Trial consisting of an 8-week double-blind placebo-controlled part to evaluate efficacy, safety, tolerability and pharmacokinetics of prucalopride in paediatric subjects with functional constipation, aged ???6 months to <18 years, followed by a 16-week open-label comparator (PEG) controlled part, to document safety and tolerability up to 24 weeks

Published: 25-02-2011
Last updated: 04-05-2024

The primary objective is to evaluate the efficacy of prucalopride compared to placebo for the treatment of functional constipation in a paediatric population, aged *6 months to

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

Summary

ID

NL-OMON36457

Source
ToetsingOnline

Brief title
Not applicable

Condition

- Gastrointestinal motility and defaecation conditions

Synonym
constipation, obstruction

Research involving
Human

Sponsors and support

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

Intervention

Keyword: efficacy, pediatric constipation, prucalopride, safety

Outcome measures

Primary outcome

Efficacy is evaluated by the proportion of responders in the prucalopride vs.

placebo arm.

A subject is defined as a responder when the average spontaneous* defecation

frequency is *3 times/week AND the average number of faecal incontinence

episodes per 2 weeks is * 1 episode# (as calculated over week 5 to 8 of the

double-blind treatment phase).

*A spontaneous bowel movement (SBM) is defined as a non-laxative induced BM,

i.e. not preceded within a period of 24 hours by the intake of a laxative agent

or by the use of an enema.

#Faecal incontinence will only be taken into account in children after

acquisition of toileting skills.

Secondary outcome

* Het aantal patiënten met een gemiddelde spontane defecatiefrequentie van * 3 maal/week

* Het aantal episodes van fecale incontinentie per week

* Wekelijkse frequentie van retentieve houding of overmatig, wilskrachtig ophouden van stoelgang

* Frequentie van defecatiepijn (6-puntsschaal; alleen bij patiënten van 3 jaar of ouder)

* Consistentie van de stoelgang per week (4-puntsschaal voor kinderen die een luier dragen of 7-punts Bristol-schaal voor kinderen die geen luier dragen)

* Wekelijks aantal grote stoelgangen

Study description

Background summary

Prucalopride has been developed for chronic constipation in adults not adequately relieved by laxative treatment (approved dose 2 mg o.d.). Prucalopride may also be of use in paediatric patients with functional constipation. However, limited efficacy, safety and pharmacokinetic data are available in this population.

The current trial in functional constipation in paediatric subjects (n=210) from 6 months to 18 years old consists of an 8-week, double-blind, placebo-controlled period to evaluate efficacy, safety, tolerability and pharmacokinetics of prucalopride followed by a 16-weekopen-label, active comparator (PEG)-controlled period to evaluate long term safety and tolerability. Thus, the total treatment duration is 24 weeks. The design is based on a review of published data on the effect of prokinetics and/or laxatives in children with constipation, and is in line with the paediatric investigational plan of prucalopride as agreed with the Paediatric Committee of the EMA.

Two double-blind, placebo-controlled studies of drugs approved for the

treatment of functional constipation in children (PEG) have been published. Both studies had a short (2-week) treatment duration and a small sample size. The first study (Nurko, 2008) examined 3 doses of PEG vs. placebo in approximately 25 patients per treatment group. Response rate was defined as the percentage of patients with *3 bowel movements in the second week of treatment. A placebo response of approximately 40% was shown vs. 70% after treatment with PEG. In the cross-over study of Thomson (2007), 51 children were included. No response rates were mentioned but an increase in bowel movements vs. placebo was observed after treatment with PEG. Both the short treatment duration and the small sample size made it difficult to document a real benefit of existing laxative treatment over placebo. Movetis therefore prefers the inclusion of a placebo arm over inclusion of a control arm. A treatment period longer than 2 weeks is considered necessary, because constipation is a chronic recurring condition. Subjects will be allowed to use rescue medication.

Limited or no pharmacokinetic information on prucalopride is available in the various age groups to be studied. Therefore this study will also document the pharmacokinetics of prucalopride.

Study objective

The primary objective is to evaluate the efficacy of prucalopride compared to placebo for the treatment of functional constipation in a paediatric population, aged *6 months to <18 years.

Secondary objectives include:
1. Investigation of the individual symptoms defined by the Rome III criteria: bowel frequency, faecal incontinence, retentive posturing or excessive volitional stool retention, defecation pain, stool consistency, occurrence of large diameter stools. In addition use of rescue medication, abdominal pain and toilet training*.
2. Pharmacokinetics: sparse blood sampling at single dose and steady state to enable population pharmacokinetic modelling.
3. Safety and tolerability: evaluation of prucalopride treatment up to 24 weeks.

*Only for older children after acquisition of toileting skills (as standard of care).

Study design

Run-in period (1-2.5 week): After screening, eligible subjects will enter a run-in period of 8-17 days, during which bowel habits of subjects will be recorded in a daily diary. The run-in period will consist of 1 week control measurements for the documentation of constipation symptoms, followed by treatment with an enema or an oral laxative agent for 1 to 3 days to remove any

recto-faecal impaction. The subject will be randomized as soon as the removal is finalized; the double-blind placebo controlled period should start after the removal of the faecal impaction.
In case disallowed medication is used at screening, the intake has to be stopped, and the run-in should take 2 weeks (allowing 1 week for wash-out of the disallowed medication).

