CONNECTION: A Global Phase 3, Double-Blind, Placebo-Controlled Safety and Efficacy Study of Oral Dimebon in Patients with Mild-to-Moderate Alzheimer's Disease

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To determine the benefit of Dimebon as compared to placebo on the primary measure of cognition and memory, the Alzheimer*s Disease Assessment Scale * cognitive subscale (ADAS-cog); andTo determine the benefit of Dimebon as compared to placebo on the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cranial nerve disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON33588

Source
ToetsingOnline

Brief title
CONNECTION

Condition

- Cranial nerve disorders (excl neoplasms)

Synonym
Alzheimer's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Medivation, Inc.
Source(s) of monetary or material Support: Medivation;Inc.

Intervention

Keyword: Alzheimer□s Disease, Dimebon

Outcome measures

Primary outcome

A comparison between the mean change from baseline in the Dimebon 20 mg TID treatment group and the placebo group on the ADAS-cog at Week 26; and

A comparison of the distributions of the CIBIC-plus (ADCS CGIC) at Week 26 in the Dimebon 20 mg TID treatment group and the placebo group.

Secondary outcome

* Key Secondary Endpoint: A comparison between the mean change from baseline to Week 26 of the Dimebon 20 mg TID treatment group and the placebo group on the ADCS-ADL;

* A comparison between the mean change from baseline to Week 26 of the Dimebon 20 mg TID treatment group and the placebo group on the NPI;

* A comparison between the Dimebon 20 mg TID treatment group and the placebo group in the emergence of new delusions and hallucinations or in the reduction of delusions and hallucinations as assessed by subdomains of the NPI;

* A comparison between the mean change from baseline to Week 26 of the Dimebon 20 mg TID treatment group and the placebo group on the MMSE;

* A comparison between the mean change from baseline to Week 26 of the Dimebon 20 mg TID treatment group and the placebo group on the RUD Lite;

* Comparisons of each outcome measure between the Dimebon 20 mg TID group and the placebo group using the mean change from baseline to Week 12 of the Dimebon 20 mg TID;
Comparisons of each outcome measure between the Dimebon 5 mg TID group and the placebo group using the mean change from baseline to Week 26.

The safety of Dimebon among the three treatment groups will be assessed by the frequency of serious adverse events, the frequency of discontinuation of Dimebon treatment due to an adverse event, the frequency and severity of adverse events, as well as the frequency of new laboratory and ECG abnormalities.
The impact of covariates will be evaluated in order to identify underlying factors responsible for the variability of pharmacokinetic parameters and to identify sub-populations. Every effort will be made to develop a model that links Dimebon exposure (e.g., the maximum plasma concentration at one hour [C1h], and the minimum or trough plasma concentration [Cmin]) with the co primary outcome measures, as well as with key adverse events.

Study description

Background summary

CONNECTION: A Global Phase 3, Double-Blind, Placebo-Controlled Safety and Efficacy Study of Oral Dimebon in Patients with Mild-to-Moderate Alzheimer*s Disease.
Alzheimer*s Disease (AD) is a progressive and fatal neurodegenerative disorder manifested by persistent deterioration of memory and cognitive functions, progressive impairment of activities of daily living, and a variety of

neuropsychiatric symptoms and behavioral disturbances. The classic clinical features of AD are an amnestic type of memory impairment, deterioration of language, and visuospatial deficits. Motor and sensory abnormalities, gait disturbances, and seizures are generally believed to be uncommon until the late phases of the disease. Death, most often from complications of immobility such as pneumonia or pulmonary embolism, usually ensues within five to nine years after diagnosis. This progressive and fatal brain disease affects an estimated 5.1 million Americans and represents the seventh leading cause of death in the United States (US). Approximately 26 million people worldwide suffer from AD

Study objective

To determine the benefit of Dimebon as compared to placebo on the primary measure of cognition and memory, the Alzheimer*s Disease Assessment Scale * cognitive subscale (ADAS-cog); and
To determine the benefit of Dimebon as compared to placebo on the primary measure of global function, the Clinician*s Interview-Based Impression of Change, plus caregiver input (CIBIC-plus).

Study design

This study is a global Phase 3, randomized, double-blind, placebo-controlled safety and efficacy study of two doses of oral Dimebon (5 mg three times a day [TID] and 20 mg TID) administered for 26 weeks to patients with mild-to-moderate Alzheimer*s Disease (AD).

