A Phase 3, Open-label, Long-term Safety Study of Oral Linaclotide Administered to Pediatric Participants with Functional Constipation (FC) or Irritable Bowel Syndrome with Constipation (IBS-C)

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Ethical review	Approved WMO
Status	Completed
Health condition type	Anal and rectal conditions NEC
Study type	Interventional

Summary

ID

NL-OMON52547

Source
ToetsingOnline

Brief title
LIN-MD-66

Condition

- Anal and rectal conditions NEC

Synonym
Functional constipation, Irritable Bowel Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie Deutschland GmbH & Co. KG
Source(s) of monetary or material Support: AbbVie B.V.

Intervention

Keyword: Children, Functional Constipation, Linaclotide, Phase 3

Outcome measures

Primary outcome

No endpoints are specified for this long-term safety study. The safety assessments will include monitoring of adverse events (AEs), clinical laboratory assessments (clinical chemistry, complete blood count [CBC], urinalysis), vital sign measurements (including postural vital signs), electrocardiograms (ECGs), physical examinations, height, and weight.

Secondary outcome

N/A

Study description

Background summary

Functional constipation (FC) is a common healthcare problem in children of all ages, with a worldwide prevalence ranging between 0.7% and 29.6%. Symptoms include infrequent, hard stools, and painful defecation, and affected children may have abdominal pain and fecal incontinence, which is usually the result of fecal impaction leading to overflow incontinence. These symptoms can have a severe impact on a child*s quality of life and may lead to school absenteeism and substantial costs related to healthcare utilization. Initial non-pharmacological interventions include education, behavioral modifications, and keeping a bowel diary. Despite these interventions, many children require pharmacological interventions. Treatment consists of dis-impaction (ie, removal of the rectal fecal mass), followed by maintenance treatment and eventually a weaning phase. Multiple pharmacological agents are available for the treatment of FC in children. Despite chronic pharmacological treatment, approximately 40%

of children with FC referred to a pediatric gastroenterologist remain symptomatic after 5 years and 20% of children still have symptoms after 10 years. In some cases, symptoms may persist into adolescence or adulthood despite medical treatment. Potential reasons for ineffectiveness of treatment include suboptimal dosage regimens, poor compliance with treatment, or the use of drugs with action mechanisms that do not address the underlying pathophysiological etiology.

Irritable bowel syndrome (IBS) is characterized by symptoms of abdominal discomfort or pain associated with altered bowel movement characteristics. In adults, Rome III criteria has classified IBS with constipation (IBS-C), IBS with diarrhea, mixed IBS, and unsubtyped IBS, depending on the stool consistency. In children, although IBS subtypes are encountered in clinical practice, a classification based on stool consistency had not been specified at the time the Phase 2 dose ranging study (LIN -MD-63) was originally developed. Such classification is important as the management will, in part, depend on the presenting stool pattern.

The overall prevalence of IBS in the pediatric population is low. IBS prevalence in children across the United States, based on parental reports, ranges from 1.2% to 2.9%, while school - based studies in Colombia and Sri Lanka found a prevalence of IBS of 4.9% and 5.4%, respectively. In adults, although not life-threatening, because of its chronic relapsing course, IBS is associated with impaired quality of life and high direct and indirect medical costs such as absenteeism from work. In children and adolescents, IBS has been associated with significant impairment as increased rates of school absenteeism, health-care utilization and family disruption are common

Study objective

The objective of this study is to assess the long-term safety of linaclotide in pediatric participants with FC (total exposure with linaclotide for 24 weeks) or IBS-C (total exposure with linaclotide for 52 weeks) who have completed study intervention in Study LIN-MD-62, LIN-MD-63, or LIN-MD-64.

Study design

LIN-MD-66 is a Phase 3 open-label study with 24 weeks (FC participants) or 52 weeks (IBS-C participants) of linaclotide exposure that will enroll pediatric participants (6-17 years of age) with FC or IBS-C who completed study intervention in Study LIN-MD-62, LIN-MD-63, or LIN-MD-64 based on the individual study criteria.

Intervention

Participants will receive open-label linaclotide 72 µg or 145 µg once daily for

24 weeks (FC participants) or open-label linaclotide 72 µg, 145 µg, or 290 µg once daily for 52 weeks (IBS-C participants) as follows based on their age and/or weight at the time of enrollment into LIN-MD-66. Participants will be instructed to take their assigned dose orally as a single daily dose at approximately the same time each day, 30 minutes prior to any meal, except for the Day 1 Visit, at which the linaclotide dose will be administered in the clinic.

