An explorative, randomized, placebo-controlled, double-blind, parallel-group trial, to evaluate the pharmacodynamic effect of M0003 on reflux parameters in subjects with gastroesophageal reflux disease and with persistent symptoms despite taking a stable dose of proton pump inhibitors.

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The objectives of this exploratory trial are:1. To measure the pharmacodynamic (PD) effect on parameters derived from 24-hpH/impedance (MII) monitoring,2. To explore the effect on symptoms,3. To evaluate the safety and tolerabilityof treatment with...

Ethical review	Approved WMO
Status	Pending
Health condition type	Gastrointestinal motility and defaecation conditions
Study type	Interventional

Summary

ID

NL-OMON34276

Source
ToetsingOnline

Brief title
N/A

Condition

- Gastrointestinal motility and defaecation conditions

Synonym
gastrooesophageal reflux disease (GERD), heartburn, regurgitation

Research involving
Human

Sponsors and support

Primary sponsor: Movetis NV
Source(s) of monetary or material Support: farmaceutisch bedrijf

Intervention

Keyword: GERD, pH/MII-monitoring, pharmacodynamic effect, refractory PPI treatment

Outcome measures

Primary outcome

The three main PD endpoints for the evaluation of PD effects of M0003 will be:

* the average number of liquid-containing reflux events per 24-h period;

* the average proximal extent of all liquid-containing reflux events in the

24-h period;

* average bolus clearance times of all liquid-containing reflux events in the

24-h period;

Secondary outcome

Secundary endpoints are:

- to explore the effect on symptoms by means of the pH-impedance measurements,

de information from the ediary and the 2 questionnaires (PAGI-SYM and PAGI-QoL)

- to evaluate safety and tolerability by means of adverse events, lab tests,

physical examinations, ECGs, blood pressure and heartbeat measurements en

concomitant medication.

Study description

Background summary

M0003 is an investigational drug, it has not yet been granted marketing approval by regulatory agencies such as the European Medicines Agency (EMA). M0003 is being studied as a potential treatment for gastro-esophageal reflux disease (GERD) in patients who do not experience adequate relief from their current medication (proton pump inhibitors, PPIs). M0003 is expected to reduce the number of reflux events, which in turn could also improve GERD symptoms (i.e. heartburn and regurgitation). Heartburn can be described as burning pain rising in the chest or throat; regurgitation can be described as fluid or liquid from the stomach coming up into the throat.

Although M0003 has not yet been evaluated in GERD patients, 9 Phase I trials (in healthy volunteers) and 1 Phase II trial (in patients suffering from delayed emptying of the stomach) have been conducted. So far, 181 subjects have received M0003, evaluating a wide dose range that covers (and exceeds) the dose that will be used in the current trial.

The current clinical trial is being performed to gain and extend the knowledge on the safety, tolerability and therapeutic effect of M0003 in GERD patients. In total, 90 patients will be included. Half of the participants will receive M0003 tablets, the other half will be treated with placebo tablets, which look exactly the same, but do not contain active medicinal product.

Study objective

The objectives of this exploratory trial are:
1. To measure the pharmacodynamic (PD) effect on parameters derived from 24-h pH/impedance (MII) monitoring,
2. To explore the effect on symptoms,
3. To evaluate the safety and tolerability
of treatment with 0.5 mg M0003 (on top of PPI treatment), t.i.d. for 4 weeks, in subjects with GERD and with persistent symptoms despite taking a stable dose of proton pump inhibitors.

Study design

This is a multi-centre, randomized, placebo-controlled, double-blind, parallel-group trial. Each subject will receive M0003 tablets (0.5 mg t.i.d.) or matching placebo tablets (t.i.d.) on top of their stable PPI treatment for 4 weeks. Subjects will be randomized in a double-blind manner to either M0003 or placebo in a 1:1 ratio.

Intervention

Half of the patients wil receive 4 weeks (28 days) of treatment with 0,5 mg M0003 t.i.d. on top of their PPI treatment and the other half of patients will receive 4 weeks (28 days) of treatment with placebo t.i.d. on top of their PPI treatment

Study burden and risks

The proposed trial offers distinct benefits to all participants, regardless of randomization to
placebo or active dose, and is expected to improve the current understanding of refractory
GERD through detailed diagnostic evaluation.

The treatment period will have a duration of 4 weeks, preceded by a potential wash-out period of 7 days in case the subject takes disallowed medication, and a run-in period of 14 days. The total trial duration will be at least 43 days.
At most, 6 visits will be scheduled during the entire trial.

