A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of Linaclotide Administered Orally to Children, Ages 6 to 17 Years, With Functional Constipation (FC)

Published: 09-04-2020
Last updated: 10-04-2024

To evaluate the safety and efficacy of 12 weeks of linaclotide therapy in comparison with placebo in pediatric participants aged 6 to 17 years who fulfill modified Rome III Criteria for Child/Adolescent FC

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

Summary

ID

NL-OMON52398

Source
ToetsingOnline

Brief title
Allergan LIN-MD-64

Condition

- Anal and rectal conditions NEC

Synonym
and painful defecation, Functional Constipation; infrequent, hard stools

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

Change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period

Secondary outcome

Change from baseline in 12-week stool consistency during the study intervention period

Safety and tolerability assessment

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 (i.e., 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.

There are no pharmacologic therapies approved in the pediatric population for the treatment of FC. Thus, there is a need for new agents with favorable safety and tolerability profiles that are effective in providing relief for the symptoms associated with FC in pediatric patients.

For the primary and key secondary endpoints in the Phase 2 dose ranging study with linaclotide in FC participants, none of the 3 linaclotide doses (low dose, medium dose, and high dose) indicated clear improvement over placebo based on analysis of the intent-to-treat (ITT) population. However, a numerical trend towards efficacy at the higher doses (>= 72 µg) was observed for the primary endpoint of change from baseline in 4-week overall spontaneous bowel movement (SBM) frequency rate (SBMs/week). Overall, linaclotide was well tolerated across all doses in participants 6 to 17 years of age. The safety profile was consistent with prior adult linaclotide chronic idiopathic constipation (CIC) studies.

The primary objective of this LIN-MD-64 study is to evaluate the safety and efficacy of 12 weeks of linaclotide therapy in comparison with placebo in pediatric participants aged 6 to 17 years who fulfill modified Rome III Criteria for Child/Adolescent with FC.

Study objective

To evaluate the safety and efficacy of 12 weeks of linaclotide therapy in comparison with placebo in pediatric participants aged 6 to 17 years who fulfill modified Rome III Criteria for Child/Adolescent FC

Study design

LIN-MD-64 is a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group, confirmatory safety and efficacy study comparing linaclotide at 72 mcg and placebo in pediatric participants, 6 to 17 years of age, with a diagnosis of FC based on modified Rome III Child/Adolescent Criteria (ie, who fulfill modified Rome III criteria for child/adolescent FC).

Intervention

The study will include a total of 8 visits and will be 17 to 20 weeks in duration: a 2-to 4-week Screening Period, a 2- to 3-week Preintervention Period, followed by a 12-week double-blind Study Intervention Period and 1-week Postintervention Period.
Participants that complete LIN-MD-64 have the option to enroll into the open-label, long-term safety study, if they meet the eligibility criteria.
Participants will be considered to have completed LIN-MD-64 if they have completed 12 weeks of double-blind study intervention, the End of treatment (EOT) visit (Visit 7), and the End of Study (EOS) visit (Visit 8). However, the EOS visit in LIN-MD-64 is not required for participants who enroll into the open-label, long-term safety study prior to that visit.
Participants will be randomized in a 1:1 ratio to receive either linaclotide 72 mcg or placebo for 12 weeks during the double blind study intervention period. Participants will be instructed to take their assigned dose orally as a single daily dose 30 minutes prior to any meal at approximately the same time each day, with the exception of the first dose at Day 1 (Randomization Visit) when participants will receive linaclotide or placebo in the clinic.

Study burden and risks

The study will include a total of 8 visits and will be 17 to 20 weeks in duration: a 2-to 4-week Screening Period, a 2- to 3-week Preintervention Period, followed by a 12-week double-blind Study Intervention Period and 1-week Postintervention Period.
Subjects are expected to undergo procedures/assessments as described in the section 1.3 of the study protocol, which includes:Physical exam, vital signs, fecal impaction, demographic and medical history, ECG, completion of eDiary (reporting information on symptoms/signs of disease, frequency of stools, use of rescue medication, etc.) Blood and urine tests (including urine drug screening), pregnancy and use of effective contraception. 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 to 17 years of age) with functional constipation who took linaclotide, the side effects were similar to those reported by adults who took linaclotide to treat constipation.
Some side effects that adults who have taken linaclotide have reported are:Diarrhea or loose stools; Abdominal pain - including upper and lower abdominal pain (stomach pain); Gas; Abdominal distension (feeling bloated); Upper respiratory tract infection (the common cold); Sinusitis (sinus infection); Headache; Viral Gastroenteritis (stomach flu)
Diarrhea and loose stools are the most common side effects. In the earlier study of linaclotide in children 6 to 17 years of age, side effects which occurred in more than 1 patient included the following: Diarrhea; Fecaloma (a hardened mass of stool in the colon or rectum); Headache; abdominal pain (stomach pain); Vomiting

