A Phase I Partially Blinded Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of Rivastigmine with Glycopyrrolate or Trospium in Healthy Elderly Volunteers

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Primary:To establish the safety and tolerability of rivastigmine when given with concomitant glycopyrrolate at an accelerated dose escalation schedule up to 12 mg BID.To establish the safety and tolerability of rivastigmine when given with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Dementia and amnestic conditions
Study type	Observational invasive

Summary

ID

NL-OMON44454

Source
ToetsingOnline

Brief title
RVT-104-1001 (CS0283)

Condition

- Dementia and amnestic conditions

Synonym
Alzheimer's disease, dementia

Research involving

Human

Sponsors and support

Primary sponsor: Axovant Scienced GmbH
Source(s) of monetary or material Support: Axovant Sciences GmbH

Intervention

Keyword: Pharmacodynamics, Pharmacokinetics, Safety, Tolerability

Outcome measures

Primary outcome

* Number of subjects completing full dose escalation

* Number of subjects in each group completing the 6 mg BID dosing period

Secondary outcome

* Highest dose achieved before stopping due to intolerability

* Nausea score by visual analog scale

* Number of vomiting episodes and time to first vomiting episode

* Abdominal pain score by visual analog scale

* Number of diarrhea episodes

* Percent of subjects reporting nausea

* Percent of subjects reporting vomiting

* Percent of subjects reporting diarrhea

* Percent of subjects reporting dizziness

* Other AEs

* General safety and tolerability parameters also include adverse events,

clinical laboratory, electrocardiogram (ECG), and vital sign assessments

* Plasma PK parameters of rivastigmine and metabolite as data permit

* Change from baseline in REM sleep parameters, including shortening of REM latency, increase in REM density and increase in the percentage duration of REM sleep during the night

* Spectral parameters in non-REM sleep (spindle power, spindle density)

* Change from baseline in nausea intensity based on a Visual Analog Scale (VAS) assessment

* Change from baseline in abdominal pain based on a VAS assessment

Study description

Background summary

Alzheimer*s disease (AD) is a progressive neurodegenerative disorder. According to the Alzheimer*s Association, a leading voluntary health organization in Alzheimer*s disease care, support and research, Alzheimer*s disease affects approximately 5.3 million people in the United States, and it is estimated that between 70% and 90% of those patients are classified as having mild-to-moderate Alzheimer*s disease [Alzheimer*s Association, 2013].

Dementia with Lewy bodies (DLB), also termed major neurocognitive disorder with Lewy bodies is a progressive neurocognitive illness characterized pathologically by the presence of diffuse clusters comprised of alpha synuclein and other proteins that aggregate in the brain and disrupt cognitive function (McKeith et al., 1996; McKeith et al., 2005). DLB is considered to be the second most prevalent cause of degenerative dementia in the elderly population (McKeith, 2004), accounting for up to 15 * 25% of dementia presentations (McKeith et al., 2000). While few studies of the exact prevalence of DLB have been published, the Lewy Body Dementia Association estimates that 1.4 million individuals are affected by Lewy body dementia in the US alone.

One of the pathophysiological hallmarks of AD and DLB is reduced cholinergic neurotransmission, based on the degeneration of key anatomical areas, which provide acetylcholine. These are primarily the Nucleus basalis Meynert (NBM) and, of particular relevance for cholinergic activation of the hippocampus, the medial septal area (MSA). As the hippocampus is primarily responsible for memory task the MSA could play a key role a decline in memory.

No new chemical entities have been approved by the U.S. Food and Drug

Administration (FDA) for the treatment of AD since 2003 or by the European Medicines Agency (EMA) since 2002. There are currently no approved treatments for DLB. Thus, new treatments or strategies that can improve or delay the decline in cognitive function are warranted.

Study objective

Primary:
To establish the safety and tolerability of rivastigmine when given with concomitant glycopyrrolate at an accelerated dose escalation schedule up to 12 mg BID.

To establish the safety and tolerability of rivastigmine when given with concomitant trospium at an accelerated dose escalation schedule up to 12 mg BID.

Secondary:
To characterize the pharmacokinetics of rivastigmine when given with concomitant glycopyrrolate or trospium at an accelerated dose escalation schedule up to 12 mg BID.

To characterize the pharmacodynamics of rivastigmine when given with concomitant glycopyrrolate or trospium at an accelerated dose escalation schedule up to 12 mg BID.

Study design

This study will be partially blinded where subjects will be randomized to rivastigmine plus glycopyrrolate or trospium. Rivastigmine will not be blinded. However, subjects and the Investigator will be blinded to the concomitant medication. In both parts, subjects will have a screening visit within 30 days of first dose.

Twenty-four subjects will be randomized to receive rivastigmine BID plus glycopyrrolate 2 mg BID or trospium 60 mg QD on an accelerated rivastigmine dose escalation schedule (12 subjects per arm) starting at 1.5 mg BID and escalating every three days for the first 4 doses, and every 6 days for the remaining 4 doses with a maximum dose of 12 mg BID. Subjects will be admitted to the clinical unit the day before the first rivastigmine dose and will remain in the unit for the duration of the rivastigmine dosing.

