowed. Effective methods of birth control must be used from the time of signing the ICF, throughout the entire study and for 30 days following the last dose of the study drug.
- Male patients: due to the potential risk of the effect on the sperm appropriate method of contraception must be used starting at screening and continuing for at least 30 days following the last dose of study drug.
- Diary for the caregiver to complete

The patient must appoint someone such as a family member or professional caregiver who knows them well enough to provide information about the patient to the study doctor and staff during the study. This person must attend all study visits with them and will be required to sign the caregiver informed consent form.

Common risks: (occurred in equal to or greater than 1% and less than 10% of participants)
• Abdominal discomfort
• Anxiety
• Fall
• Somnolence (sleepiness)
• Dizziness
• Upper Respiratory Tract Infection
• Dry Mouth
• Headache
• Contusion (bruise)
• Nasopharyngitis (common cold)
• Nausea
• Vomiting
• Hyperhidrosis (excessive sweating)
• Hypertension (high blood pressure)
• Skin abrasion (scrape)
• Arthralgia (joint pain)
• Electrocardiogram Qt Prolonged (a measurement related to the heart rhythm)
• Laceration (cut)
• Dehydration
• Pneumonia (chest infection)
• Sinus bradycardia (slow heartbeat)
• Syncope (passing out; brief loss of consciousness caused by insufficient blood flow to the brain and a fall in blood pressure)
• Increase in Blood Creatine Phosphokinase (a protein found in your heart,

brain, and skeletal muscles)

Rare Serious Side Effects Reported from Quinidine, a Component of AVP-786:
• Decrease of platelets in the blood (increases risk of bleeding)
• Vasculitis (inflammation of blood vessels)
• Lupus-like syndrome (a disorder of the immune system presenting with a rash)
• Swelling and inflammation of the liver (symptoms include jaundice [yellowing color of the eyes or skin], nausea, loss of appetite)
• Changes to your heart rate

Severe side effects that have been reported from dextromethorphan overdose may include:
• Respiratory depression (decrease in respiratory function)
• Seizures (convulsions)
• Coma

The studies conducted to date showed a favorable safety and tolerability profile for AVP-786. The plasma concentrations of d6-DM (and metabolites) observed in these studies were shown to be generally well tolerated. The combined safety data from the AVP-786 clinical studies, in addition to risk minimization measures taken in the clinical studies, support further development of AVP-786.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Elderly (65 years and older)

Inclusion criteria

1. Males and females 50 to 90 years of age (inclusive) at the time of informed consent.
2. Diagnosis of probable Alzheimer*s disease according to the 2011 NIA-AA working groups criteria. Either outpatients or residents of an assisted living facility, a skilled nursing home, a dementia unit, or any other type of facility providing long-term care.
3. MMSE score between 8 and 24 (inclusive) at Screening and Baseline.
4. Patient has clinically significant, moderate-to-severe agitation for at least 2 weeks prior to Screening that interferes with daily routine per the Investigator*s judgment.
5. Patients who require pharmacotherapy for the treatment of agitation per the Investigator*s judgment, after:
* An evaluation of reversible factors (eg, pain, infection, or polypharmacy), and
* A course of nonpharmacological interventions (eg, redirecting behavior, group activities, music therapy).
6. Diagnosis of agitation must meet the International Psychogeriatric Association (IPA) provisional definition of agitation.
7. NPI-AA total score (frequency × severity) must be >= 4 at Screening and Baseline.
8. Patient must meet an additional predetermined blinded eligibility criterion.
9. Patient has stable cardiac, pulmonary, hepatic, and renal function per the Investigator*s judgment.
10. No clinically significant findings on the Screening ECGs based on central review and on the Baseline predose ECG based on the machine read and Investigator*s evaluation.
11. Women who are of childbearing potential and are sexually active must use an effective method of birth control for at least 1 month prior to the Baseline, during participation in the study, and for at least 30 days after the last dose of study drug. The following requirements must be met:
* Women who are of childbearing potential must use 2 of the following precautions in order to minimize the risk of failure of 1 method of birth control: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device,

