A single center, randomized study investigating the safety, tolerability, and pharmacokinetics of AZ-009 (Staccato apomorphine) in healthy volunteers and the safety, tolerability, pharmacokinetics, and pharmacodynamics of AZ-009 in subjects with established Parkinson*s Disease.

Published: 05-09-2018
Last updated: 10-01-2025

To examine the safety, tolerability, and pharmacokinetic profile of single ascending doses of AZ-009 compared to placebo (part B and C) or to Apo-Go (part A) in healthy volunteers being pretreated with domperidone and in patients with Parkinson...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48728

Source
ToetsingOnline

Brief title
SAD study of AZ-009 in HV and PD patients

Condition

- Other condition

Synonym
Parkinson's Disease, PD

Health condition

Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Alexza Pharmaceuticals Inc.
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: AZ-009, Parkinson's Disease, Staccato

Outcome measures

Primary outcome

* safety, tolerability, and pharmacokinetic profile of a single dose of AZ-009

(1 mg) compared with that of ApoGo (2 mg)

* tolerability and safety and pharmacokinetics of single ascending doses of

AZ-009 in healthy volunteers

- tolerability, safety, and pharmacokinetics of AZ-009 in subjects with

established Parkinson*s disease

Secondary outcome

NA

Study description

Background summary

AZ009 is a novel formulation of apomorphine. Apomorphine is a registered drug

indicated for the treatment of off-periods in patients with Parkinson's disease. Currently, the only available product with apomorphine is the injection-pen Apo-Go. Injection of Apo-Go can cause pain, local injection site reactions en may be difficult to use for patients when they are experiencing an off-period. AZ-009 is an inhalation device, which makes apomorfine available for absorption through the lungs. This is expected to have a quick effect on off-periods, and has the advantage of being a painless, easy to use administration route.

Study objective

To examine the safety, tolerability, and pharmacokinetic profile of single ascending doses of AZ-009 compared to placebo (part B and C) or to Apo-Go (part A) in healthy volunteers being pretreated with domperidone and in patients with Parkinson's Disease.

Study design

In Part A: AZ 009 safety and bioavailability will be compared with ApoGo in 8 healthy volunteers
In Part B: single ascending doses of AZ 009 will be administered in three groups of 8 healthy volunteers
In Part C: single ascending doses of AZ 009 will be administered in three groups of 8 Parkinson's Disease patients. When the highest dose is well tolerated, it can be decided to add a 4th cohort. However, dose will never exceed 6 mg.

Intervention

AZ-009/placebo/APO-Go

Study burden and risks

Subjects will be admitted to CHDR during 1 night and 1 day (part C) to 6 days (part A).
During the study period, blood will be drawn and an ApoGo injection (part A) and/or AZ 009 inhalation (all parts) will be administered.
Also, ECGs will be done, blood pressure will be measured, and other safety assessments will be done.

In Part C, patients with PD will experience off-periods because the last night-time dose of antiparkinson medication will be omitted. After administration of the study drug, it will be allowed to use their regular antiparkinson medication if the study drug is not effective in reducing symptoms of the off-period within 25 minutes.

The use of apomorphine is related to a risk of nausea and vomiting. To prevent this, subject will start using domperidon 3 days before the study drug administration and during the treatment period.

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

* Healthy adult males and females between 18 and 60 years of age, inclusive at the time of signing the informed consent document.
* Female subjects, who are:
o Surgically sterile (including bilateral tubal ligation) for at least 3 months prior to screening
o Postmenopausal, defined as 1 of the following:
* Last menstrual sequence greater than 12 months prior to screening
* Last menstrual sequence greater than 6 months prior to screening and a serum follicle-

stimulating hormone (FSH) concentration > 40 mIU/mL
o Of childbearing potential (i.e. do not meet the criteria outlined above); subjects must:
* Have a negative urine pregnancy test at Screening and Day -1, as verified by the study doctor prior to starting study therapy.
* Either commit to true abstinence from heterosexual contact or agree to use, and be able to comply with, effective contraception without interruption with one of the following methods during the study participation up until 90 days after administration of study drug:
* Oral contraceptive medications
* Intra uterine devices
* Hormonal implants
* Injectable contraceptive medications
* Double-barrier methods
* Male subjects must practice true abstinence from heterosexual contact or, during sexual contact with a pregnant female or a female of childbearing potential, agree to use a condom.;* Healthy, as determined by the responsible physician, based on a medical evaluation including history, physical examination, vital signs, electrocardiograms (ECGs) and laboratory tests assessed at the screening visit and prior to the first dose of study drug. A subject with a non-clinically significant abnormality or laboratory parameters outside the reference range may be re-screened and included if the parameter or abnormality is acceptable per protocol. ;* Body weight * 50 kg and BMI within the range of 18 to 32 kg/m2, inclusive, at screening.;* Negative urine tests for selected drugs of abuse and alcohol breath test at screening and Day -1.;* Dietary habits that fall within the range of normal, as determined by the investigator. Examples of unusual diets are liquid diets, protein-only diets, high fat-diets, or low-carbohydrate diets.;* Willing and able to be confined at the clinical research center for the study period, and adhere to overall study visit schedule, procedures and other protocol requirements.;* Understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted. ;Main criteria for Study Part C in PD Subjects IN ADDITION to above:
Inclusion Criteria
* Subjects between the ages of 30 and 85 with a clinical diagnosis of advanced PD who experience motor fluctuation and have recognizable OFF periods.
* Classified as Hoehn & Yahr stage I-IV in the ON state and have clear, self-described motor fluctuations (confirmed by the Motor Fluctuation Questionnaire) on optimized oral l-dopa or dopamine agonist therapy.
* Negative urine tests for selected drugs of abuse. However, positive urine drug screen for prescribed medication is allowed at the discretion of the PI.