Double-blind placebo-controlled period (8 weeks): Subjects will be randomized at Day 1 to placebo or prucalopride (1:1). Randomization will be stratified by country and age group (<4 years; 4 to <12 years; *12 years).
* Subjects with weight *50 kg will receive placebo or a dose of 0.04 mg/kg body weight prucalopride once daily given as an oral solution of 0.4 mg/mL (prucalopride succinate equivalent to 0.4 mg/mL prucalopride). After 4 weeks of treatment the dose might be adjusted:

1) a dose increase to 0.06 mg prucalopride/kg should occur in case of no safety concerns and insufficient response (i.e. average frequency of < 3 spontaneous* defecations per week and/or on average >1 episodes of faecal incontinence# per 2 weeks (based on diary data)). Irrespective of body weight the maximum dose per intake will be 2 mg prucalopride (i.e max. intake 5 mL).
2) a dose decrease to 0.02 mg prucalopride/kg should occur if the subject has safety/tolerability concerns (e.g. diarrhea) that are likely related to treatment with prucalopride AND is a responder (i.e. an average frequency of *3 spontaneous* defecations per week and an average *1 episode of faecal incontinence# per 2 weeks).
Subjects with a dose adjustment will remain on this dose for the remaining 4 weeks of the double-blind treatment period.

*A spontaneous bowel movement (SBM) is defined as a non-laxative induced BM, i.e. not preceded within a period of 24 hours by the intake of a laxative agent or by the use of an enema.
#Faecal incontinence will only be taken into account in children after acquisition of toileting skills.

* Subjects with weight >50 kg will receive placebo or a tablet of 2 mg prucalopride once daily.

An interim analysis will be performed to evaluate the possible effects of the dose adjustments when approximately 70 subjects completed the double-blind treatment phase.
Use of rescue medication is allowed during the double-blind period as explained in Section 4.6.2. Concomitant medication.

Open-label active controlled period (16 weeks):
Subjects who have completed the 8-week double-blind treatment phase will be re-randomised in a 1:1 ratio to receive 16-week open-label treatment with prucalopride once daily or active control (PEG 4000 (Forlax Junior® <8 years

and Forlax® *8 years)). This randomisation will be stratified by the preceding treatment (prucalopride or placebo), by country and age group (<4 years; 4 to <12 years; *12 years).
Subjects with weight *50 kg as measured at start of trial, assigned to the prucalopride arm, will be dosed with 0.04 mg/kg body weight. After the interim analysis this dose might be adjusted to 0.06 mg prucalopride/kg once daily when the 0.06 mg/kg results in substantially higher response rate for efficacy and when there are no safety concerns. In case of safety/tolerability concerns and a sufficient response rate for efficacy it might be decided to decrease the dose to 0.02 mg/kg .
Subjects with weight >50 kg as measured at start of trial, assigned to the prucalopride arm, will be dosed with 2 mg prucalopride as tablet.
Use of rescue medication is recommended during this period as explained in Section 4.6.2. Concomitant medication.

Intervention

For subjects with weight *50 kg, as measured at start of trial, prucalopride will be administered, as an oral solution of 0.4 mg/mL (prucalopride succinate equivalent to 0.4 mg/mL prucalopride). Subjects who are *50 kg at onset will remain on treatment with the oral solution for the remainder of the treatment period.

Other excipients: Sucralose, methylparaben, propylparaben, hydrochloric acid, sodium hydroxide and purified water.

Dosing will be based on body weight (dose 0.04 mg/kg body weight=0.1mL/kg). The dosing volume will be indicated by the investigator at every visit based on body weight (max. daily dose of 2 mg). Daily dosing will occur before the evening meal.

The taste and appearance of the placebo solution will be identical to the prucalopride solution.

For subjects with weight >50 kg, as measured at start of trial, prucalopride will be administered, as a 2 mg film-coated tablet (prucalopride succinate equivalent to 2.0 mg prucalopride) for the remainder of the trial. Daily dosing will occur before the evening meal.

Other excipients: lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate and coating powder pink.

Placebo tablets are identical in appearance and taste to the prucalopride tablets.

Study burden and risks

The most common side effects of the study drug are headacje, nausea, diarrhea and abdominal pain.
Blood sampling can cause pain, swelling, bruising or infection.
In total there will be 8 study visits.

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Contacts

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Scientific
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BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Boys and girls, aged *6 months to <18 years
2. Subjects with a confirmed diagnosis of functional constipation as defined by the Rome III criteria3 in the following way: Subjects should have *2 spontaneous* defecations per week together with at least 1 out of 5 of the following symptoms during one month (for <4 years of age) or two months (for *4 years of age) prior to the selection: 1) at least one episode of faecal incontinence per week (after the acquisition of toileting skills), 2) history of retentive posturing or excessive volitional stool retention, 3) history of painful or hard bowel movements (BMs), 4) presence of large faecal mass in the rectum, and 5) history of large diameter stools.
3. Subject and/or parent(s) or legally authorised representative agree to stop laxative use and agree to use the rescue medication according to the rescue rule.
4. Subject and/or parent(s) or legally authorised representative agree to stop the use of disallowed medication.
*A spontaneous bowel movement (SBM) is defined as a non-laxative induced BM, i.e. not preceded within a period of 24 hours by the intake of a laxative agent or by the use of an enema.

Exclusion criteria

1. Children with underlying GI abnormalities and causes for defecation disorders such as Hirschsprung*s disease, spina bifida occulta, cystic fibrosis, GI malformations, or significant developmental delays that are associated with musculoskeletal or neurological conditions affecting the GI tract.
2. Children who are breast fed.
3. Subjects suffering from secondary causes of chronic constipation, e.g.: Endocrine disorders, Metabolic disorders, Neurological disorders, Organic disorders, Surgery, Hernia, Autoimmune disorders.

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):	28-04-2011
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Forlax®
Generic name:	Macrogol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Forlax® Junior
Generic name:	Macrogol (PEG 4000)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Resolor®
Generic name:	Prucalopride
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-02-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-04-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2011
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-05-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2012
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	EUCTR2010-022402-40-NL
CCMO	NL34937.018.10
Other	Not applicable