A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study to Evaluate the Safety and Efficacy of Eluxadoline in Pediatric Participants (Age 6 to 17 Years) with Irritable Bowel Syndrome with Diarrhea (IBS-D)

Published: 09-08-2018
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The primary objectives of this study are:- To explore the therapeutic effect of eluxadoline in treating IBS-D in pediatric patients 6-17 years of age.- To evaluate the pharmacokinetics (PK) of eluxadoline in pediatric patients with IBS-D.- To…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal disorders
Study type	Interventional

Summary

ID

NL-OMON49257

Source
ToetsingOnline

Brief title
Allergan 238275

Condition

- Gastrointestinal disorders

Synonym
chronic gastrointestinal functional bowel disorder, Irritable Bowel Syndrome with Diarrhea,

sensitive intestines

Research involving
Human

Sponsors and support

Primary sponsor: Allergan
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: Eluxadoline, Irritable Bowel Syndrome with Diarrhea, Pediatric Patients

Outcome measures

Primary outcome

The primary efficacy assessment is the change from baseline in the 24-hour (combined daytime and nighttime) stool consistency averaged over the 4-week Treatment Period. Baseline average will be determined for the daytime scores over the 2 weeks prior to randomization. For each assessment of stool consistency, participants will be asked to characterize each bowel movement based on the p-BSFS where 1 corresponds to small hard lumps or balls, like pebbles, and 7 corresponds to milkshake, watery stool.

Secondary outcome

Secondary efficacy endpoints will be determined over the 4-week Treatment Period:

Stool Consistency:

Change from baseline in 4-week average for daily daytime and nighttime stool consistency scores.

Abdominal pain:

Change from baseline in 4-week average for daytime, nighttime and 24-hour

(combined daytime and nighttime) abdominal pain scores.

Bowel Movement Frequency:

Change from baseline in 4-week average daytime, nighttime, and 24-hour

(combined daytime and nighttime) bowel movement frequency.

Urgency:

Change from baseline in 4-week average daytime, nighttime, and 24-hour

(combined daytime and nighttime) urgency-free days in a week.

Fecal incontinence:

Change from baseline in 4-week average daytime, nighttime, and 24-hour

(combined daytime and nighttime) number of fecal incontinence-free days in a

week.

Study description

Background summary

Eluxadoline may offer a therapeutic option to treat the symptoms in the pediatric population with IBS-D. IBS-D in adults and children share many overlapping features,including its pathophysiology and natural course of waxing and waning symptoms. Pharmacokinetic (PK)/ pharmacodynamics (PD) modeling data from a Phase 2 study in adults suggests that extrapolation of adult efficacy to the pediatric population (age 12-17 years) based solely on PK data will be insufficient since the relationship between systemic exposure and beneficial effects is not entirely clear. This is especially
true since the measurement of systemic exposure may likely not be reflective of local concentration in the gut.
Thus, it is intended to conduct a parallel-group, dose-ranging study with eluxadoline in children with IBS-D age 6 to 17 years, to determine its safety and effectiveness.
The effectiveness of eluxadoline to treat the signs and symptoms of IBS-D in pediatric patients will be evaluated based on comparisons of change from baseline in the daily daytime stool consistency scores averaged over the 4-week

Treatment Period.

Study objective

The primary objectives of this study are:
- To explore the therapeutic effect of eluxadoline in treating IBS-D in pediatric patients 6-17 years of age.
- To evaluate the pharmacokinetics (PK) of eluxadoline in pediatric patients with IBS-D.
- To evaluate the safety and tolerability of eluxadoline in pediatric patients with IBS-D.
The results of this dose-ranging study will allow the selection of an optimal dose(s) of eluxadoline to evaluate in the subsequent confirmatory efficacy study.

Study design

This study is a multi-center, randomized, double-blind, placebo-controlled, parallelgroup, dose-ranging study in pediatric patients (age 6-17 years) with IBS-D.
Approximately 120 eligible participants will be randomly assigned in a ratio of 1:1:1:1 to 1 of 4 treatment groups as follows:
- Group 1: 25 mg eluxadoline BID for 28 days (n~30)
- Group 2: 50 mg eluxadoline BID for 28 days (n~30)
- Group 3: 100 mg eluxadoline BID for 28 days (n~30)
- Group 4: placebo BID for 28 days (n~30)

At least 24 eligible participants being age 6- 11 years old (in North-America only) will be randomly assigned in a ratio of 1:1:1 to 1 of 3 treatment groups as follows:
- Groep 1: 25 mg eluxadoline BID (n=8)
- Groep 2: 50 mg eluxadoline BID (n=8)
- Groep 3: 25 mg placebo BID (n=8)

Treatments will be administered as oral tablets.
The study will consist of a 1-2-week Screening Period and a 2-3-week Pre-treatment Period, a 4-week double-blind Treatment Period and a 2-week Post-treatment follow-up Period.

