A 12-week, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of prucalopride in subjects with chronic non-cancer pain suffering from opioid induced constipation

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1. Primary objective:To evaluate the efficacy of prucalopride versus placebo over 12 weeks of treatment in subjects aged 18 years and older with chronic non-cancer pain, suffering from OIC.2. Secondary objectives:To assess the safety and...

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

Summary

ID

NL-OMON38356

Source
ToetsingOnline

Brief title
A randomised trial in subjects with chronic pain suffering from OIC

Condition

- Gastrointestinal motility and defaecation conditions

Synonym
Constipation

Research involving

Human

Sponsors and support

Primary sponsor: Shire-Movetis NV
Source(s) of monetary or material Support: Shire-Movetis NV

Intervention

Keyword: Constipation, Opioids, Phase III, Prucalopride

Outcome measures

Primary outcome

Primary efficacy parameter: the proportion (%) of subjects with an average weekly frequency of at least 3 SBM/week (i.e. a responder) over the 12-week treatment period. A minimum of 28 days with e-diary data has to be present for a valid derivation of the primary endpoint. If less e-diary data are present the subject will be considered a non-responder. The Cochran-Mantel-Haenszel test controlling for controlling for the randomisation stratification factors (age class, country and gender) will be used to compare treatment groups.

Secondary outcome

Secondary efficacy parameters:

- The proportion (%) of subjects with an increase of >=1 (spontaneous complete) bowel movement [(SC)BM]/week over the entire treatment period.

- The proportion (%) of subjects with >=3 SCBM/week evaluated over the entire treatment period.

- Average number of (SC)BM/week and change from baseline.

- Number of (SC)BM/week: descriptive statistics and distribution in categories: 0, (0;1), [1;2); [2;3), [3;->).

- Consistency per (SC)BM: descriptive statistics of 5-point score and % (SC)BM with normal consistency (Type 3 or 4 on the Bristol stool scale) and % (SC)BM with hard/very hard consistency (Type 1 or 2 on the Bristol stool scale).
- Straining per (SC)BM: descriptive statistics of 5-point score and % (SC)BM with no straining and with severe/very severe straining.
- The proportion (%) of subjects with >=3 SBM/week and with >=50% of SBM with Type 3 or 4 on the Bristol stool scale and mild or moderate straining.
- Sensation of complete evacuation per (S)BM: % (S)BM with sensation of complete evacuation.
- Average time to first (SC)BM after intake of the trial medication on Day 1 and on Day 29.
- Average number of Dulcolax® (bisacodyl) tablets taken per week and the average number of days with laxatives per week.

The following scales will be summarised by descriptive statistics and by tabulations of proportions of subjects with an increase of >=1 point:

- Subject*s global assessment of severity of constipation.
- Subject*s global assessment on efficacy of treatment.
- PAC-SYM total, subscale and individual item scores.
- PAC-QOL total, subscale and individual item scores.

Data on SF-12TM [Physical component summary (PCS) and mental component summary (MCS)] will be presented as descriptive statistics.

All efficacy analyses will be evaluated on the intent-to-treat population. In case of a substantial number of major protocol violations or early discontinuations, a per-protocol population will be used for a sensitivity

analysis. Continuous variables will be analysed using an analysis of variance (ANOVA) model. Between-group comparisons on ordinal categorical variables will be evaluated using the Van Elteren test. For nominal categorical variables the Cochran-Mantel-Haenszel test will be used.

Study description

Background summary

See page 21 of the protocol.

Study objective

1. Primary objective:
To evaluate the efficacy of prucalopride versus placebo over 12 weeks of treatment in subjects aged 18 years and older with chronic non-cancer pain, suffering from OIC.
2. Secondary objectives:
To assess the safety and tolerability of prucalopride in subjects aged 18 years and older with chronic non-cancer pain, suffering from OIC.
To document the plasma concentrations of prucalopride in subjects aged 18 years and older with chronic non-cancer pain, suffering from OIC.

