A Phase 3, Randomized, Double-Blind, Placebo-Controlled Safety and Efficacy Study of Dimebon in Patients with Mild-to-Moderate Huntington Disease

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To determine the safety and efficacy of Dimebon in patients with mild-to-moderate Huntington Disease

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON35412

Source
ToetsingOnline

Brief title
HORIZON

Condition

- Neurological disorders congenital

Synonym
Huntington's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Medivation Inc.
Source(s) of monetary or material Support: By the Sponsor

Intervention

Keyword: HORIZON, Huntingdon's Disease

Outcome measures

Primary outcome

Co-Primary Objectives:

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To determine the effect of Dimebon as compared to placebo on cognition as measured by the Mini-Mental State Examination (MMSE); and

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To determine the effect 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).

Secondary outcome

Secondary Objectives:

• To determine the effect of Dimebon as compared to placebo on a measure of behavior, the Neuropsychiatric Inventory (NPI);

• To determine the effect of Dimebon as compared to placebo on a measure of self-care and daily function, the Alzheimer*s Disease Cooperative Study - Activities of Daily Living (ADCS-ADL);

• To determine the effect of Dimebon as compared to placebo on a measure of motor impairment, the Unified Huntington Disease Rating Scale (UHDRS*99) Total Motor Score;

• To determine the safety of treatment with Dimebon as compared to placebo; and

• To examine the relationship between Dimebon plasma concentrations and

efficacy and safety outcomes.

Study description

Background summary

Dimebon is a drug that is well tolerated by persons and of which it has been proved in a small group that it results in an improvement in mental capacity and general functioning. The purpose of the study is to examine the effect of the drug on the mental capacity and functioning of persons who have Huntington Disease when it is administered for more than 6 months. It will be compared with a non-active substance, a so-called placebo. The drug has not been registered and it is not for sale in the Netherlands. The study will be carried out at about 50 research centers of the Huntington Research Group in North-America and the European Huntington Disease Network (EHDN) in Europe and Australia. In total 350 patients will participate in the study.

Study objective

To determine the safety and efficacy of Dimebon in patients with mild-to-moderate Huntington Disease

Study design

This study is a multicenter Phase 3, randomized, double-blind, placebo-controlled safety and efficacy study of Dimebon treatment in subjects with mild-to-moderate Huntington disease (HD). The study will evaluate Dimebon 20 mg three times daily (TID) administered orally (PO) for six months (26 weeks) compared with matching placebo TID for the primary safety and efficacy analyses. Eligible subjects will have clinical features of HD and a Cytosine Adenine Guanine (CAG) polyglutamate repeat expansion >= 36; a UHDRS*99 Total Functional Capacity (TFC) between five and 13, inclusive; subjective and objective evidence of cognitive impairment as determined by the Investigator and the MMSE respectively, and be at least 30 years old. Subjects will be required to participate in the study with a caregiver who assists/spends time with the subject at least five days per week for at least three hours per day. Approximately 350 subjects will be centrally randomized 1:1 into two groups of 175 subjects each (Dimebon 20 mg TID and placebo). Randomization will be stratified by the use of concomitant tetrabenazine. Subjects randomized to Dimebon will receive Dimebon 10 mg TID for the first seven days of therapy, followed by titration up to Dimebon 20 mg TID for the remainder of the treatment period. Subjects randomized to placebo will receive identical matching tablets without the active ingredient.
Efficacy assessments including the MMSE, Clinician*s Interview-Based Impression

of Severity (CIBIS)/CIBIC-plus, NPI, ADCS-ADL, and the UHDRS*99 Total Motor Score will be performed at the Baseline visit, and at the Weeks 13, and 26 visits. The MMSE will also be performed at the Week 6 visit. An independent rater not involved in and blinded to other aspects of the trial will administer the CIBIC-plus. The CIBIC-plus instrument in this trial will be the 7-point Alzheimer*s Disease Cooperative Study - Clinician*s Global Impression of Change (ADCS-CGIC). All other efficacy assessments will be performed consistently by a second rater. The same raters will perform the same efficacy assessments for a specific subject in the same order throughout the study.
Safety and tolerability will be assessed by recording of adverse events and by monitoring of vital signs, physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs). In addition, the Columbia Suicide Severity Rating Scale will be administered at each study visit to collect and record suicidal ideation and attempts in a standardized fashion. Central laboratories will be utilized for laboratory safety assessments and ECG assessments. An independent Data Monitoring Committee (DMC) will monitor safety data in the trial by blinded treatment group on an ongoing basis. The DMC may request treatment group unblinding if safety concerns arise.
Plasma samples to assess Dimebon concentrations will be collected at the Baseline/Day 1, Week 6, Week 13, and Week 26 visits at specified times pre-and post-dose. These data will be used to evaluate the relationship between plasma exposure to Dimebon and efficacy and safety outcomes.
Subjects who complete the 26-week treatment course and Week 26 efficacy assessments will be offered the opportunity to enroll into an open-label extension study under a separate protocol. This study will begin at the Week 26 visit and allow subjects to receive Dimebon through marketing authorization in their respective countries. Subjects who decline enrollment into the open-label extension study will return to the clinic 30 days after cessation of study drug for follow-up safety evaluations.