PK samples will be collected over a 12-hour period after the last morning dose of the 6 mg and 12 mg BID dosing periods if they reach that level of dose escalation. Trough samples will be collected the morning prior to each dose escalation. Subjects will return to the clinic for a follow-up visit 7 to 10 days after their last dose of rivastigmine.

The following assessments will be completed:
* Subjects will undergo a polysomnographic assessment three times: once before the first administration of study medication (overnight from Day -1 to Day 1 as baseline) and then again after the final evening dose of the 3 mg rivastigmine BID dose and the 6 mg BID rivastigmine dose.
* Subjects will complete a 100-mm VAS to assess nausea at multiple timepoints on the mornings of the first day of multiple dose escalations.
* Subjects will complete a 100-mm VAS to assess abdominal pain at multiple timepoints on the mornings of the first day of multiple dose escalations.

Study burden and risks

The dose levels of the study drugs are selected on the basis of the clinical experience with these drugs. The risk to health at these dose levels is limited but you may experience one of the in the ICF mentioned side-effects or other symptoms not previously reported. Your health will be closely monitored during the study to minimize these risks. If you experience any side effects, the research physician will treat these where necessary. If new information becomes available about the safety of the study drug, you will be informed as soon as possible.

The blood collection procedure is not dangerous, but may cause discomfort or bruising. Occasionally, fainting, bleeding or an infection at the blood sampling site can occur.

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

1. Healthy as determined by the Investigator, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if, in the opinion of the Investigator, the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. The Medical Monitor may be consulted as needed.
2. Male or female age 55 and above at screening.
3. A female subject is eligible to participate if she is of:
* Non-childbearing potential defined as pre-menopausal females with a documented bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries) or hysterectomy; hysteroscopic sterilization, or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 mIU/ml is confirmatory]. Documented verbal history from the subject is acceptable.
* Child-bearing potential and agrees to use one of the contraception methods listed in Section 5.6.1 for an appropriate period of time (as determined by the product label or Investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until the follow-up visit.
4. Male subjects must agree to use one of the contraception methods listed in Section 5.6.1. This criterion must be followed from the time of the first dose of study medication until 14 days after the last dose of study medication.
5. Body weight * 50 kg for men and * 45 kg for women and Body Mass Index within the range 18.5 31.0 kg/m2 (inclusive).
6. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

Exclusion criteria

1. The subject has a positive drug/alcohol screen at screening or Day 1. A minimum list of drugs that will be screened for is included in Section 7.3.4.
2. A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result at

screening.
3. A positive pre-study test for human immunodeficiency virus (HIV) antibody.
4. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct bilirubin values greater than 1.25x the upper limit of normal (ULN) at screening or Day 1. A single repeat is allowed for eligibility determination.
5. Current use of tobacco/nicotine/vaping/e-cig/ products within 1 month prior to screening.
6. History of regular alcohol consumption within 6 months of the study defined as:
* An average weekly intake of >14 drinks/week for men or >7 drinks/week for women. One drink is equivalent to (12 g alcohol) = 5 ounces (150 ml) of wine or 12 ounces (360 ml) of beer or 1.5 ounces (45 ml) of 80 proof distilled spirits.
7. The subject has received an investigational product (including placebo) within the following time period prior to the first dosing day in the current study: 60 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
8. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John*s Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and Medical Monitor the medication will not interfere with the study procedures or compromise subject safety (Section 6.9.2).
9. Consumption of Seville oranges or grapefruit (or their juices) from 7 days prior to the first dose of study medication.
10. History of clinically significant sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.
11. If heparin is used during PK sampling, subjects with a history of sensitivity to heparin or heparin-induced thrombocytopenia should not be enrolled.
12. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 60 day period.
13. Pregnant females as determined by positive serum or urine human chorionic gonadotropin test at screening or prior to dosing.
14. Lactating females.
15. Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy, function, or motility, hepatic and/or renal function that could interfere with the absorption, metabolism, and/or excretion of the study drugs. Subjects with a history of cholecystectomy, peptic ulceration, inflammatory bowel disease or pancreatitis should be excluded.
16. History of significant pulmonary, renal, gastrointestinal, ophthalmologic, genitourinary, or hepatic diseases.
17. History/evidence of symptomatic arrhythmia, angina/ischemia, coronary artery bypass grafting surgery or percutaneous transluminal coronary angioplasty or any clinically significant cardiac disease.
18. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):
Heart rate <45 and >100 bpm
PR Interval <120 and >220 msec
QRS duration <70 and >120 msec
QTcF interval >450 msec ;* Any conduction abnormality (including but not specific to AV block [2nd degree or higher], Wolff Parkinson White syndrome.
* Sinus pauses > 3 seconds.

19. The subject*s systolic blood pressure is outside the range of 90-150 mmHg, diastolic blood pressure is outside the range of 60-100 mmHg or heart rate is outside the range 45-100 bpm.
20. Positive orthostatic challenge test at screening.
21. Recent travel (less than seven days) with a time change greater than 1 hour.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-07-2017
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Exelon
Generic name:	Rivastigmine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Placebo
Generic name:	Placebo

Ethics review

Approved WMO Date:	06-06-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-06-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-09-2017
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	EUCTR2017-002010-31-NL
CCMO	NL61990.056.17