Study design

This is a multi-centre, stratified, randomised, parallel-group, double-blind, placebo-controlled phase III trial in subjects with chronic non-cancer pain suffering from OIC.
Subjects will be screened and enter a 2-week run-in period (or a 3-week run-in period if the subject is using agents that influence bowel habit) during which the presence and severity of OIC will be documented. At the start of the run-in period, all existing laxative medication will be withdrawn and subjects will be instructed not to change their diet or lifestyle during the trial. Subjects will be allowed to take a laxative [Dulcolax® (bisacodyl)] as rescue medication throughout the trial, but only if they have not had a bowel movement for the preceding 48 hours. An enema can only be taken after unsuccessful use of Dulcolax® (bisacodyl). No Dulcolax® (bisacodyl) should be taken or enemas used within 24 hours before and 24 hours after the start of the double-blind treatment period.
After the run-in, subjects will be randomly assigned to placebo or prucalopride in an equal ratio (1:1) if the subject fulfils the constipation criteria for

inclusion and is anticipated to stay on a minimal stable daily maintenance dose of opioids for at least an additional 12 weeks. The randomisation will be stratified by age (>=18 to <65 years, >=65 to <75 years, >=75 years), country, and gender to assure balanced
treatments in each class.
Adult subjects (>=18 to <65 years of age) will take 2 mg prucalopride or matching placebo once daily before breakfast during the entire 12-week treatment period. Elderly subjects (>=65 years of age) will start at a dose of 1 mg prucalopride or matching placebo once daily before breakfast. In case of insufficient response, defined as an average of <3 spontaneous bowel movements (SBM)/week during the preceding 2 weeks of treatment (i.e. since the previous visit) at Week 2 or Week 4, the daily dose has to be increased to 2 mg (i.e. changed to 2 mg prucalopride or matching placebo). Once the dose is increased to 2 mg once daily the subject will stay on this dose for the remainder of the trial. It is not allowed to further increase the dose or decrease the dose to 1 mg once daily afterwards, i.e. no changes in dose will occur at the Week 8 visit or thereafter.

Intervention

- Form-dosing route: The investigational drug product will be administered once daily as an oral tablet.
- Investigational drug:
* Prucalopride (M0001): white 1-mg or pink 2-mg film-coated tablets (prucalopride succinate eq. 1.0 or 2.0 mg, respectively).
* Placebo: white or pink film-coated tablets matching 1-mg and 2-mg prucalopride tablets.
- Dosage: 1 or 2 mg prucalopride or placebo once daily before breakfast
- Duration of treatment: 12 weeks

Study burden and risks

Cfr. flow chart : page 9 of the protocol.

Concerning risks:
On the basis of earlier trials with prucalopride in patients with chronic constipation, the following side effects can be expected: headache and gastrointestinal symptoms (abdominal pain, nausea or diarrhoea) occurring in approximately 20% of patients each. The adverse reactions occur predominantly at the start of therapy and usually disappear within a few days with continued treatment. Other adverse reactions have been reported occasionally. The majority of adverse reactions were mild to moderate in intensity.

The specific procedures made within the scope of this trial may also cause complaints or bear some risks (allergic reactions). Blood sampling may cause pain, swelling, bruising or infection from the needle puncture sites.

There may be risks with the use of prucalopride that are not yet known.