Intervention

Patients will be treated with oral Dimebon.

Study burden and risks

RISKS AND DISCOMFORTS
The safety, tolerability, and effectiveness of Dimebon in HD are being investigated in this study. You may experience side effects from taking the study drug. The study drug may cause all, some or none of the following side effects. Dimebon has occasionally been associated with a sedative (a state of calm, restfulness, or drowsiness) effect, dry mouth, constipation, depressed mood, headache, nausea and difficulty sleeping. In addition, there is always the risk of unknown side effects occurring.

BENEFITS

There is no guarantee of any direct benefit as a result of participating in this research study. It is possible that the study drug may be effective in reducing your symptoms of HD, but this cannot be guaranteed. It may have no effect or even worsen your HD symptoms. However your participation may provide information that is useful to our understanding of the study drug and HD.

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

Subjects eligible to participate in this study are persons who:
1. Have clinical features of HD and a CAG polyglutamate repeat expansion >= 36;
2. Have Stage 1, 2, or 3 HD with a UHDRS*99 TFC between five and 13 (inclusive) at the Screening visit;
3. Have cognitive impairment as noted by the following:

a. A Screening MMSE AND a baseline (pre-dose) MMSE score between 10 and 26 (inclusive); and
b. A subjective assessment of cognitive impairment with decline from pre-HD levels by the Investigator after interviewing the subject and caregiver;
4. Are willing and able to give informed consent for study participation and cytochrome P450 (CYP) 2D6 genotyping. If the subject is not competent, a mentally-competent legally-acceptable representative must provide informed consent on his/her behalf, and the subject must provide assent;
5. Are ambulatory and do not require skilled nursing care;
6. Are aged 30 years or older;
7. If female, are either a) of childbearing potential and compliant in using adequate birth control or b) not of childbearing potential. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception (hormone-based, intrauterine device, barrier contraception [e.g., condom or occlusive cap {diaphragm or cervical/vault caps} with spermicidal foam/gel/film/cream/suppository], vasectomized partner, or sexual abstinence) throughout the duration of the study. Women not of childbearing potential may have undergone menopause or permanent sterilization (hysterectomy, bilateral oophorectomy, or bilateral tubal ligation). Menopause is defined as one year without menses. If the patient*s menopausal status is in question, a follicle-stimulating hormone (FSH) level of > 40 milli-international units per milliliter (mIU/mL) must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented;
8. If male, is either a) of reproductive potential and compliant in using adequate birth control through 30 days after the last dose of study drug or b) not of reproductive potential. Surgical sterilization must be documented. Adequate birth control for males is defined as a condom and spermicidal gel or foam, or abstinence throughout the duration of the study;
9. If currently taking psychotropic medications (including antidepressants and neuroleptics) or other medications to treat the symptoms of HD (with the exception of tetrabenazine) must be on stable doses for at least 30 days prior to randomization;
10. If currently taking tetrabenazine must be tolerating it well, on a stable dose for at least 60 days prior to randomization, and have the intent to continue the current dose throughout the study duration. For subjects who have previously taken tetrabenazine, subjects must be off therapy for at least 60 days prior to randomization and have the intent to remain off therapy throughout the study duration. Note: Subjects will not be allowed to initiate tetrabenazine during the study period;
11. Have at least eight years of prior education and should have previously (in pre-HD condition) been capable of reading, writing, and communicating effectively with others;
12. Have a caregiver who assists/spends time with the subject at least five days per week for at least three hours per day and has intimate knowledge of the subject*s cognitive, functional, and emotional states, and of the subject*s personal care. The caregiver must be willing to accompany the subject to as many study visits as possible, but at a minimum the Screening, Baseline, Week 13 and Week 26 visits, and be available to speak by telephone for other study visits if they are not in attendance. The caregiver must be willing to supervise study drug administration and be able to give informed consent for his/her participation, be able to read and write, and be capable of providing responses to the CIBIC-plus, NPI, and the ADCS-ADL;
13. Capable of complying with study procedures, including being able to swallow tablets the size of the study drug.