Screening Period:
After providing assent and after consent has been obtained from the parent/guardian/LAR, eligible patients will enter a Screening Period of 1-2 weeks in duration.
Pre-treatment Period:
At the beginning of the Pre-treatment Period, participants will receive full training on the use and completion of the eDiary. Throughout this protocol,

eDiary is understood to refer to the particpant-administered version of the electronic patient reported outcome (ePRO) diary on a handheld electronic device. The eDiary will be completed by all participants BID throughout the Pre-treatment Period. The Pre-treatment Period will be 2-3 weeks in duration. During the Pre-treatment Period, compliance with the eDiary will be defined as completion of both morning and evening assessments for at least 8 out of the 14 days immediately preceding Visit 3 (randomization) and must be documented before participants are included in the double-blind Treatment Period.
Double-blind Treatment Period:
Participants who meet all conditions for study entry will enter the double-blind Treatment Period and be randomly assigned to receive either eluxadoline or matching placebo. Following randomization, patients will return to the clinic at Visit 4 (week 2) and Visit 5 (week 4 * end of treatment). Participants prematurely discontinued from study treatment should return to the study center to complete the end-of-treatment assessments as soon as possible after stopping the study treatment. In addition to the end-of-treatment assessments, all patients discontinuing the study prematurely should enter the Post-treatment Period and complete Visit 6 (2-week post-treatment * end of study).
Post-treatment Period:
A 2-week post-treatment period after Visit 5 (week 4 * end of treatment) is planned to assess any potential withdrawal effects based upon new AEs occurring during the period off treatment and any potential rebound worsening of IBS-D symptoms based on continuing assessments of daily symptoms. Participants will undergo a final follow-up visit (Visit 6).

Intervention

Eluxadoline: 25 mg twice daily (BID), 50 mg BID, 100 mg BID (age group 12-17 years only), or placebo BID, administered as oral tablets for maximum 9 weeks.

Study burden and risks

In general, study participants can experience physical or psychological discomfort through examination tests, examination procedures and questionnaires. In addition, subjects can experience side effects from the study medication.

The study load consists of (maximum):
- Visits to the doctor: 6 visits
- Physical examination: 3 times
- Measuring vital functions / weight: 5 times
- Neurological examination: 4 times
- ECG: 2 times
- Enter diary: 112 times

- Blood collection: 7 times
- Blood test: 4 times
- Urine test: 2 times
- Swallowing pills: 56 doses

Contacts

Public
Allergan

Marlow International Parway 1
Marlow SL7 1YL
GB
Scientific
Allergan

Marlow International Parway 1
Marlow SL7 1YL
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

To be eligible to participate in the study, participants must meet the following criteria:, 1. Participant must provide written or verbal informed assent and the parent/guardian/LAR must provide written informed consent before the initiation of any study-specific procedures., 2. Participant is a male or female outpatient, 6 to 17 years of age inclusive, at the time the participant

provides assent for the study and parent/guardian/LAR has provided signed consent., 3. Participant is able to read and understand the assessments in the eDiary., 4. Female participants of childbearing potential must have a negative serum pregnancy test at Visit 1 (screening) and a negative urine pregnancy test at Visit 3 (randomization) prior to dosing., 5. 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 as:, a) Hormonal contraception (eg, oral contraceptive, contraceptive implant, or injectable hormonal contraceptive)., b) Double-barrier method (eg, condom plus intrauterine device, diaphragm plus spermicide)., 6. Participant has a diagnosis of IBS-D as defined by the modified Rome IV child/adolescent criteria*: Must include all of the following:, 1. Abdominal pain at least 4 days per month over at least 2 months associated, with one or more of the following:, a. Related to defecation, b. A change in frequency of stool, c. A change in form (appearance) of stool, 2. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition, 3. Participant has predominantly diarrheal stool symptoms defined as Bristol stool types 6 or 7 for >25% of bowel movements and Bristol stool types 1 or 2 for <25% of bowel movements that occur in the absence of laxatives, *All criteria fulfilled for at least 2 months prior to Visit 1 (screening)., 7. Participant has been compliant with the eDiary by completing both the morning and evening assessments for at least 8 out of the 14 days immediately preceding Visit 3 (randomization)., 8. Participant has an average daytime abdominal pain score *2.0 over the 2 weeks prior to randomization., 9. Participant has at least 1 daytime bowel movement with a consistency of Type 6 or Type 7 on the pediatric Bristol Stool Form Scale (p-BSFS) on at least 2 days per week during the 2 weeks prior to randomization that occurs in the absence of laxatives., 10. Participant has no clinically significant findings on a physical examination, vital sign assessment, electrocardiogram (ECG), and clinical laboratory tests (clinical chemistry panel, liver biochemical tests, complete blood count, urine drug screen, urinalysis) after providing informed assent and after written consent is obtained, but before receiving the first dose of study treatment. (A central laboratory will be used to evaluate all urine [except urine pregnancy tests] and blood samples and will, utilize reference ranges specific to a patient*s age and gender. ECGs will be performed and electronically transmitted to a central ECG laboratory for analysis by a pediatric cardiologist in accordance with the instructions provided by the central ECG laboratory. The Investigator will determine if a particular finding is clinically significant. [In making this determination, the Investigator will consider whether the particular finding could represent a condition that would exclude the participant from the study, could represent a safety concern if the participant participates in the study, or could confound the study-specific assessments of safety or efficacy.])

