A Phase 2, Dose-Finding, Randomized, Parallel-Group, Double-Blind, Placebo-Controlled Study, Evaluating the Safety and Efficacy of Pridopidine 45 mg, 67.5 mg, 90 mg, and 112.5 mg Twice-Daily versus Placebo for Symptomatic Treatment in Patients with Huntington*s Disease

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The primary objective of this study is to assess the efficacy of pridopidine 67.5 to 112.5 mg twice daily (bid) on motor impairment in patients with HD after 26 weeks of treatment using the Unified Huntington*s Disease Rating Scale (UHDRS) Total...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON44821

Source
ToetsingOnline

Brief title
TV7820-CNS-20002 (0075/0070) Huntington's Disease.

Condition

- Movement disorders (incl parkinsonism)

Synonym
Huntington's Disease, neurodegenerative genetic disorder

Research involving
Human

Sponsors and support

Primary sponsor: TEVA Pharma
Source(s) of monetary or material Support: TEVA Branded Pharmaceutical Products R&D

Intervention

Keyword: Huntington's Disease, TV7820-CNS-20002

Outcome measures

Primary outcome

The primary objective of this study is to assess the efficacy of pridopidine

67.5 to 112.5 mg twice daily (bid) on motor impairment in patients with HD

after 26 weeks of treatment using the Unified Huntington*s Disease Rating Scale

(UHDRS) Total Motor Score (TMS).

Secondary outcome

The secondary efficacy objective of the study is to assess the effect of 26

weeks of treatment with pridopidine 67.5 to 112.5 mg bid on the modified

Physical Performance Test (mPPT).

The other secondary objectives are as follows:

* To evaluate the safety and tolerability of a range of pridopidine doses in

patients with HD the entire 52-week of study period.

* To explore the pharmacokinetics (PK) of pridopidine in the study population

* To investigate the relationship between exposure to pridopidine and outcome

measures (eg, clinical efficacy and toxicity parameters)

Study description

Background summary

Huntington's disease (HD) is een fatale neurodegeneratieve aandoening met een autosomaal dominante overerving. De ziekte is gekoppeld aan motor, gedrags- en cognitieve- symptomen. Motorische verstoringen zijn het belangrijkste kenmerk van de ziekte. Arbeidsongeschiktheid en ernstigheid van de ziekte correleren met negatieve motorische functies zoals achteruitgang van fijne motoriek en grove motorische coördinatievaardigheden, inclusief spraakmoeilijkheden en lichaamshouding.
Dopamine wordt alom beschouwd als een belangrijke neurotransmitter die verscheidene aspecten van de hersenfuncties moduleert, waaronder motoriek. Een gestoorde dopaminerge signalering is geimpliceerd in een aantal neurologische en psychiatrische aandoeningen en er zijn aanzienlijke klinische en preklinische aanwijzingen dat dopaminerge functies ook zijn gecompromitteerd in HD.
Een aantal medicijnen wordt voorgeschreven ter verbetering van de motorische en emotionele problemen die samenhangen met HD, maar het wetenschappelijke bewijs voor het nut van verschillende medicatie in HD is slecht. Slechts 1 medicijn, tetrabenazine, wat de dopamine beschikbaarheid en overdracht vermindert, is geregistreerd voor de behandeling van patiënten met HD. Geen geregistreerde geneesmiddelen zijn beschikbaar voor het beheren van de veelzijdige motorische symptomen. Zo is er een aanzienlijke onvervulde medische noodzaak om medicijnen te ontwikkelen om de symptomen van HD te verzachten.
Pridopidine (TV-7820, eerder bekend als ACR16) is a medicijn in ontwikkeling. Pridopidine hoort bij een nieuwe klasse van farmaceutische middelen, de dopidines, die worden beschouwd dopaminerge stabiliserende eigenschappen te hebben.
Dopidines zijn verbindingen die zowel dopamine-afhankelijke functies in het centrale zenuwstelsel (CZS) kunnen versterken en verzwakken, afhankelijk van het beginniveau van de dopaminerge activiteit. Het primaraire effect van pridopidine op HD-gerelateerde motorische symptomen wordt daarom verwacht plaats te vinden via de dopamine transmissie-modulerende eigenschappen van pridopidine.

Study objective

The primary objective of this study is to assess the efficacy of pridopidine 67.5 to 112.5 mg twice daily (bid) on motor impairment in patients with HD after 26 weeks of treatment using the Unified Huntington*s Disease Rating Scale

(UHDRS) Total Motor Score (TMS).

Study design

This is a multicenter, multinational, randomized, parallel-group, double-blind, placebo-controlled study to compare the efficacy and safety of pridopidine 45, 67.5, 90, and 112.5 mg bid versus placebo in the treatment of motor impairment in HD. The 45 mg dose level will not be formally included in the efficacy analyses. It is planned to enroll a total of 400 patients (80 patients within each treatment arm).
Patients will be equally randomized (1:1:1:1:1) to receive pridopidine 45, 67.5, 90, or 112.5 mg or placebo bid for 52 weeks, including a 4-week progressive titration period.

