2 SYNOPSIS

Title:
A Phase IIa, Proof of Concept, Randomized, Double-Blind, Dose-Finding, Cross-Over Study of the Efficacy, Safety and Tolerability of a New Enteric-Coated Cholestyramine Capsule in Adult Short Bowel Syndrome Patients

Study Start Date (First Patient First Visit):	**Phase:**
01-OCT-2019	Phase IIa

Primary Objective:
The primary objective of this study was to investigate the clinical efficacy of a new Enteric-Coated Cholestyramine (ECC) capsule formulation and select the most effective dose in adult patients with Short Bowel Syndrome (SBS).

Secondary Objectives:
The secondary objectives of this study were to evaluate the safety and tolerability of a new ECC capsule formulation in adult patients with SBS, and to evaluate the patients' experience of related symptoms using a 11-point Visual Analog Scale (VAS).

Study Design:
Multiple-center, randomized, double-blind, double dummy, 2-period, 2-sequence cross-over design.

Study Participants:
Eighteen patients were to be recruited at 3 sites in Poland. The trial was terminated early due to difficult enrollment in the context of the COVID-19 pandemic. Despite considerable effort by the Sponsor and JSS, recruitment was too slow to reach the planned number of patients as per project timeline. As a result, there was no longer any scientific or commercial interest in the continuation of the ECC development program.

One patient was ongoing on the termination date and completed the trial on 22-DEC-2021. In total 13 patients were randomized, and they all completed the trial.

Inclusion Criteria:

1. Adult, ambulatory male and female subjects
2. Provision of signed and dated informed consent form (ICF)
3. Age ≥ 18 years and ≤ 80 years
4. Stable SBS of:
    a. Non-surgical origin; OR
    b. Surgical origin where the last surgical ileal resection was performed at least 6 months prior to enrolment
5. Partial, Home Parenteral Nutrition and/or parenteral fluids are allowed, at a maximum frequency of 6 times a week throughout the trial, as long as the regimen has been stable for at least 2 weeks prior to screening and is expected to remain unchanged during the study
6. At least 50 % of the colon being intact
7. Intact duodenum
8. Body Mass Index (BMI) ≥ 18
9. Presence of stable chronic diarrhea for at least 3 months prior to enrolment as evidenced by medical history
10. Presence of stable chronic diarrhea during the 2-week screening diary period before randomization, as evidenced by completion of a screening diary demonstrating:
    a. Mean daily production of at least 3 soft or watery stools (BSFS scores 6 or 7); **or**
    b. More than 3 bowel movements per day on average with >25% of them being BSFS type 6 or 7
11. Stated willingness and ability to comply with all study procedures, including daily recording of bowel movements and BSFS in the patient diaries, and availability for the duration of the study
12. Clinical laboratory values within the laboratory's stated normal range; if not within this range, they must be without clinical significance, as determined by the investigator
13. Female subjects must meet one of the following criteria:
    a) Participant is of childbearing potential and agrees to use one of the accepted contraceptive regimens from at least 30 days prior to the first study treatment administration through to at least 30 days after the last dose of the study treatment. An acceptable method of contraception includes one of the following:
        a. Abstinence from heterosexual intercourse
        b. Systemic contraceptives (combined birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch)
        c. Intrauterine device (with or without hormones)
        d. Condom with spermicide

    b) Participants of non-childbearing potential, defined as surgically sterile (i.e. has undergone complete hysterectomy, or bilateral oophorectomy) or is in a menopausal state (i.e. at least 1 year without menses prior to the first study drug administration) are eligible

Exclusion Criteria:

1. Patients with known or suspected intestinal strictures of clinical relevance as judged by the Investigator
2. Active inflammatory bowel disease (IBD) or fistula during the screening period as judged by the Investigator
3. Crohn's disease patients not being in clinical remission for the last 12 weeks prior to randomization
4. Diarrhea caused by other causes than SBS
5. Presence of clinically significant steatorrhea, requiring pancreatic enzymes supplementation
6. Presence of complete biliary obstruction
7. Presence of active cancer (except resected cutaneous basal or squamous cell carcinoma and except *in situ* cervical cancer) and/or need to receive chemotherapy or radiotherapy during the study
8. History of allergic reaction to cholestyramine or any excipient of the investigational drug product or placebo, or packaging components
9. Females who are lactating at screening
10. Females who are pregnant according to the pregnancy test at screening or prior to the first study treatment administration
11. Significant history (at least 3 consecutive months in the year prior to Screening) of drug dependency or alcohol abuse (> 3 units of alcohol per day, intake of excessive alcohol, acute or chronic)
12. Subjects who took an Investigational Product (IP) in the 30 days prior to the first study drug administration
13. Any other clinically significant condition that is considered by the principal investigator as being susceptible to put the patient at greater safety risk, influence response to study product, or interfere with study assessments.

Randomization and Treatment:

Investigational Medicinal Product: ECC capsules, 425 mg (size 00) and matching placebo
Manufacturer: Pharmascience Inc.

In this cross-over design, patients were randomized to either:

- Low dose ECC 1.7 g daily in period 1 for 14 days followed by a washout period of 14 days and then High dose ECC 4.25 g daily for 14 days in period 2

OR

- High dose ECC 4.25 g daily in period 1 for 14 days followed by a washout period of 14 days and then Low dose ECC 1.7 g daily for 14 days in period 2.