birth control pills, birth control depot injection, birth control implant, or condom with spermicide or sponge with spermicide. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, or withdrawal are not acceptable methods of contraception.
* Women who are sterile (ie, had an oophorectomy and/or hysterectomy), postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause), or practice true abstinence (when this method is in line with the preferred and usual lifestyle of the patient) are exempt from this requirement.
* Women who are lactating, pregnant, or plan to become pregnant are not eligible for participation in the study.
12. For restricted and prohibited concomitant medications, patients willing and able to meet all protocol requirements for duration of stability or washout prior to study entry and during the study (see protocol Table 3 Restricted and Prohibited Concomitant Medications and Appendix 1 Prohibited Concomitant Medications).
13. Caregiver must be willing and able to comply with all study procedures, including adherence to administering study drug and not administering any prohibited medications during the study. The caregiver must spend a minimum of 2 hours with the patient per day for at least 4 days per week to qualify as caregiver.
14. Patient/caregiver must be willing to sign and receive a copy of patient/caregiver informed consent form (ICF) after the nature and risks of study participation have been fully explained. Patients who are not capable of signing the ICF but are able to provide assent, or the patient*s authorized representative agrees to participation (for patients unable to provide assent) are allowed.

Exclusion criteria

1. Caregiver is unwilling or unable, in the opinion of the Investigator, to comply with study instructions. 2. Patient has dementia predominantly of non-Alzheimer*s type (eg, vascular dementia, frontotemporal dementia, Parkinson*s disease, substance-induced dementia). 3. Patients with symptoms of agitation that are not secondary to Alzheimer*s dementia (eg, secondary to pain, other psychiatric disorder, or delirium). 4. Patients who have been diagnosed with an Axis 1 disorder (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision [DSM-5] criteria) including, but not limited to: * Schizophrenia, schizoaffective disorder, or other psychotic disorders not related to dementia * Bipolar I or II disorder, bipolar disorder not otherwise specified * Current Major Depressive Episode: Patients with a history of major depressive disorder, that is currently not symptomatic, are eligible. Patients currently on a stable dose(s) of allowed antidepressant medication(s) for at least 3 months prior to the Screening visit are eligible.

5. Patients with myasthenia gravis (contraindication for quinidine). 6. Patients with any personal history of complete heart block, QTc prolongation, or torsades de pointes. a. Screening and Baseline predose QT interval corrected for heart rate using the Fridericia*s formula (QTcF) of > 450 msec for males and > 470 msec for females unless due to ventricular pacing (See Section 8.1.5). Screening ECGs will be based on central review. Baseline predose ECG will be based on the machine read and Investigator*s evaluation; if the QTcF result from the machine read is exclusionary, do not administer study drug and please contact a Medical Monitor. b. Presence of premature ventricular contractions (PVCs) as evaluated by a central reader and deemed clinically significant by the Investigator. 7. Patients with any family history of congenital QT interval prolongation syndrome. 8. Patients with known hypersensitivity to DM, Q, opiate drugs (codeine, etc), or any other ingredient of the study drug. 9. Patients who have ever received DM co-administered with Q or d6-DM co-administered with Q. 10. Patients who would be likely to require a prohibited concomitant medication during the study (see Table 3, Restricted and Prohibited Concomitant Medications and Appendix 1 Prohibited Concomitant Medications). 11. Patients with co-existent clinically significant or unstable systemic diseases that could confound the interpretation of the safety results of the study (eg, malignancy [except skin basal cell carcinoma], poorly controlled diabetes, poorly controlled hypertension, unstable pulmonary, renal or hepatic disease, unstable ischemic cardiac disease, dilated cardiomyopathy, or unstable valvular heart disease). Certain other nonmetastatic cancer may be allowed. Each case is to be evaluated individually with a Medical Monitor. 12. Patients who are currently participating in or who have participated in other interventional (drug or device) clinical study, or found to be a *Virtually Certain* match in Clinical Trial Subject Database (CTSdatabase) with a patient who has participated in another interventional drug or device study within 30 days of Baseline. 13. Patients with history of postural syncope or any history of unexplained syncope (evaluated on a case-by-case basis) within 12 months of Baseline. 14. Patients with a history of substance and/or alcohol abuse within 12 months of Baseline. 15. Patients determined to have a high imminent risk of falls during the study based on a clinical evaluation by the Investigator. 16. Patients with evidence of serious risk of suicide at Screening and Baseline based on the Sheehan Suicidality Tracking Scale (S-STS), ie, a score of 3 or 4 on any one question 2 through 6 or 11, or a score of 2 or higher on any one questions 1a, 7 through 10, or 12, or who in the opinion of the Investigator present a serious risk of suicide. 17. Patients who, in the opinion of the Investigator, Medical Monitor, or sponsor, should not participate in the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	02-07-2021
Enrollment:	22
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	AVP-786
Generic name:	deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]

Ethics review

Approved WMO Date:	01-03-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-10-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	04-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-11-2023
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	EUCTR2020-000799-39-NL
ClinicalTrials.gov	NCT04464564
CCMO	NL76317.056.21