Placebo Risks: If the study subject is in the group which is assigned placebo,

study subject*s symptoms of functional constipation may not improve or may worsen. Even if the study subject is in the group that gets the active drug during the study, the symptoms may not improve or may worsen.
Blood Sample Risks: Subjects may feel a slight needle prick when blood is drawn. Some participants may have a slight bruise that will go away within a few days. Sometimes, participants feel light headed or feel dizzy. Other rare complications associated with the blood sample collection include: infections, nerve lesions, accidental arterial puncture (when the needle pierces an artery instead of a vein) and bleeding, inflammation of vein, and dizziness.
Electrocardiogram (ECG) Risks: The ECG procedure may cause minimal discomfort and skin irritation during or after the attachment/removal of the leads (and adhesive).
Washout Risks: If a subject is taking medication for functional constipation or other conditions, he/she may be asked to stop some or all of these medications before Visit 2. During this time, the subject*s symptoms of functional constipation and/or other conditions may get worse.
Allergic Reaction Risks: As with taking any treatment, there is a risk of allergic reaction. Some symptoms of allergic reactions are: Rash; Wheezing and difficulty breathing; Dizziness and fainting; Swelling around the mouth, throat or eyes; A fast pulse; Sweating
Linaclotide has a safety profile that has been well established in adults with IBS-C and CIC. Moreover, the safety profile in the first completed pediatric linaclotide study in FC was consistent with prior adult linaclotide studies in CIC. There were no new safety signals observed in the pediatric participants and linaclotide was well tolerated across all doses and age groups. .
There are no pharmacologic therapies approved in the pediatric population specifically for the treatment of FC. Thus, there is a need for new agents with favorable safety and tolerability profiles that are effective in providing relief for the variety of symptoms associated with FC in pediatrics.
Linaclotide provides an important treatment option for adult patients with CIC. Linaclotide may offer a therapeutic option to treat the symptoms in the pediatric population with FC. The sponsors consider the benefit-risk balance to be favorable and supports further clinical development of linaclotide as a treatment for FC in the pediatric population.

Contacts

Public
AbbVie Deutschland GmbH & Co. KG

Knollstrasse
Ludwigshafen 67061
DE
Scientific

AbbVie Deutschland GmbH & Co. KG

Knollstrasse
Ludwigshafen 67061
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age and Weight
1.01. Male and female participants must be ages 6 to 17 years, (inclusive) at the time the participant provides assent for the study and parent/guardian/legally authorized representative (LAR) has provided signed consent
1.02. Participant weighs >=18 kg at the time the participant provides assent and the parent/guardian/LAR has provided signed consent
2. Type of Participant and Disease Characteristics
2.01. Participants who meet the modified Rome III criteria for Child/Adolescent FC. For
at least 2 months before the Screening Visit, the participant has had 2 or fewer defecations (with each defecation occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) in the toilet per week. In addition, participant meets one or more of the following criteria at least once
per week for at least 2 months before the screening visit:
• History of retentive posturing or excessive volitional stool retention
• History of painful or hard BMs
• History of large diameter stools that may obstruct the toilet
• Presence of a large fecal mass in the rectum
• At least 1 episode of fecal incontinence per week

2.02. Participant is willing to discontinue any laxatives used before the Preintervention Visit in favor of the protocol- permitted rescue medicine.
2.03. Participant has an average of fewer than 3 SBMs per week during the 14 days before the randomization day and up to the randomization (including the morning eDiary assessments reported before administration of first dose of double-blind study intervention on the randomization day). An SBM is defined as a BM that occurs in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM
2.04. Participant or parent/guardian/LAR or caregiver is compliant with eDiary requirements by completing both the morning and evening assessments for 10 out of the 14 days immediately preceding the Randomization Visit
3. Contraceptives
3.01.Female participants of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Randomization Visit prior to dosing.
3.02. Female participants who have had their first menstrual period and are sexually active must agree to use a reliable form of contraception. Reliable contraception is defined in Section 10.7.
4. Informed Consent
4.01. Participant must provide written or verbal informed assent and the parent/guardian/LAR and caregiver must provide written informed consent before the initiation of any study-specific procedures.
4.02. Participant is able to read and/or understand the assessments in the eDiary device. If the participant is 6 to 11 years of age and does not meet this criterion, the interviewer-administered version of the eDiary must be used and the parent/guardian/LAR or caregiver who will be administering the interviewer-administered version of the eDiary must undergo training
5. Other
5.01. Participant must have acquired toilet training skills