Intervention

All patients will receive two tablets of study drug TID during Week 1 and one tablet of study drug TID for the remaining 25 weeks.
Low-Dose Group: Dimebon, 5 mg (one 5 mg tablet plus one placebo tablet) orally TID × 1 week, then Dimebon, 5 mg (one 5 mg tablet) orally TID × 25 weeks.
High-Dose Group: Dimebon, 10 mg (two 5 mg tablets) orally TID × 1 week, then Dimebon 20 mg (one 20 mg tablet) orally TID × 25 weeks.

Study burden and risks

Occasionally Dimebon can cause dry mouth, drowsiness, headache, inability to sleep or interrupted sleep, depressed mood, or irritability. In addition, there is always the risk of unknown side effects occurring.

During the study, blood samples will be taken for testing. The risks of giving blood include temporary discomfort from the needle in the arm, bruising, swelling at the needle site, or (rarely) infection.

It is possible that Dimebon may reduce symptoms of Alzheimer*s disease, but

there is no guarantee. The results of the study may help doctors to understand Dimebon and Alzheimer*s disease.

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

Patients must meet the following inclusion criteria:
*Males or females * 50 years of age;
*Diagnosis of probable AD according to the following criteria:
*Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision (DSM-IV-TR) as listed in Appendix A;
*National Institute of Neurological and Communicative Disorders and Stroke * Alzheimer*s Disease and Related Disorder Association*s Criteria (NINCDS-ADRDA) for probable AD as listed in Appendix B;

*MMSE score between 10 and 24, inclusive;
*Modified Hachinski Ischemic Score * 4 (Appendix C);
*Brain imaging such as magnetic resonance imaging and/or computed tomography within three months of enrollment;
*Patients must have at least six years of prior education and should have previously (in pre-AD condition) been capable of reading, writing, and communicating effectively with others;
*Patients must be able to cooperate with study drug administration and study procedures and to abide by the study restrictions;
*Patients must be willing and able to give informed consent. If the patient is not competent, a mentally-competent legally-acceptable representative must provide informed consent on their behalf, and the patient must provide assent;
*Patients must have a caregiver who assists the patient at least five days per week for at least three hours per day and has intimate knowledge of the patient*s cognitive, functional, and emotional states, and of the patient*s personal care. The caregiver must be willing to accompany the patient to all study visits, and must be willing to supervise study drug administration. The caregiver must be willing and able to give informedconsent, be able to read and write, and be capable of providing responses to the CIBIC-plus, ADCS-ADL, NPI, and the RUD Lite assessment tools;
*Patients may be living in an assisted care facility if living independently;
*Female patients must be surgically sterile or postmenopausal (for at least two years) or agree to use double-barrier method of birth control. Male patients must agree to utilize a double-barrier method of birth control during the study and for at least 30 days following the last dose of study drug. The double-barrier method includes two of the following forms of contraception: condom, contraceptive sponge, diaphragm, or cervical ring with spermicidal gel or foam.

Exclusion criteria

Patients must NOT meet any of the following exclusion criteria:
*Major structural brain disease (e.g., ischemic infarcts, subdural hematoma, hemorrhage, hydrocephalus, brain tumors, multiple subcortical ischemic lesions, or a single lesion in a critical region [e.g., thalamus, hippocampus]);
*Any major medical illness or unstable medical condition within six months of screening that may interfere with the patient*s ability to comply with study procedures and abide by study restrictions including:
*Any physical disability that would prevent completion of study procedures or assessments (e.g., blindness, deafness, non-AD-related speech impairment, sensory or motor dysfunction);
*Active peptic ulcer disease within the last three months;
*Diabetes mellitus requiring insulin treatment;
*History of cancer within five years of enrollment with the exception of non-melanoma skin cancers or prostate cancer that has been stable for six months;
*Hypotension (SBP < 86 mmHg) or bradycardia with heart rate less than 46 beats per minute at screening or on more than one occasion within three months prior to enrollment;
*Uncontrolled hypertension as indicated by a resting systolic blood pressure > 170 millimeters of mercury (mmHg) or diastolic blood pressure > 105 mmHg at screening or on