Exclusion criteria

Participants who meet any of the following criteria will not be eligible to participate in the study:, 1.has no gallbladder, 2.has had any of the following surgeries:, a)Any abdominal surgery within the 3 months prior to trial;, b)A history of major gastric, hepatic, pancreatic, or intestinal surgery, 3.has known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction, 4.has a history of pancreatitis; structural diseases of the pancreas, known or, suspected pancreatic duct obstruction, 5.has a history of cholecystitis within 6months before trial., 6.has known or suspected bile acid malabsorption., 7.is a current regular alcohol drinker and/or binge drinker, and/or has a history, of alcoholism, alcohol abuse, or alcohol addiction, and/or intends to consume alcohol during the trial. , 8.has had chronic or severe constipation or sequelae from constipation,, or known or suspected mechanical GI obstruction or pseudo obstruction., 9.has had or current diagnosis of constipation with encopresis., 10.meets the child/adolescent Rome IV criteria of IBS with constipation, IBS, with constipation and diarrhea (mixed), unspecified IBS, or functional constipation., 11.has had intestinal obstruction, stricture, toxic megacolon, GI perforation, fecal impaction, gastric banding, bariatric surgery, adhesions, ischemic colitis, or impaired intestinal circulation., 12.has a history of hepatic impairment as defined by Child-Pugh Classification Grade A,B or C, 13.has a history or current diagnosis of inflammatory or immune-mediated lower, GI disorders including inflammatory bowel disease, 14.has celiac disease,or a positive serological test for celiac disease and the, condition has not been ruled out by endoscopic biopsy, 15.has any congenital and/or acquired malabsorption syndrome, 16.has a history of a microbiologically documented GI infection within 3months prior to trial, 17.has a known lactose or fructose intolerance, 18.has a history of diverticulitis within 3 months prior to trial, 19.has had within 5 years prior to trial or current evidence of laxative abuse, 20.has a history of either hypo-or hyperthyroidism that is untreated or treated, with medication at a dose that has not been stable for at least 3months prior to, trial., 21.Participant*s diarrhea is deemed by the Investigator to be caused by infectious, 22.has had or current evidence of blood in the stool , 23.currently has both unexplained and clinically significant alarm symptoms and systemic signs of infection or colitis, or any neoplastic process, 24.has a history or current diagnosis of eosinophilic gastroenteritis, 25.has Cystic Fibrosis, and or any other causes of pancreatic exocrine insufficiency, 26.is receiving enteral tube feeding, 27.has a history of a cardiovascular event, including stroke, myocardial infarction, congestive heart failure, or transient ischemic attack within 6months prior to trial, 28.has an unstable renal, hepatic, metabolic, or hematologic condition, 29.has a history of malignancy within 5 years before Screening, which includes any new diagnosis of malignancy or any treatment for or recurrence of a malignancy that was diagnosed 5 or more years prior. In order to be eligible for the study, patient must be malignancy free for the past 5years, 30.has a history of immunodeficiency, 31.has a history of drug

abuse, 32.has a positive urine drug result, 33.has a weight and BMI less than the 3rd percentile., 34.has had an unintentional weight loss greater than or equal to 5% of his/her, body weight within the last 3months, 35.Female participants who are pregnant or nursing, or plan to become pregnant or nurse during the trial, 36.has known allergies or hypersensitivity to opioids, 37.used a prohibited medication or failed to meet the stable dose, 38.is unable to tolerate the placebo oral tablets prior to randomization., 39.has any condition that, in the opinion of the Investigator, would contribute to, the patient*s IBS-D symptoms or confound the evaluation of safety or efficacy of the IMP, 40.has neurodevelopmental disabilities producing a cognitive delay that precludes comprehension and completion of the daily eDiary or other study-related questionnaires, 41.has a poorly treated or poorly controlled psychiatric disorder that might, influence the patient*s ability to participate in the study, 42.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, 43.has any condition that, in the opinion of the Investigator, would compromise, the well-being of the patient, 44.received an investigational product during the 30 days before Visit1 or is planning to receive an IMP or use an investigational device at any time during the, study, 45. Participant*s parent/guardian/LAR has been directly or indirectly involved in the conduct and administration of this study as an Investigator, Sub-Investigator, Study Coordinator, or other study member

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:	Recruitment stopped
Start date (anticipated):	16-09-2020

Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Truberzi
Generic name:	Eluxadoline

Ethics review

Approved WMO Date:	09-08-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-02-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	21-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2021
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	EUCTR2017-003770-14-NL
ClinicalTrials.gov	NCT03339128
CCMO	NL66207.018.18