Study burden and risks

There will be a total of 6 study visits and 1 phone call with the study doctor over a period of 6 months. During the visits, the following will take place: personal questions, health and medication questions, vital signs, physical examination, fecal impaction assessment, blood sample, urine sample, electrocardiogram and pregnancy testing (if applicable).
Functional constipation (FC) is a common healthcare problem in children of all ages.Many children require pharmacological treatments, however, the available treatments are not always effective.There are currently no approved treatments for FC in children. Linaclotide is not currently approved for use in people younger than 18 years old, and the effects on children are still being studied. In an earlier study in children (6-17 years of age) with FC who took linaclotide, the side effects were similar to those reported by adults who took linaclotide to treat constipation. Some of the most commonly reported side effects in adults are: diarrhea and loose stools; upper or lower stomach pain; gas; bloating; common cold; sinus infection; headache; stomach flu. Diarrhea and loose stools are the most common side effects. In an earlier study of linaclotide in children aged 6-17 years, side effects that occurred in more than 1 patient included: diarrhea; a hardened mass of stool in the colon or rectum; headache.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Participant weighs >= 18 kg at the time the parent/guardian/LAR and/or caregiver has provided signed consent.
2. Female participants who have had their first menstrual period and are sexually active must agree to use a reliable form of contraception.
3. Male or female participants must be 6 to 17 years of age (inclusive), at the time the parent/guardian/LAR and/or caregiver provides written informed consent and the participant must provide assent before the initiation of any study-specific procedures.
4. Participants must have completed study intervention in their lead-in study as defined in Section 4.1 of protocol.
5. Female participants of childbearing potential must have a negative pregnancy test at both Screening (Visit 1) and at Study Day 1 (Visit 2).
6. Participants who turn 18 years of age prior to enrollment must provide consent for the study.
7. Female participants of childbearing potential must have a negative serum pregnancy test at the Screening Visit (Visit 1) and negative urine pregnancy test prior to the first dose on the Day 1 Visit (Visit 2).

Exclusion criteria

1. Participant has an unresolved AE or a clinically significant finding on aphysical examination along with ECG or clinical laboratory tests that; in the opinion of the investigator, could represent a safety concern or a condition that would be exclusionary, could prevent the participant from performing any protocol assessments, or could confound study assessments.
2. Participant has a known allergy or sensitivity to the study interventionor

its components or other medications in the same drug class.
3. Participant is not willing or able to abide by the restrictions regarding concomitant medicine use defined in Section 6.5.
4. Participant received an investigational drug, other than linaclotide, during the 30 days before the Screening Visit (Visit 1) or is planning to receive an investigational drug (other than that administered during this study) or use an investigational device at any time during the study.
5. Female participants who are currently pregnant or nursing, or plan to become pregnant or nurse during the clinical study.
6. Participant has fecal impaction at the Day 1 Visit (Visit 2).
7. Participant has required manual disimpaction any time prior to study intervention.
8. Participant has any of the following conditions:
a) Down's syndrome or any other chromosomal disorder
b) Anatomic malformations (eg, imperforate anus, anal stenosis, anterior displaced anus)
c) Intestinal nerve or muscle disorders (eg, Hirschprung disease, visceral myopathies, visceral neuropathies)
d) Neuropathic conditions (eg, spinal cord abnormalities, neurofibromatosis, tethered cord, spinal cord trauma).
e) Neurodevelopmental disabilities (early-onset, chronic disorders that share the essential feature of a predominant disturbance in the acquisition of cognitive, motor, language, or social skills, which has a significant and continuing impact on the developmental progress of an individual) producing a cognitive delay that precludes comprehension by the participant.
9. Participant has an acute or chronic condition that, in the investigator'sopinion, would limit the participants' ability to complete or participate in this clinical study.
10. The participant has a condition or is in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study.

For further exclusion criteria, please refer to the protocol section 5.2

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	08-02-2022
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Linaclotide
Generic name:	Linaclotide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	28-04-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	27-10-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	17-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	23-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	17-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2022
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	EUCTR2019-001955-38-NL
ClinicalTrials.gov	NCT04166058
CCMO	NL72614.018.21

Study results

Date completed:	05-10-2022
Results posted:	12-12-2024

First publication
12-11-2024