A double-blind, randomized, placebo-controlled, two-centre, phase IIa pharmacodynamic cross-over study to assess the effect of AZD2516 on the total number of reflux episodes in healthy male volunteers

Published: 18-05-2010
Last updated: 03-05-2024

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Ethical review	Approved WMO
Status	Pending
Health condition type	Gastrointestinal conditions NEC
Study type	Interventional

Summary

ID

NL-OMON34821

Source
ToetsingOnline

Brief title
PoP study AZD2516

Condition

- Gastrointestinal conditions NEC

Synonym
heartburn, Reflux

Research involving

Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Farmaceutisch bedrijf AstraZeneca

Intervention

Keyword: AZD2516, low esophageal sphincter relaxation, reflux

Outcome measures

Primary outcome

The assessment of the effect of three single doses of AZD2516 on the function

of the sphincter between esophagus and stomach, compared to placebo, in healthy

volunteers. As primary variable the number of reflux episodes is chosen.

Secondary outcome

Among others the number of relaxations of the lower esophageal sphincter,

pharmacokinetics and tolerability of AZD2516.

Study description

Background summary

In patients with reflux disease, acid fluids from the stomach can flow back into the esophagus, which can give rise to symptoms of heartburn and inflammation of the esophagus. The current treatment consists of medication that reduces the production of acid in the stomach. This approach is effective for many patients, but in some patients problems remain. It has been shown, that temporary relaxations of the lower esophageal sphincter (TLSER*s) are the most prominent mechanism, by which reflux episodes are caused. Antagonizing a certain receptor: metabotrope glutamate receptor type 5 (mGluR5) is inhibiting TLSERs and hereby reflux of stomach contents into the esophagus. The exact mechanism for the action of mGluR5 antagonists is yet unclear, but mGluR5 in nerve endings in de stomach play a role.

AZD2516 is a selective, non competitive antagonist of mGluR5. It has a proven

inhibiting effect op TLSER*s in dogs, which is a relevant model for humans. The current study with AZD2516 is of importance to study the effects of the mGluR5 antagonist on TLSERs and reflux episodes in healthy volunteers. The results will form the basis for a further evaluation of AZD2516 in the area of gastroenterology and will enlarge the experience in the field of esophageal motility. Influencing TLSERs and reflux episodes can have therapeutic advantages for patients with gastro-esophageal reflux diseases, having insufficient benefit of acid-reducing therapies.

Study objective

The primary aim of the study is to determine the effect of orally administered AZD2516 as a reduction of the number of reflux episodes, in comparison with placebo, over a period of approximately three hours after a meal, in healthy male volunteers.

Study design

The study consists of two parts. In part A 20 healthy volunteers will be included (approximately 10 in The Netherlands in Amsterdam, the other 10 in Leuven, Belgium) and in part B also 20 (10 in Amsterdam, 10 in Leuven). In part A three dosages will be tested (5, 16 en 40 mg AZD2516) and in part B two dosages of AZD2516, these dosages will be determined from the results of part A, but will not be higher than 40 mg. After a screening visit, in which the suitability of the volunteer is assessed, based on a physical examination, blood and urine tests and an interview with a psychiatrist or psychologist, in part A four long testdays and in part B three long test days will happen (with 5 to 28 days interval) and finally there is a follow-up visit. On the long testdays, during 4 hours, using a catheter, which is inserted through the nose into the stomach and esophagus, the pH in the stomach and esophagus is measured and the pressure in the esophagus is measured. During 22 hours blood will be sampled for pharmacokinetic investigations. Side effects are being questioned continuously. There is an optional genetic sub-study in which genetic variation and the effects of AZD2516 are investigated.

Intervention

On the testdays (after fasting since midnight) the catheter is inserted via the nose, after stabilisation the first dose of the study drug is taken (3 capsules), after 45 minutes a second dose of 3 capsules and after again 45 minutes the third dose of 3 capsules. Immediately after the second dose a standardised meal is served with potatoes and meat. Approximately 4 hours after the first capsule intake the catheter is removed. The total dose of AZD2516 in part A of the study will be 5 mg, 16 mg or 40 mg, given divided as 3+1+1 mg, 10+3+3 mg, 20+10+10 mg or placebo. De dosage on the three testdays in part B (two dosages AZD2516 and placebo) will be determined on the outcomes of part A.