Exclusion criteria

Subjects ineligible to participate in this study are persons who:
1. Had onset of HD symptoms prior to age 18;
2. Have active suicidality as measured by responding *yes* to question 4 or 5 on the Columbia Suicide Severity Rating Scale (Baseline version)
3. Have any major medical illness or unstable medical condition within 180 days of screening that may interfere with the subject*s ability to comply with study procedures and abide by study restrictions, or with the ability to interpret safety data, including:
a. Any physical disability that would prevent completion of study procedures or assessments (e.g., blindness or significant visual impairment, deafness or significant hearing impairment, non-HD-related speech impairment);
b. A diagnosis of diabetes mellitus requiring treatment with insulin;
c. A history of cancer within five years of randomization with the exception of non-melanoma skin cancers or prostate cancer that has been stable for at least six months, or American Joint Committee on Cancer Grade 0 or Grade 1 cancers that have a remote probability of recurrence, in the opinion of the Site Investigator, in consultation with the Medical Monitor and study Principal Investigator;
4. Have any of the following cardiovascular parameters:
a. Hypotension (systolic blood pressure < 86 millimeters of mercury [mmHg]) or bradycardia with heart rate less than 45 beats per minute at Screening or on more than one occasion within three months prior to Screening;
b. Uncontrolled hypertension as indicated by a resting systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg at Screening or on more than one occasion within three months prior to Screening;
c. Active cardiovascular disease including any of the following: unstable angina, decompensated congestive heart failure, clinically relevant arrhythmias. NOTE: A history of these conditions is acceptable, if stable under medical management. Subjects with pacemakers, subjects on anticoagulant therapy, and subjects who are stable with a prior history if MI may be included;
d. A corrected QT interval by the Fridericia correction formula (QTcF) of greater than 470 milliseconds (msec), second degree or higher heart block, or left bundle branch block on an ECG at the Screening visit;
5. Have a history of traumatic brain injury with residual neurological deficit or stroke;
6. Have another disease known to affect cognition other than HD (e.g., Parkinson disease, frontotemporal dementia, normal pressure hydrocephalus);
7. Have a history of a seizure disorder requiring ongoing treatment, febrile seizures, or any seizure including loss of consciousness within 180 days preceding randomization. NOTE: Use of anti-epileptic medication for non-seizure related treatment is allowed if the dose has remained stable for at least 30 days prior to randomization;
8. Have any current psychiatric diagnosis that may interfere with the subject*s ability to perform the study and all assessments (e.g., alcohol or drug-related abuse or alcohol dependence, or alcohol or drug-related dementia, major depression, mental retardation, schizophrenia, bipolar disorder, etc.); NOTE: Depression arising in the context of HD is not an Exclusion Criterion if on stable pharmacologic and/or non-pharmacologic management for 30 days preceding randomization. Subjects who require anxiolytics, sedatives, sleeping

medications, or antipsychotic medications prior to randomization are allowed if doses have remained stable for 30 days prior to randomization;
9. Are pregnant or lactating females;
10. Reside in a nursing home or assisted care facility with need for 24-hour care and supervision;
11. Have a paid caregiver who is not clinically trained that cares for more than two subjects;
12. Have been informed of their treatment assignment after participation in a previous blinded clinical study with Dimebon;
13. Have experienced a serious adverse event assessed as at least possibly related to study drug use in a previous clinical study of Dimebon;
14. Have a known history of human immunodeficiency virus (HIV) seropositivity; NOTE: HIV testing will not be performed as part of the Screening visit laboratories;
15. Have any of the following laboratory abnormalities at the Screening visit:
a. Total bilirubin, alanine aminotransferase (ALT), or aspartate aminotransferase (AST) levels greater than two times the upper limit of normal;
b. Renal impairment with a serum creatinine (Cr) > 1.5 mg/dL (133 µmol/L);
c. Hematocrit less than 37% for males and less than 32% for females, absolute neutrophil cell count of less than 1,500/µL, or platelet cell count of less than 120,000/µL;
16. Have taken or plan to take a cholinesterase inhibitor (donepezil, rivastigmine, galantamine, tacrine, or huperzine) or memantine within 90 days prior to randomization through the end of the study;
17. Have taken or plan to take non-selective antihistamines within seven days prior to randomization through the end of the study including diphenhydramine, chlorpheniramine;
18. Have taken or plan to take clozapine or bupropion within 30 days prior to randomization through the end of the study;
19. Have taken or plan to take narcotic analgesics more frequently than two times per week as needed for pain within 30 days prior to randomization through the end of the study;
20. Have participated in an investigational drug or device study within 30 days prior to randomization, or 90 days prior to randomization if the investigational drug study involved therapy for HD;
21. Have donated blood or blood products within 30 days of randomization or plan to donate blood during the study.
22. Are immediate family members or employees of the participating Site Investigator, or any of the participating site staff;
23. Are living in the same household with another subject that is enrolled in the study;
24. Have any condition or reason that, in the opinion of the Site Investigator, interferes with the ability of the subject to participate in or complete the study, which places the subject at undue risk, or complicates the interpretation of safety or efficacy data.

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):	08-03-2010
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dimebon
Generic name:	Dimebon

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2009-011800-44-NL
ClinicalTrials.gov	NCT00920946
CCMO	NL29212.058.09