During the trial following assessments will be performed:
- 4 x a blood sample (in total approx. 28 mL)
- 3 x an ECG
- 3 x a physical examination and weight measurement
- 1 x measurement of height
- 3 x blood pressure and heartrate
- 3 x a urine sample
- 3 x a urine pregnancy test (woman of childbearing potential only)
- 2x a 24h pH-impedancy measurement (possibly preceded by an initial manometry)

The patient needs to keep an ediary during the trial and will be asked to complete 2 questionaires at 3 occasions during the trial.

Importantly, M0003 has a wide safety margin, and AEs through action at receptors other than 5-HT4 receptors are highly unlikely. Based on data from previous trials, the dose chosen for this trial is expected to be well tolerated. The most common AEs (i.e., GI symptoms, headache, dizziness) usually occurred on Day 1 of treatment, became less frequent during repeated dosing and all resolved by the end of the trials. With M0003 alone, AEs were mild to moderate in intensity, and did not result in discontinuation. M0003-related SAEs have not been reported.

Furthermore, safety is monitored throughout the entire trial duration and rescue medication
(Rennie) will be provided in case of excessive GERD symptoms.

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. Written ICF signed voluntarily before the first trial-related activity.
2. Aged between 18 and 70 years, extremes included.
3. Subjects with a history of GERD symptoms (i.e., heartburn and/or regurgitation) during the last 6 months (as assessed by anamnesis/medical history).
4. Subjects on a stable dose of PPIs, compliant for at least 6 weeks prior to screening.
5. Subjects with heartburn and/or regurgitation, with at least one of these symptoms of moderate severity or worse, and at a minimum average frequency of three days a week during the two-week run-in period (determined by completion of a daily diary).
6. A minimum of 25 liquid-containing reflux events over 24 h (pH/MII monitoring).
7. BMI < 35.
8. If the subject is a woman of childbearing potential she must have a negative urine pregnancy test at screening and before the start or treatment and must agree to either use

an effective form of birth control or a combination of a barier method and a spermicidal agent until 30 days after the end of treatment, or until onset of menses.
9. Endoscopy within the last 5 years prior to randomisation, negative for grade C & D oesophagitis (according to the Los Angeles classification).

Exclusion criteria

1. History of cardiac arrhythmias, uncontrolled bronchospastic disease and controlled bronchospastic disease with symptoms, cardiovascular disease (e.g., ischemic heart disease or cerebrovascular accident), thyrotoxicosis.
2. Subjects with a family history of sudden death or a congenital QT syndrome.
3. Presence of prolonged QTc (Bazett and Fridericia) on ECG at screening (QTc * 450 msec for males and QTc * 470 msec for females).
4. Subjects with a documented history of long segment (>3 cm) Barrett*s oesophagus.
5. Subjects with documented or suspected large (> 3 cm) hiatus hernia.
6. Subjects with fundoplication, endoscopic anti-reflux procedure or major prior GI surgery.
7. Subjects with clinically significant abnormalities as judged by the investigator at screening physical examination, or in blood haematology and biochemistry tests performed at screening.
8. Subjects with a structural abnormality or structural disease condition of the GI tract.
9. Severe oesophageal motility disorders (e.g., scleroderma, achalasia, nutcracker oesophagus).
10. Subjects who suffer from frequent vomiting (>1/week, as assessed during anamnesis).
11. Current diagnosis of co-existing psychiatric disease (including alcohol or drug abuse); controlled depression and anxiety are allowed, when treated with at most one drug, at a stable dose.
12. Subjects suffering from severe and/or uncontrolled endocrine, metabolic and neurologic diseases. Endocrine and metabolic disorders controlled by appropriate medical therapy will not be excluded, except for insulin-dependent diabetes mellitus.
13. Presence of severe and clinically uncontrolled cardiovascular, liver or lung disease, neurologic, cancer or AIDS.
14. Alarm symptoms suggestive of malignancies or organic disease such as: obstructive dysphagia, odynophagia, GI bleeding, blood in stool or anaemia, weight loss; unless investigated and found to be negative.
15. Impaired renal function, i.e., serum creatinine concentration >2 mg/dl (>180 micromol/l).
16. Use of prohibited co-medication less than 7 days before the start of the 2-week run-in period (baseline symptom assessment).
17. Any condition that, in the opinion of the Investigator(s), would complicate or compromise the trial or the well-being of the subject, or evidence of any clinically relevant pathology that could interfere with the trial results or put subject safety at risk.
18. Participation in an investigational drug trial in 30 days prior to enrolment.
19. Breast-feeding subjects.

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:	Pending
Start date (anticipated):	15-11-2010
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NAP
Generic name:	NAP

Ethics review

Approved WMO Date:	20-10-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	24-01-2011
Application type:	Amendment
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	EUCTR2010-021397-12-NL
CCMO	NL33807.018.10
Other	wordt later geregistreerd