STUDY REPORT SYNOPSIS

Multi-center, single arm, observational study to evaluate the safety of linaclotide in IBS-C patients in China

Milestones:
Clinical Study Protocol v1.0 Approval: 06 Mar 2019
Clinical Study Protocol v2.0 Approval: 18 Feb 2020
Clinical Study Protocol v3.0 Approval: 26 Jan 2021
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This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale:

Irritable bowel syndrome (IBS) is a common disorder that affects the stomach and intestines, also called the gastrointestinal tract. IBS is subtyped based on predominant stool pattern: approximately one-third of IBS patients are classified as having IBS with constipation (IBS-C). IBS-C is characterized by abdominal symptoms (pain, discomfort, and bloating), reduced stool frequency, hard/lumpy stools, straining during bowel movements (BMs), and a sensation of incomplete evacuation. The prevalences of IBS according to Rome III and Rome IV criteria in China are 7.4% and 2.3% respectively based on an Internet survey, and 3.8% and 1.4% respectively based on a household survey. One disease burden study of IBS in China indicated that total annual costs per patient were estimated as China Yuan (CNY) 18262. IBS imposes a huge economic burden on patients and healthcare systems.

Linaclotide, a minimally absorbed 14-amino-acid peptide structurally related to the endogenous guanylin

peptide family of hormones that regulate fluid and electrolyte homeostasis in the intestine, binds to and activates guanylate cyclase-C (GCC) on the luminal surface of the intestinal epithelium. Activation of GCC results in the generation of cyclic guanosine monophosphate (cGMP) which is increased in both the intracellular and extracellular compartments. The increase in cGMP within intestinal epithelial cells triggers a signal transduction cascade activating the cystic fibrosis transmembrane conductance regulator. This activation causes secretion of chloride and bicarbonate into the intestinal lumen; sodium ions and water follow, resulting in increased luminal fluid secretion and a reflex acceleration of intestinal transit. Extracellular cGMP, actively transported out the intestinal epithelial cells, is believed to reduce visceral hyperalgesia by modulating the activity of afferent pain fibers.

Linaclotide was approved for the treatment of IBS-C and chronic idiopathic constipation (CIC) by Food and Drug Administration (FDA) in 2015. The end point which was recommended by FDA to evaluate the efficacy of IBS treatment drugs, was met by 33.6% linaclotide-treated patients compared with 21% placebo-treated patients. A greater percentage of linaclotide patients, compared with placebo patients, reported for at least 6/12 treatment period weeks, a reduction of ≥30% in abdominal pain (50.1% vs 37.5%) and an increase of ≥1 complete spontaneous bowel movement (CSBM) from baseline (48.6% vs 29.6%). Another phase III study demonstrated consistent efficacy and good tolerance for IBS patients. The Chinese phase III 12-week clinical trial in IBS-C patients supported and expanded on the results observed in two earlier North America studies.

It is required by National Medical Products Administration (NMPA) (formerly named China Food and Drug Administration [CFDA]) to assess the additional safety data in Chinese population of newly approved drug within the first five years after imported drug license (IDL) approval.

Objectives:

The primary objective of current study was to demonstrate the safety of linaclotide therapy by assessment of the incidence of any adverse events (AEs), serious adverse events (SAEs), AEs by severity, adverse drug reactions (ADRs), and AEs leading to linaclotide-associated interruption, discontinuation, and death during 3-month follow up in Chinese patients.

The secondary objectives were to assess the treatment satisfaction and the impact of linaclotide treatment in patient's quality of life.

- To observe patients' treatment satisfaction status after treatment via a 5-point treatment satisfaction scale (1=not at all, 2=a little, 3=somewhat, 4=very, 5=extremely)
- To describe patient's quality of life after treatment via the IBS-QoL Measure

Study design:

The study was a multi-center, one arm, prospective observational study which enrolled 3000 Chinese patients who had taken at least one dose of linaclotide or according to the physician's decision, had prescribed and agreed to start taking at least one dose of linaclotide.