Venapunctures:
On het Screening visit and the Follow-up visit by means of single venapuncture blood is sampled, on the long testdays an indwelling catheter is placed for blood sampling during the first 12 hours. In total maximally 300 ml blood is sampled in part A and maximally 250 ml in part B.

Catherisation:
On the screening visit, via the nose a catheter is inserted in the esophagus to determine the position of the lower esophageal sphincter between the esophagus and the stomach and to measure the pressure of this sphincter. On the four long testdays in part A and the three testdays in part B of the study a catheter is inserted via the nose to measure the pressure of the sphincter and the pH in the esophagus during approximately 4 hours.

Study burden and risks

The usual discomfort of venapunctures and the insertion of the indwelling catheter for blood sampling, with the associated small risks. For part A the volunteers must be admitted to the AMC hospital four times for one day, in part B three times, in order to make the assessments in a standardized way and to record any adverse events. On the long testdays the catheter is inserted through the nose and must stay in the esophagus and stomach for 4 hours. This must be tolerated and capsules must be taken with some fluid and food must be eaten while this catheter is in place. That can give some discomfort, but is without major risks. The dosage of maximal 40 mg AZD2516 as a single dose has in previous studies in healthy volunteers not lead to significant adverse events. During the study days the participants must refrain from using alcohol, nicotine and caffeine and they are not allowed during the study period and for three months thereafter to donate sperm or making their partner pregnant.

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

1. Provision of informed consent prior to any study specific procedures
2. Healthy male subjects, age 18-45 years, inclusive
3.Clinically normal physical findings and laboratory values as judged by the investigator.
4.Body Mass Index (BMI<=weight/height2) 19-30 kg/m2 calculated from height and weight given in the demographic data.

Exclusion criteria

1. Clinically significant illness within the 2 weeks prior to the first dose of the investigational product, including a suspected/manifested infection according to WHO risk categories 2, 3 or 4, as judged by the investigator
2. Basal LES pressure of < 5 mmHg
3. History of previous or ongoing psychiatric disease/condition including psychosis, affective disorder, anxiety disorder, borderline state and personality disorder according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, as assessed by using the MINI psychiatric interview.
4. Suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale in the last month
5. History of psychotic disorder among first-degree relatives
6. History of use of antipsychotic, antidepressant or anxiolytic drugs, prescribed as well as non-prescribed use. History of antidepressants or anxiolytics for non-psychiatric conditions such as pain or postoperative insomnia is allowed
7. History of clinically significant cardiovascular, respiratory, renal, hepatic, neurological, mental or gastrointestinal disease, as judged by the investigator
8. Use of prescribed medication and over-the-counter drugs (including herbal remedies minerals and vitamins) during 2 weeks before administration of investigational product. However, paracetamol may be taken occasionally for pain relief as well as OTC adrenergic

nasal spray for relief of nasal congestion
9. Administration of any investigational product within 8 weeks prior to the first dose of AZD2516
10. Any condition that could modify the absorption of the drug, as judged by the investigator
11. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity
12. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG obtained at the pre-entry visit, that may interfere with the interpretation of QTc interval changes. This includes subjects with any of the following: Clinically significant PR (PQ) interval prolongation, Intermittent second or third degree AV block, Incomplete, full or intermittent bundle branch block (QRS<120 msec with normal QRS and T wave morphology is acceptable if there is no evidence of left ventricular hypertrophy), Abnormal T wave morphology, particularly in the protocol defined primary lead (lead V2), Prolonged QTcF >450 msec or shortened QTcF <350 msec or family history of long QT syndrome
13. Need for concomitant medications during the study (with the exception of OTC nasal spray for relief of nasal congestion and occasional paracetamol for pain relief)
14. Habitual smoker (ie, the subjects smokes every day) or daily use of other nicotine products
15. Blood donation, or similar blood loss, within 12 weeks prior to the first dose of the investigational product
16. Plasma donation within 2 weeks prior to enrolment
17. Positive drug of abuse screen or history of drug addiction and/or alcohol abuse or other circumstances which in the investigators judgment may compromise the subject*s ability to comply with the study requirements
18. Use of anabolic steroids within 12 months prior to the first dose of investigational product
19. Excessive use of caffeine (more than 5 cups of coffee or equivalent per day).
20. Involvement in the planning and conduct of the study
21. Previous randomization or treatment in the present study or previous exposure to AZD2516.
For the optional genetic substudy:
1: Previous allogenic bone marrow transplant
2: non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2010
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
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	EUCTR2010-018608-98-NL
CCMO	NL31653.018.10