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Colesevelam hydrochloride in patients with idiopathic bile acid diarrhoea

Submission date 10/08/2024	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 25/11/2024	**Overall study status** Completed	
Last Edited 09/12/2024	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims
Bile acid diarrhoea (BAD) is a type of chronic diarrhoea which is a very painful, embarrassing and debilitating condition causing numerous episodes of watery and urgent bowel motions sometimes resulting in faecal accidents. It is estimated that it affects 1:100 people.
This study is focused on people who suffer from or show symptoms of Type 2 BAD (also referred to as idiopathic/primary bile acid malabsorption). People are diagnosed with Type 2 BAD when there is no other disorder affecting the small bowel. In people with bile acid diarrhoea the production of bile fails to be switched off meaning more bile is produced than can be absorbed, causing the watery diarrhoea. Research studies suggest that one in three people who have irritable bowel syndrome with diarrhoea (IBS-d) as a prominent feature could have primary BAD.
Colesevelam hydrochloride-MMX is a large molecule made of a chain of smaller units specifically engineered to bind to bile acids. When Colesevelam binds to bile acids it reduces their effects on the colon (a section of the large intestine) with consequent improvement of symptoms like diarrhoea, irritable bowel, abdominal bloating and swelling and faecal urgency.
This study aims to evaluate the effectiveness of Colesevelam hydrochloride-MMX in treating idiopathic bile acid diarrhoea. Two different daily doses of the drug will be compared with a placebo (inactive tablets). The study will follow a double-blind design, which means neither the participants nor their study doctor and his/her staff will know if the participants are receiving the study drug or placebo.

Who can participate?
Patients aged 18 or over with suspected or diagnosed BAD

What does the study involve?
Participation in the study will last a maximum of 4.5 months and include six visits to the study centre. During the study participants will also receive five phone calls from the study team. Participants will attend follow-up visits and will be compensated for travel expenses.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
Cosmo Technologies Ltd (Ireland)

When is the study starting and how long is it expected to run for?
August 2024 to November 2025

Who is funding the study?
Cosmo Technologies Ltd (Ireland)

Who is the main contact?
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Contact information

Type(s)
Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
2024-511993-55

Integrated Research Application System (IRAS)
1010417

Protocol serial number
CB-01-33/01

Study information

Scientific Title
A randomised, double-blind, multicentre, international placebo-controlled phase II study aimed at investigating the efficacy and safety of a novel modified-release tablet formulation of colesevelam hydrochloride in patients with idiopathic bile acid diarrhoea

Study objectives

The primary objective of the study is to investigate the efficacy of two dose regimens of the test Colesevelam hydrochloride-MMX® 900 mg modified release tablets as compared to the matching placebo, in terms of the proportion of study participants with a diagnosis of idiopathic bile acid diarrhoea (BAD) who are stool consistency responders.

The secondary objective of the study is to evaluate the efficacy, safety and tolerability of Colesevelam hydrochloride-MMX® 900 mg modified release tablets as compared to placebo in study participants with a diagnosis of idiopathic BAD.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 04/11/2024, Scotland A Research Ethics Committee (South East Scotland Research Ethics Service, 2nd Floor, Waverley Gate 2-4 Waterloo Place, Edinburgh , EH1 3EG, United Kingdom; +44 (0)781 460 9032; loth.sesres@nhs.scot), ref: 24/SS/0075

Primary study design
Interventional

Study design
Double-blind randomized placebo-controlled trial

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Idiopathic bile acid diarrhoea (BAD)

Interventions
Patients will be randomly assigned to one of the treatment schedules for 8 consecutive weeks. During the first 2 weeks, the study medication will be administered only in the evening. From Day 15 to Day 56, the medication will be taken twice daily, in the morning and evening.

Intervention Arm 1:Colesevelam hydrochloride 3,600 mg:
Day 1 to Day 14: 2 x 900 mg tablets in the evening delivering a total of 1,800 mg of colesevelam hydrochloride daily.
Day 15 to Day 56: 2 x 900 mg tablets in the morning and 2 x 900 mg tablets in the evening, delivering a total of 3,600 mg of colesevelam hydrochloride daily.

Intervention Arm 2: Colesevelam hydrochloride 1,800 mg:
Day 1 to Day 14: 1 x 900 mg tablet and 1 placebo tablet in the evening delivering a total of 900 mg of colesevelam hydrochloride daily.
Day 15 to Day 56: 1 x 900 mg tablet and 1 placebo tablet in the morning and 1 x 900 mg tablet and 1 placebo tablet in the evening delivering a total of 1,800 mg of colesevelam hydrochloride daily.

Intervention Arm 3: Placebo tablets:
Day 1 to Day 14: 2 placebo tablets in the evening, with no active treatment.
Day 15 to Day 56: 2 placebo tablets in the morning and 2 placebo tablets in the evening, with no active treatment.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Colesevelam hydrochloride

Primary outcome(s)
The proportion of study participants who are stool consistency responders at Week 8 after treatment with T1 or T2, compared to placebo (P). A stool consistency responder is defined as a participant who experiences a ≥50% reduction in the number of days with at least one stool of Type 6 or 7 consistency on the 7-point Bristol Stool Form Scale (BSFS) compared to baseline. Participants will complete a daily assessment of stool consistency using the BSFS.