Intervention

Study Drug Dose, Mode of Administration, and Administration Rate:
The dose levels of pridopidine are 45, 67.5, 90, and 112.5 mg bid. Every patient will receive 3 capsules bid, ie,
3 capsules in the morning and 3 capsules in the afternoon, during the whole study period. There will not be an
afternoon dose at the final visit (Day 364/Early Termination).

Investigational Product: Pridopidine oral capsules 22.5 mg and 45mg

Study burden and risks

See section E9.

Contacts

Public
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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. Diagnosis of Huntington*s Disease (HD) based on clinical features and the presence of *36 cytosine-adenosine-guanine (CAG) repeats in the huntingtin gene (from historical data).;b. Male or female age *21 years, with an onset of HD after 18 years* old.;c. Females of child bearing potential have to be compliant in using adequate birth control throughout the duration of the study, including the follow-up period. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception (hormone-based, intrauterine device, or double-barrier contraception i.e. condom and diaphragm). Abstinence is an acceptable method of contraception only when this is preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male study participants have to be compliant in using adequate birth control with their partners throughout the duration of the study.;d. Body weight *50 kg.;e. A sum of *25 points on the UHDRS-TMS at the screening visit;f. UHDRS Independence Score (IS) equal to or less than 90% at the screening visit.;g. Able and willing to provide written informed consent prior to any study related procedure being performed at the screening visit. Patients with a legal guardian should be consented according to local requirements.;h. Willing to provide a blood sample for genetic analyses (including CAG analysis, cytochrome P450[CYP] 2D6 status, genetic long QT syndrome in patients who had QT prolongation following study drug administration or any other genetic analyses related to pridopidine response or HD) at the screening visit.;i. Willing and able to take oral medication and able to comply with the study specific procedures.;j. Ambulatory, being able to travel to the study centre, and judged by the investigator as likely to be able to continue to travel for the duration of the study.;k. Availability and willingness of a caregiver, informant or family member to accompany the patient to the clinic at study visits assessing CIBIC-Plus, HD QoL, and CGI-S/ CGI-C. ;l. For patients taking allowed antipsychotic, antidepressant or other psychotropic medication, the dosing of medication must have been kept constant for at least 6 weeks before baseline and must be kept constant during the study.

Exclusion criteria

a. A prolonged Fridericia-corrected QT (QTcF) interval (defined as a QTcF interval of >450 msec) at the screening visit. ;b. Patients with clinically significant heart disease at the screening visit.;c. Patients with a known history of Long QT Syndrome or a first degree relative with this condition.;d. Patients with a history of epilepsy or seizures within the last 5 years.;e. Have other serious medical illnesses which in the opinion of the investigator may put the patient at risk when participating in the study or may influence the results of the study or affect the patient's ability to take part in the study.;f. Patients with serum potassium, magnesium and/or calcium levels outside of the central laboratory*s reference range at the screening visit.;g. Patients receiving medications (within the last 6 weeks prior to baseline) that have been proven to prolong QT interval or who may require such medications during the course of the study such as but not limited to non allowed anti psychotic medications, tricyclic antidepressants and/or Class I antiarrhythmics.;h. Patients receiving medications (within the last 6 weeks prior to baseline) that are metabolized by CYP2D6 and have the potential of reducing seizure threshold.;i. Creatinine clearance <60 mL/min at screening, calculated using the Cockcroft-Gault equation. It is allowed to repeat the test once, if clinically appropriate.;j. Any clinically significant, abnormal, screening laboratory result which in the opinion of the investigator, affects the patients* suitability for the study or puts the patient at risk if he/she enters the study.;k. Alcohol and/or drug abuse within the 6 months prior to screening as defined by Diagnostic and Statistical Manual * Fourth Edition Text Revision criteria for substance abuse.;l. Patients with active suicidal ideation as measured by a most severe suicide ideation score of 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) or patients who answer *Yes* on any of the 5 C-SSRS Suicidal Behavior Items, if the attempt or acts were performed within 1 year of screening, or patients who, in the opinion of the investigator, present a serious risk of suicide.;m. Patients with known intracranial neoplasms, vascular malformations, history of cerebrovascular accident, or intracranial hemorrhage.;n. Females who are pregnant or breastfeeding.;o. Known allergy to any ingredients of the study medication or placebo. ;p. Previous exposure with pridopidine.;q. Treatment with tetrabenazine within 6 weeks of study baseline.;r. Treatment with any investigational product within 6 weeks of screening or patients planning to participate in another clinical study assessing any investigational product during the study.

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):	27-05-2014
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pridopidine
Generic name:	Pridopidine

Ethics review

Approved WMO Date:	20-12-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-04-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	23-09-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-12-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-04-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-06-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-06-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-09-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-10-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	27-05-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-06-2016
Application type:	Amendment
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	EUCTR2013-001888-23-NL
CCMO	NL46857.058.13