Exclusion criteria

1. Medical Conditions
1.01. Participant meets Rome III criteria for Child/Adolescent IBS: At least once per week for at least 2 months before the Screening Visit, the participant has experienced abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time:
a. Improvement with defecation
b. Onset associated with a change in frequency of stool
c. Onset associated with a change in form (appearance) of stool
1.02. Participant reports having more than 1 loose, mushy stool (eDiary-recorded stool consistency of 6 on the Pediatric Bristol Stool Form Scale [p-BSFS]) or any watery stool (eDiary-recorded stool consistency of 7 on the p-BSFS) with any SBM that occurred in the absence of laxative use on the

calendar day of the BM or the calendar day before the BM during the 14 days before the randomization day and up to the randomization (including the morning eDiary assessments reported before administration of first dose of double-blind study intervention on the randomization day)
1.03. Participant has a history of non-retentive fecal incontinence
1.04. Participant has (a) fecal impaction at Visit 2 and has failed outpatient clean-out during the Screening Period (b) fecal impaction at Visit 3.
1.05. Participant has required manual disimpaction any time prior to randomization
1.06. Participant currently has both unexplained and clinically significant alarm symptoms (lower GI bleeding [rectal bleeding or heme-positive stool], iron deficiency anemia, or any unexplained anemia, or weight loss) and systemic signs of infection or colitis, or any neoplastic process
1.07. Participant has clinically significant findings on a physical examination, vital sign assesment, ECG, or clinical laboratory test as determined by the investigator based on consideration of whether the finding 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.
1.08. Participant has a history of drug or alcohol abuse.
1.09. Participant has any of the following conditions:
a. Celiac disease, or positive serological test for celiac disease and the condition has not been ruled out by endoscopic biopsy
b. Cystic fibrosis
c. Hypothyroidism that is untreated or treated with thyroid hormone at a dose that has not been stable for at least 3 months prior to the Screening Visit
d. Down's syndrome or any other chromosomal disorder
e. Active anal fissure (Note: History of anal fissure is not an exclusion)
f. Anatomic malformations (eg, imperforate anus, anal stenosis, anterior displaced anus)
g. Intestinal nerve or muscle disorders (eg, Hirschprung disease, visceral myopathies, visceral neuropathies)
h. Neuropathic conditions (eg, spinal cord abnormalities, neurofibromatosis, tethered cord, spinal cord trauma)
i. Lead toxicity, hypercalcemia
j. 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 and completion of the daily eDiary or other study related questionnaires (Note: Participants are excluded if the person who will be completing the daily eDiary or other study-related questionnaires meets this criterion.)
k. Inflammatory bowel disease
l. Childhood functional abdominal pain syndrome
m. Childhood functional abdominal pain
n. Poorly treated or poorly controlled psychiatric disorders that might

influence his or her ability to participate in the study
o. Lactose intolerance that is associated with abdominal pain or discomfort and could confound the assessments in this study
p. History of cancer other than treated basal cell carcinoma of the skin. (Note: Participants with a history of cancer are allowed provided that the malignancy has been in a complete remission for at least 5 years before the Randomization Visit. A complete remission is defined as the disappearance of all signs of cancer in response to treatment.)
q. History of diabetic neuropathy
1.10. Participant has an acute or chronic condition that, in the investigator's opinion, would limit the participants* ability to complete or participate in this clinical study.
1.11. Participant has a known or suspected mechanical bowel obstruction or pseudo-obstruction.
1.12. Participant has a known allergy or sensitivity to the study intervention or its components or other medications in the same drug class.
1.13. Participant has had surgery that meets any of the following criteria:
a. Bariatric surgery for treatment of obesity, or surgery to remove a segment of the GI tract at any time before the Screening Visit
b. Surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit
c. An appendectomy or cholecystectomy during the 60 days before the Screening Visit
d. Other major surgery during the 30 days before the Screening Visit
2. Prior/Concomitant Therapy
2.01. Participant used a protocol-specified prohibited medicine before the start of the Preintervention Period or failed to meet the stable-dose requirements of certain medications.
2.02. Participant used rescue medication on the calendar day before the Randomization Visit and on the day of the Randomization Visit until randomized.
3. Prior/Concurrent Clinical Study Experience
3.01. Participant received a study intervention during the 30 days before the Screening Visit or is planning to receive a study intervention (other than that administered during this study)
3.02. Participant has been randomized into any clinical study in which linaclotide was a study intervention.
4. Other
4.01. 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.
4.02. Participants who have positive urine drug screen results for cocaine, barbiturates, opiates, or cannabinoids will be excluded from study participation
4.03. Female participants who are currently pregnant or nursing, or plan to become pregnant or nurse during the clinical study. Details regarding pregnancy and contraception are provided in Section 10.7.

4.04. Participant*s parent/guardian/LAR or caregiver has been directly or indirectly involved in the conduct and administration of this study as an investigator, study coordinator, or other study staff member. In addition, any participant, parent/guardian/LAR or caregiver who has a first-degree family member, significant other, or relative residing with him/her directly or indirectly who is involved in this study

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:	Recruitment stopped
Start date (anticipated):	12-08-2021
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:	09-04-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	26-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-03-2022
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	EUCTR2019-001500-38-NL
ClinicalTrials.gov	NCT04026113

Register	ID
CCMO	NL71673.018.19