Exclusion criteria

* Any significant medical condition, psychiatric illness or history of depression that could, in the investigator*s opinion, compromise the subject*s safety or interfere with the completion of this protocol.
* Any condition including the presence of laboratory abnormalities, which according to the investigator places the subject at unacceptable risk if he/she were to participate in the study.
* Any condition that according to the investigator confounds the ability to interpret data from

the study such as a virus, seasonal allergy, concurrent skin rash, etc. on screening or prior to drug treatment phase that may be difficult to discern from further health status changes from an investigational product.
* History of clinically significant central nervous system (e.g., seizures), cardiac, pulmonary (e.g., asthma, COPD), metabolic, renal, hepatic, or gastrointestinal (GI) conditions including gastric bypass or other weight loss surgical procedure; or history of such conditions that, in the opinion of the investigator, may place the subject at an unacceptable risk as a participant in this trial, may interfere with the interpretation of safety and/or tolerability data obtained in the trial, or may interfere with the absorption, distribution, metabolism, or excretion of the study drugs.
* Use of 5HT3 antagonists, drugs known to prolong QTc and use of antihypertensives.
* PR interval > 220 msec or QRS duration > 120 msec or QTcF interval > 450 msec for men and 470 msec for women obtained at screening visit or prior to the first dose of study drug.
* Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), serum creatinine, or total bilirubin > 1.5 upper limit of normal (ULN) at screening or prior to the first dose of study drug. These laboratory tests may be repeated once, if they are abnormal on first screening, and if there is a medical reason to believe the results may be inaccurate. If the repeat test is within the reference range, the subject may be included only if the investigator considers that the previous finding will not compromise the subject*s safety and will not interfere with the interpretation of safety data.
* Use of non-prescription medications, including herbal and dietary supplements within 5 days or 5 half-lives (whichever is longer) prior to the first dose of study drug, (The subject may take paracetamol (* 2 grams/day) or ibuprofen (* 1600 mg/day) for up to 48 hours prior to the first dose of study drug. Females may take oral contraceptives. The investigator and study team may review medication use on a case-by-case basis to determine if its use would compromise subject safety or interfere with study procedures or data interpretation.
* Use of medication that is inhibitor or inducer of CYP450-3A4/5 within 3 days of dosing and during the course of the study.
* Consumption of grapefruit, grapefruit juice, star fruit, oranges, orange juice, Seville oranges within 3 days prior to administration of study drug.
* Consumption of any caffeine and/or xanthine products (i.e., coffee, tea, chocolate and caffeine containing sodas, colas, etc.) within 24 hours prior to entry to the clinical unit on Day -1.
* Donation of blood, plasma or other blood products or blood collection in excess of 470 mL within 8 weeks prior to dosing.
* Subjects with a contra-indication for domperidone as per current SPC;Main criteria for Study Part C in PD Subjects IN ADDITION to above:
* Use of 5HT3 antagonists and drugs known to prolong QTc (so antihypertensives allowed)
* Has a current or a history of cancer within the last 10 years, with the exception of basal cell carcinoma.
* Systolic blood pressure less than 100 mmHg at screening or baseline
* Previous intolerance to apomorphine
* Previous significant complication from oral dopamine agonist therapy including hospitalization, hallucinations, or any other clinically relevant neuropsychiatric adverse event.
* Symptomatic clinically relevant and medically uncontrolled orthostatic hypotension.
* Subjects with a borderline QT interval corrected for heart rate according to Fridericia's

formula (QTcF) of >470 ms for male and >480 ms for female at screening or history of long QT syndrome
* Dementia indicated by MMSE <18 at Screening
* Known current major uncontrolled depression or bipolar disease
* Active hallucinations or history of hallucinations in the past 3 month.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	28-09-2018
Enrollment:	56
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Apo-Go Pen
Generic name:	Apomorfinehydrochloride
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Staccato Apomorfine
Generic name:	AZ-009
Product type:	Medicine
Brand name:	Staccato Apomorfine Placebo
Generic name:	Placebo

Ethics review

Approved WMO Date:	05-09-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-09-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-12-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-01-2019
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	EUCTR2018-003055-38-NL
CCMO	NL67063.056.18

Study results

Date completed: 16-05-2019

Results posted: 11-02-2020

First publication
01-01-1900