The study was performed under real clinical practice setting. Patients would be eligible for the study after taking at least one dose of linaclotide or according to the physician's decision, had prescribed and agreed to start taking at least one dose of linaclotide. The potential study patient would be identified by an investigator in the study site by reviewing the medical record. Whether a potential patient had taken at least one dose of linaclotide or according to the physician's decision, had prescribed and agreed to start taking at least one dose of linaclotide would be confirmed by a patient-investigator face-to-face visit (Visit 1). However, the initiation and dosing of linaclotide would be at the discretion of a physician based on her or his clinical judgement. And, the discontinuation of linaclotide would be determined by either physicians or study patients according to their own decision. No investigator, AZ employee, or member of the research operation team shall propose

initiation and/or dosing of linaclotide to any physician or patient with any path, at any time during the study was being carried out. Any investigator, AZ employee, or member of research operation team must not intervene the decision making of any physician or patient with any path, at any time during the study was being carried out. Every patient would be followed maximum of 3 months after enrolment. Patients, who stopped linaclotide during the study period, would be tracked for 7 days after discontinuation. A telephone call would be used for this tracking at least once at the end of the 7 days. According to the real clinical practice, patients need to re-visit the physician in the first month for the symptom relief assessment. The treatment of linaclotide would be tracked by reviewing medical records and confirmed by patient-investigator face-to-face visit at week 4 (Visit 2) and week 12 (Visit 3).

Data source:

The patients were recruited from qualified clinical research center. The investigator was specialized in gastrointestine. The Medical Department of AZ/delegate selected the investigators based upon clear inclusion/exclusion criteria that were approved by the Medical Director (investigator must be qualified by experience and ability to perform the study).

Study population:

Up to 3000 patients who had already taken at least one dose of linaclotide or according to the physician's decision, had prescribed and agreed to start taking at least one dose of linaclotide were enrolled.

Inclusion criteria:

- ≥18 years old
- Provision of patient informed consent prior to any study procedures
- Had taken at least one dose of linaclotide or according to the physician's decision, had prescribed and agreed to start taking at least one dose of linaclotide
- NOT participating in any interventional study currently or during the last 3 months

Exclusion criteria:

- If linaclotide was contraindicated according to the product prescribing information
- Being unable to comply with study-specified procedure
- Had ever participated in current study before

Statistical methods:

All statistical procedures were conducted using SAS version 9.4. Analysis for this study were mostly descriptive. For continuous measurements, descriptive statistics were calculated as n, mean, standard deviation (SD), medium, minimum, and maximum. For categorical measurements, the frequency and/or percentage of patients in each category were presented. Counts that are zero were displayed as "0". Percentages were calculated based on non-missing data unless otherwise specified. 95% confidence intervals (CIs) were calculated for the estimated incidence wherever appropriate.

There was no pre-planned hypothesis testing for this study. Two-sided 95% CIs were be presented, where applicable. P-values were rounded to three decimal places. If a p-value was less than 0.001 it would be reported as "<0.001" . If a p-value was greater than 0.999 it would be reported as ">0.999."

Baseline was defined as the last non-missing evaluation at the screening visit.

Two analysis sets were planned for this study and defined as below:

- Safety analysis set (SAS): All patients who received at least one dose of linaclotide were included in SAS. It was the primary analysis set for all safety analyses. Patients who withdraw consent to participate in the study were included up to the date of their study termination.
- Efficacy analysis set (EAS): All patients who received at least one dose of study treatment and had at least one non-missing baseline and one post-baseline efficacy assessments were included in EAS. The analysis of efficacy (treatment satisfaction scale and IBS-QoL) were performed based on this analysis set.

The primary variable was the incidence of AEs. The analysis of AE was based on SAS. All the verbatim terms of AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) (Version 25.1).

Secondary variables included assessment on treatment satisfaction and patients' quality of life. Both measurements captured towards patient report outcome (PRO) questionnaire. Analyses were based on EAS.

Other analyses included patient disposition, patient demographics and baseline characteristics, medical history, prior and concomitant medications, extent of exposure, and vital signs. The analyses above were all based on SAS except for the patient disposition.

Results:

Study participatation and patients

Till database bock (DBL) (26 May 2023), 3000 patients were screened and enrolled into this study. Among the enrolled patients, 2963 patients (98.8%) were included in SAS and 1926 patients (64.2%) were included in EAS.

Among the 2963 patients in SAS, 832 patients (28.1%) were male and 2131 patients (71.9%) were female. All the patients in SAS were Asian. The mean (±SD) age was 49.8±16.52 years (n=2963), and the mean (±SD) BMI was 22.3±3.08 kg/m^2 (n=2951).

Among them, 2195 patients (74.1%) reported as least one medical history, and 654 patients (22.1%) reported IBS-C disease history. The mean (±SD) duration of IBS-C disease was 0.96±2.485 years. The mean (±SD) total dosing of treatment of concomitant anti IBS and anti-constipation was 658.163±5487.3526 g, while the mean (±SD) duration was 143.8±505.75 days.

The mean (±SD) duration of treatment of linaclotide was 42.4±34.53 days, and the mean (±SD) proportion of days covered was 64.34±28.911. Most patients (2007 patients, 67.7%) did not adjusted the dose of linaclotide. Ten patients took overdose linaclotide, and the mean (±SD) overdose duration was 14.6±28.13 days.