Key secondary outcome(s)
1. Change in the proportion of stool consistency responders at Weeks 2 and 4 after T1 or T2, compared to P, assessed using the 7-point BSFS, comparing responses to baseline measurements.
2. Remission of diarrhoea at Week 8, defined according to Hjortswang criteria: fewer than 3 bowel movements per day and fewer than 1 stool per day with a consistency of Type 6 or 7 on the BSFS, calculated as the mean of the last 7 days prior to Week 8. Participants will record stool frequency (number of bowel movements) daily in a diary. Plasma levels of 7αC4 and FGF19 will also be measured at baseline and at Week 8 to support this evaluation.
3. Change in the proportion of stool frequency responders at Week 8. A stool frequency responder is defined as a participant experiencing a ≥50% reduction in the number of days with ≥3 bowel movements compared to baseline. Stool frequency will be assessed through daily diary entries recording the number of bowel movements.
4. Change in the proportion of participants achieving remission in urgency at Weeks 2, 4, and 8. Remission in urgency is defined as a score of <3 on the 11-point numerical rating scale for stool urgency. Participants will record daily stool urgency scores (0 to 10) in a diary.
5. Change in the proportion of patients experiencing adverse drug reactions after 8 weeks of treatment, assessed through diary entries and adverse event form entries recorded throughout the study period and evaluated after 8 weeks of treatment

Completion date
16/12/2025

Eligibility

Key inclusion criteria
1. Informed consent: signed written informed consent before inclusion in the study
2. Sex and age: men/women, ≥18 years old inclusive
3. Diagnosis or symptoms of bile acid diarrhoea: suspected or diagnosed type II (idiopathic) bile acid diarrhoea or subjects presenting with symptoms compatible with bile acid diarrhoea, including subjects with suspected functional diarrhoea or IBS-D as per Rome IV criteria, who fulfil the following criteria:
3.1. Have a fasting serum 7αC4 >46.0 ng/mL
3.2. Have at least 4 days per week during the screening period with ≥1 bowel movement with a

stool consistency of Type 6 or 7 in the 7-point BSFS
4. Contraception (women only): women of childbearing potential must use at least one of the following highly effective methods of contraception:
4.1. Hormonal combined oral, intravaginal, or transdermal, contraceptives associated with inhibition of ovulation for at least 2 months before the screening visit
4.2. Progestogen-only hormonal oral, implantable, or injectable contraceptives for at least 2 months before the screening visit
4.3. A non-hormonal intrauterine device [IUD] or an intrauterine hormone-releasing system (IUS) for at least 2 months before the screening visit
4.4. Bilateral tubal occlusion
4.5. A sterile sexual partner
4.6. True abstinence, i.e., refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject
Women of non-childbearing potential or in post-menopausal status must have been in that status for at least one year. For all women of childbearing potential, serum pregnancy test result must be negative at screening;
5. Full comprehension: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the study
6. Compliance with baseline diary entry: a minimum of 3 consecutive days of completed diary entries or 4 non-consecutive days within a 7-day period are necessary

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Prior and concomitant gastrointestinal diseases:
1.1. Current or recurrent disease that could affect the ileum and the enterohepatic circulation of bile acids, including ileal resection or bypass, short bowel syndrome, previous cholecystectomy, radiation enteritis, chronic pancreatitis, known small intestine bacterial overgrowth
1.2. Inflammatory bowel disease, including known microscopic colitis
1.3. Bowel obstruction
1.4. Biliary obstruction
1.5. Acute suspected or proven infectious (viral or bacterial) gastroenteritis within the 8 weeks prior to screening
1.6. Acute suspected or proven gastroenteritis within the 8 weeks prior to screening
1.7. Positive for Clostridium difficile as detected by appropriate specific test
1.8. Positive for coeliac disease blood test
1.9. Current or recurrent diseases that could affect the colon including diverticulitis, collagenous

colitis, colonic resection, toxic megacolon, fistula, perforation or abscess
2. Prior and concomitant diseases other than gastroenteric:
2.1. Fasting triglycerides level above 3.4 mmol/L (300.9 mg/dL)
2.2. Current or relevant previous history of serious, severe or unstable (acute or progressive) physical or psychiatric illness
2.3. Any medical disorder that may require treatment or make the patient unlikely to fully complete the study or any condition that presents undue risk from the study medication or procedures
2.4. Malignancy in the last 5 years prior to screening
2.5. Hyperthyroidism
3. Previous unsuccessful treatments: unsuccessfully treating BAD with bile acid sequestrants (cholestyramine, colestipol or colesevelam) unless the reason for treatment failure was due to non-compliance/lack of tolerability
4. Prior and concomitant treatments (as listed in the study protocol):
5. Inflammatory markers: C-reactive protein >1.0 mg/dL; abnormal faecal calprotectin >100 µg/g
6. Allergy: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study
7. Pregnancy (women only): pregnant or lactating women or women wishing to become pregnant in the 3 months following the screening visit; positive or missing pregnancy test at screening
8. Liver function: chronic liver disease or clinically significant liver enzyme abnormality as evidenced by elevated aspartate aminotransferase, alanine aminotransferase >2.5 times upper limit of normal or total bilirubin >1.5 times upper limit of normal
9. Investigative drug trials: participation in experimental therapeutic trials in the last 3 months before screening
10. Physical findings: clinically relevant abnormal physical findings which could interfere with the objectives of the study

Date of first enrolment
16/12/2024

Date of final enrolment
16/12/2025

Locations

Countries of recruitment
United Kingdom

Belgium

Denmark

Italy

Romania

Spain

Study participating centre
Not provided at time of registration
United Kingdom
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Sponsor information

Organisation
Cosmo Technologies Ltd

Funder(s)

Funder type
Industry

Funder Name
Cosmo Technologies Ltd

Results and Publications

Individual participant data (IPD) sharing plan
Datasets generated and/or analyzed during this study are held by Cosmo Technologies. Study IPD is not foreseen to be shared as currently there is not any company policy in place for managing that.

IPD sharing plan summary
Not expected to be made available