The low dose of ECC, 1.7 g daily, was taken as 2 x 425 mg ECC capsules + 3 x matching placebo capsules in the morning and the same dose again in the evening.

The high dose of ECC, 4.25 g daily, was taken as 5 x 425 mg ECC capsules in the morning and the same dose again in the evening.

Patients were instructed to take the capsules at least 30 minutes before breakfast and the evening meal.

Criteria for Evaluation:

Primary Efficacy Endpoint:

- Change in the weekly frequency of bowel movements (BM) measured between baseline and the second week of treatment (i.e. Days 8 to 14, and Days 36 to 42).

Secondary Efficacy Endpoints:

- Total number of bowel movements per week, after the first week of treatment (i.e. Days 1 to 7, and Days 29 to 35)
- Total number of bowel movements for the whole 2-week treatment period (i.e. Days 1 to 14 and Days 29 to 42)
- Mean daily stool form score according to the Bristol Stool Form Scale (BSFS), measured during the first week of treatment (i.e. Days 1 to 7, and Days 29 to 35)
- Mean daily stool form score according to the BSFS, measured during the second week of treatment (i.e. Days 8-14, and Days 36-42)
- Mean daily stool form score according to the BSFS, measured during the whole 2-week treatment period (i.e. i.e. Days 1 to 14 and Days 29 to 42)
- Total number of bowel movements with a BSFS score ≥ 6 during the first week of treatment (i.e. Days 1 to 7, and Days 29 to 35)
- Total number of bowel movements with a BSFS score ≥ 6 during the whole 2-week treatment period (i.e. Days 1 to 14 and Days 29 to 42)
  Mean daily dose of loperamide in mg, if used, during the second week of treatment (i.e. Days 8-14, and Days 36-42)
- Mean Diarrhea Composite Index ([weekly bowel movement frequency X mean daily BSFS score] + loperamide use [weekly mg X 3]) during the second week of treatment (i.e. Days 8-14, and Days 36-42)
- Evaluation of severity of diarrhea, abdominal pain, urgency and bloating using an 11-point Visual Analog Scale (VAS) made on Days 0 (baseline), 15, 28 and 43

Safety Variables:

- Safety evaluated through the assessment of adverse events (AE), laboratory tests, vital signs, ECG and physical examination)
- Tolerability (to be evaluated through assessment of TEAEs and TESAEs)

Statistical Analyses:

At early study termination, 13 of the planned 18 patients had completed the study. Due to the lower than expected number of patients completing the study, it was anticipated to observe greater variability in the data distribution and less precision of the assessed estimates. The Sponsor decision was to perform abbreviated analyses on key data as detailed in Section 9.10 of the abbreviated study report. The 13 randomized patients were included in the ITT and Safety Population. Planned analyses on the PP population were not performed.

Summary of Efficacy Evaluation:
Treatment with high dose ECC (4.25 g daily) resulted in a statistically significant reduction in the mean number of weekly BMs (absolute change 13.4±9.73; range 3 – 31; p=0.015) by the second week of treatment. A slightly lower but still statistically significant reduction in mean weekly BMs (absolute change 11.5±11.38; range 1 – 36; p=0.016) was seen by the second week of treatment with low dose ECC (1.7 g daily). There was no statistically significant difference between the effects of high and low dose ECC on this endpoint (p=0.456).

Treatment with high dose ECC resulted in a statistically significant reduction in the mean daily BSFS scores (5.3 vs. 3.7; p=0.01) by the second week of treatment. A slightly lower but still statistically significant reduction in mean daily BSFS score (5.0 vs. 3.6; p=0.015) was seen by the second week of treatment with low dose ECC.

Approximately half of the patients were treated with loperamide, in equal number between the low and high dose periods. The mean daily dose of loperamide used by these patients was slightly but not statistically significantly lower during the high dose ECC period compared to the low dose ECC period (68.9 mg vs. 72.9 mg; p=0.564)

Treatment with high dose ECC resulted in statistically significant reductions in the patient self-evaluated VAS scores for severity of diarrhea (p=0.012) and urgency (p=0.045) and numerically lower VAS scores for abdominal pain and bloating. Similarly, treatment with low dose ECC resulted in numerically lower VAS scores for all symptoms but was only significantly reduced for urgency (p=0.027).

Summary of Safety Evaluation:
There were no deaths, serious adverse events (SAEs) and other significant adverse events reported in this study. There were no AEs leading to discontinuation. In total, 3 subjects experienced 5 TEAEs during the low dose ECC period, and 4 subjects experienced 9 TEAEs during the high dose ECC period. The majority of the TEAEs were mild in severity. Most were considered not related or had an unknown causal relationship to study drug. Only 1 event (decreased appetite) was considered possibly related to study drug.

Summary of Conclusions:

Overall, based on key data assessments, the data suggest that treatment with high dose ECC is well tolerated and may be effective in reducing the severity and frequency of diarrhea in adult patients with SBS, in a clinically relevant manner, with similar effects seen for low dose ECC. However, due to early termination of the study and low number of patients included in the analysis, the efficacy and safety results of ECC capsules in adult SBS patients must be interpreted with caution.

Version and Date of Report:
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