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

Main inclusion criteria to be assessed at screening:
1. Subject is a male or non-pregnant, non-breastfeeding female out-patient >=18 years of age (no upper age limit).
2. Subject has chronic pain of any aetiology (except cancer pain) requiring daily maintenance treatment with opioids; has been on a stable daily opioid dose during at least the previous 2 weeks; and is expected to remain on a stable daily dose of opioids for at least 15 weeks after Visit 1.
3. Subject is suffering from OIC (i.e. secondary to chronic opioid use), which is defined as having an average of <=2 SBM/week and one or more of the following symptoms that started

after initiating opioids:
a. Very hard (little balls) and/or hard stools at least a quarter of the stools.
b. Sensation of incomplete evacuation following at least a quarter of the stools.
c. Straining at defecation at least a quarter of the time.
The above criteria are only applicable for SBMs, i.e. bowel movements
not preceded within a period of 24 hours by the intake of a laxative agent
or by the use of an enema. Subjects who never have SBMs are considered to be constipated and are eligible for the trial.
4. Subject agrees to stop his/her current laxative treatment and is willing to use rescue medication according to the rescue rule [Dulcolax® (bisacodyl)/ enemas].
5. Subject is able and willing to complete the questionnaires (if a validated version in the language of the subject is available) and the e-diary.
6. Women of childbearing potential should have a negative serum pregnancy test at Visit 1 (screening) and should use an efficient method of birth control for the duration of the trial and until the first menses after a 30-day period after the last dose of trial medication. They must be on a stable regimen, for at least 1 month, of oral contraceptives, contraceptive implant or depot injection, contraceptive patch, intrauterine device (IUD), condom and spermicidal agent, or diaphragm and spermicidal agent, or agree upon continuous abstinence from heterosexual sexual contact and be willing to continue this contraception.
7. Subject voluntarily signed the Informed Consent Form (ICF) in accordance with the regional laws/regulations, before the first trial-related activity.
8. Subject is willing to adhere to all trial requirements.;Main inclusion criteria to be assessed at baseline (randomisation):
1. Subject has been taken a stable maintenance dose of opioids during the run-in period.
2. Subject is constipated, i.e. had an average of <=2 SBM/week during the run-in period.*
3. Subject stopped his/her laxative treatment and did not use rescue mediation on more than 75% of days of the run-in period.*
4. Subject did not use disallowed medication during the run-in period.
* Excluding the first 7 days for subjects using medication influencing bowel habit.

Exclusion criteria

Main exclusion criteria to be assessed at screening:
1. Constipation is thought to be drug-induced (except for opioids).
2. Disallowed medication is being used.
3. Subject was on chronic therapy for chronic constipation prior to the start of opioid therapy.
4. Subject is suffering from secondary causes of chronic constipation.
5. Significant history of cancer (i.e. less than 5-year disease-free survival).
6. Presence of megacolon/megarectum or diagnosis of pseudo-obstruction.
7. Known serious illnesses: clinically significant cardiac, vascular, liver, pulmonary, endocrine, neurological or psychiatric disorders (as evaluated by the Investigator), or metabolic disturbances.
8. Known terminal illnesses: anticipated lifespan is shorter than the maximum duration of the trial (i.e. <4 months).
9. Any condition that in the opinion of the Investigator would complicate or compromise the

trial or the well-being of the subject or evidence of clinically relevant pathology that could interfere with the trial results or put the subject*s safety at risk.
10. Serum creatinine concentration of greater than >180 µmol/l or calculated creatinine clearance <=30 ml/min.
11. Clinically significant abnormalities of haematology, urinalysis, or blood chemistry as determined by the Investigator.
12. Subject is known to have human immunodeficiency virus (HIV) infection or AIDS, hepatitis B or hepatitis C.
13. History of alcohol or drug abuse in the previous 6 months.
14. Subjects with lactose intolerance from whom it is expected that low doses of lactose can lead to diarrhoea, or a known allergy to ingredients or excipients of the trial medication.
15. Use of investigational medication in the 30 days preceding Visit 1 of this trial.
16. Subjects who previously used prucalopride

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-01-2011
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Resolor
Generic name:	Prucalopride

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-06-2010
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-07-2010
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-08-2010
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-09-2010
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-10-2010
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-11-2010
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-12-2010
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-03-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-07-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-10-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-12-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-12-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-12-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-02-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-02-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-05-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2009-015652-20-NL
CCMO	NL32091.028.10