more than one occasion within three months prior to enrollment;
*Clinically significant ECG abnormalities or ECG at the Screening visit with a corrected QT interval by the Fridericia correction formula of > 460 milliseconds (msec) for males and > 470 msec for females. NOTE: Evidence of an old myocardial infarction or atrial fibrillation or flutter with stable rate control for at least six months prior to the Screening visit, pacemaker, axis deviation, first degree atrioventricular block, hemi-block or right bundle branch block are acceptable;
*History of clinically-relevant ventricular arrhythmias, second-degree or complete heart block without pacemaker placement, or left bundle branch block;
*History of clinically apparent stroke;
History of traumatic brain injury with remaining neurological deficit;
Neurodegenerative disease other than AD (e.g., Parkinson*s Disease, Huntington*s Disease, amyotrophic lateral sclerosis);
*History of epilepsy or seizure disorder requiring ongoing treatment, or any seizure or loss of consciousness within the six months preceding enrollment;
*Any psychiatric diagnosis according to DSM-IV-TR that may interfere with the patient*s ability to perform the study and all assessments (e.g., alcohol or drug-related abuse or alcohol dependence [Appendix D], or alcohol or drug-related dementia, major depression, mental retardation, schizophrenia, bipolar disorder, etc.);
*Pregnant or lactating females;
*Residence in a nursing home or assisted care facility with need for 24-hour care and supervision;
*Caregiver is not clinically trained and is paid to care for more than two patients;
*History of hypersensitivity to Dimebon or other antihistamines;
*Known human immunodeficiency virus (HIV) seropositivity or Acquired Immunodeficiency Syndrome (AIDS); history of Hepatitis B (HBV) or Hepatitis C viral (HCV) infection. NOTE: HIV, HBV, and HCV testing will not be performed as part of the Screening visit laboratories;
*Any of the following laboratory abnormalities at the Screening visit:
*Clinically significant Vitamin B12 levels less than the lower limit of normal or on replacement Vitamin B12 for less than three months prior to enrollment;
*Clinically significant folate levels less than the lower limit of normal or on replacement folate therapy for less than three months prior to enrollment;
*Thyroid-stimulating hormone levels greater than the upper limit of normal AND a free thyroxine lower than the lower limit of normal;
*Positive Rapid Plasma Reagin (RPR) confirmed by Fluorescent Treponemal Antibody - Absorption [FTA-ABS]);
*Total bilirubin (Tbili), alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels greater than two times the upper limit of normal;
*Renal impairment with a serum creatinine (Cr) > 133 *mol/L (1.5 mg/dL);
*Hematocrit (Hct) less than 37% for males and less than 32% for females, absolute neutrophil cell count of less than or equal to 1,500/microliter (*L), or platelet cell count of less than 100,000/*L;
*Use of cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine, or huperzine) or memantine within 90 days prior to enrollment;
Use of prescription medical food (e.g., Axona) or nutriceuticals marketed for AD or cognitive impairment within 30 days of Screening and throughout the study;
*Use of non-selective antihistamines within 7 days prior to enrollment;

*Use of the following medications within 30 days prior to enrollment:
*Narcotic analgesics more frequently than two times per week as needed for pain;
*Low potency antipsychotics (e.g., chlorpromazine, thioridazine);
*Antihypertensive agents with frequent central nervous system side effects (e.g., clonidine);
*Anti-Parkinson*s Disease medications (e.g., selegiline, levodopa, amantadine) for the treatment of Parkinson*s Disease;
*Lithium;
*Clozapine;
*Bupropion;
NOTE: Subjects who require anxiolytics, sedatives, sleeping medications, or atypical or high potency antipsychotic medications are allowed if doses have remained stable for 30 days prior to enrollment;
NOTE: Use of anti-depressants or the use of anti-epileptic medication for non-seizure related treatment is allowed if the dose has remained stable for at least 60 days prior to enrollment;
*Participation in a previous clinical trial of Dimebon;
*Participation in an investigational drug or device study within 30 days prior to study entry, or 90 days prior to study entry if the investigational drug study involved therapy for AD;
*Treatment with immunomodulators to treat AD (vaccines, antibodies, intravenous immunoglobulin, etc.) within the last two years.

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:	Recruitment stopped
Start date (anticipated):	23-01-2009
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dimebon contains an active substance of CHEMICAL ORIGIN a synthetically prepared small molecule ami
Generic name:	Dimebon

Ethics review

Approved WMO Date:	08-09-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-12-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2008-000095-25-NL
CCMO	NL23983.029.08