Safety evaluation

- AEs were reported in 712 patients (24.0%). AEs classified by preferred term (PT) with the incidence of ≥0.5% in total included diarrhoea (297 patients [10.0%]), chronic gastritis (26 patients [0.9%]), large intestine polyp (24 patients [0.8%]), dyspepsia (24 patients [0.8%]), abdominal pain (22 patients [0.7%]), COVID-19 (19 patients [0.6%]), helicobacter infection (19 patients [0.6%]), sleep disorder (17 patients [0.6%]), nasopharyngitis (16 patients [0.5%]), gastritis erosive (15 patients [0.5%]), anxiety (15 patients [0.5%]), and gastrooesophageal reflux disease (14 patients [0.5%]).
- ADRs were reported in 319 patients (10.8%). ADRs classified by PT with the incidence of ≥0.5% in total included diarrhoea (289 patients [9.8%]) and abdominal pain (14 patients [0.5%]).
- Only 1 patient experienced AE leading to death (hepatic cancer), which was not related to study drug.

- SAEs were reported in 46 patients (1.6%). The most common SAE classified by PT was large intestine polyp (11 patients, 0.4%).
- Only 2 patients (0.1%) experienced serious ADRs, including haemorrhoids (moderate) and abortion spontaneous (severe).
- AEs leading to drug permanently discontinued were reported in 70 patients (2.4%). AEs leading to drug permanently discontiued by PT with the incidence of ≥0.5% in total included diarrhoea (54 patients [1.8%]).
- AEs leading to linaclotide associated- interruption were reported in 30 patients (1.0%), including diarrhoea (29 patients [1.0%]), abdominal distention, abdominal pain, and abdominal pain upper (1 patient for each).
- Other medically important serious events were reported in 2 patients (0.1%), including hypokalaemia and depression reported by one patient, and abortion spontaneous, and depression (each occurred in 1 patient) reported by the other patient. All the events were severe and with the outcome of recovered/resolved.
- No obvious increase/decrease was identified among the mean vital signs parameters.

Efficacy evaluation

Treatment satisfaction

- The mean (±SD) treatment satisfaction for all available patients increased after treatment, from 2.8±1.33 (baseline, n=1721) to 3.5±1.05 (Week 4, n=1705) and 3.9±1.04 (Week 12, n=833), with more patients reaching the score of 3-5.
- Patients in new treatment group and used treatment group had the similar increasing trend in treatment satisfaction to the whole EAS.

Quality of life

- The mean (±SD) IBS-QoL overall score for all available patients increased after treatment, from 73.2±16.59 (baseline, n=1924) to 80.2±15.50 (Week 4, n=1738). The subtotal scores of the eight specific subscale domains (Dysphoria, Interference with activity, Body image, Health worry, Food avoidance, Social reaction, Sexual, and Realationship) all increased after treatment, indicating the same results with that of the overall score.
- Patients in new treatment group and used treatment group had the similar increasing trend in IBS-QoL overall score. The subtotal scores of the eight specific subscale domains in each group all increased after treatment, indicating the same results with the whole EAS.

Conclusion:

In summary, this study has provided the data for the safety and efficacy profiles for linaclotide in Chinese patients with a large sample size. Linaclotide was well tolerated in Chinese patients and the safety profiles were in line with the known profiles in clinical studies. Also, the results in treatment satisfaction and quality of life showed solid efficacy profile of linaclotide.

AMENDMENT HISTORY

Amendment History of Clinical Study Rreport

The version of clinical study report is 1.0. So the amendment history is not applicable for clinical study report.

Amendment History of Clinical Study Protocol

Date	Section of study protocol	Amendment or update	Reason
22 Jul 2019	Secondary endpoints/ Study flow chart and plan/ Statistics analysis plan/ Collection of adverse events/ Safety reporting	Amendment	To evaluate the effect of linaclotide on satisfaction and quality of life of patients
08 Dec 2020	Inclusion criteria/Follow-up duration/Patients' group	Amendment	According to the actual clinical practice, the enrollment criteria and follow-up duration were adjusted to improve the feasibility of the study and the compliance of patients. According to the adjustment of the selection criteria, the grouping criteria were adjusted accordingly to assess the safety, treatment satisfaction and quality of life of patients with different linaclotide medication history.

Amendment History of Statistical Analysis Plan

Version/Date	Category*: Change refers to	In line with the clinical study protocol?	Rationale
Version 1.0/03 Aug 2020	NA (Original version)	Y	NA
Version 2.0/29 Mar 2023	Primary and secondary endpoints; Other.	Y	Updated to align with protocol version 3.0

* Pre-specified categories are

Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other

MILESTONES

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