A Phase 3, Multicenter, Randomized, Double-blind Study to Determine the Safety and Efficacy of MMX Mesalamine/Mesalazine in Pediatric Subjects with Mild to Moderate Ulcerative Colitis, in both Acute and Maintenance Phases

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Primary: The primary objective of the Double-blind Acute Phase of the study is to assess clinical response to MMX mesalamine/mesalazine between a low and high dose in children and adolescents aged 5-17 years with mild to moderate UC.The primary...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON44753

Source
ToetsingOnline

Brief title
Study of MMX® Mesalamine/Mesalazine in Paediatric Ulcerative Colitis

Condition

- Gastrointestinal inflammatory conditions

Synonym
Ulcerative Colitis; chronic inflammation of the colon

Research involving
Human

Sponsors and support

Primary sponsor: Shire Development LLC
Source(s) of monetary or material Support: Pharmaceutical company: Shire Development LLC;USA

Intervention

Keyword: MMX Mesalamine / Mesalazine, Pediatric Ulcerative Colitis, Safety and Efficacy

Outcome measures

Primary outcome

Primary Efficacy Endpoints

Double-blind Acute Phase:

The primary efficacy endpoint for the Double-blind Acute Phase is defined as the proportion of subjects with a clinical response (defined as partial UC-DAI <=1 with rectal bleeding=0, stool frequency <=1, and PGA=0) at Week 8. This endpoint will be compared between treatment arms using a chi-squared test.

Double-blind Maintenance Phase:

The primary efficacy endpoint for the Double-blind Maintenance Phase is defined as the proportion of subjects who have maintained a clinical response (defined as partial UC-DAI <=1 with rectal bleeding=0, stool frequency <=1, and PGA=0) at Week 26. This endpoint will be compared between treatment arms using a Cochran-Mantel-Haenszel (CMH) test stratifying by Week 8 responder status.

Secondary outcome

Secondary Efficacy Endpoints

Double-blind Acute Phase:

• The proportion of subjects with a clinical and endoscopic response at Week 8, defined as UC-DAI <=2 with rectal bleeding=0, stool frequency <=1, PGA=0, and mucosal healing (endoscopy score <=1) based on central reading. In addition, there must be at least a 1-point reduction in endoscopy score from baseline. This endpoint will be compared between treatment arms using a chi-squared test.

• The proportion of subjects with a clinical and endoscopic response at Week 8, defined as UC-DAI <=2 with rectal bleeding=0, stool frequency <=1, PGA=0, and mucosal healing (endoscopy score <=1) based on local reading. In addition, there must be at least a 1 point reduction in endoscopy score from baseline. This endpoint will be compared between treatment arms using a chi-squared test.

• The change in the DUCS score from baseline to Week 8 of the Double-blind Acute Phase. This endpoint will be compared between treatment arms using an analysis of covariance, including the baseline DUCS score as a covariate in the model.

• The percentage of subjects with an improvement (change of >=20 points) in PUCAI score from baseline to Week 8 of the Double-blind Acute Phase. This endpoint will be compared between treatment arms using a chi-squared test.

Double-blind Maintenance Phase:

• The proportion of subjects who have maintained a clinical and endoscopic response at Week 26, defined as UC-DAI <=2 with rectal bleeding=0, stool frequency <=1, PGA=0, and mucosal healing (endoscopy score <=1) based on central reading. This endpoint will be compared between treatment arms using a CMH test stratifying by Week 8 responder status.

• The proportion of subjects who have maintained a clinical and endoscopic

response at Week 26, defined as UC-DAI <=2 with rectal bleeding=0, stool frequency <=1, PGA=0, and mucosal healing (endoscopy score <=1) based on local reading. This endpoint will be compared between treatment arms using a CMH test stratifying by Week 8 responder status.

• The change in the DUCS score from Double-blind Maintenance Phase Week 0 to Week 26. This endpoint will be compared between treatment arms using an analysis of covariance , including the DUCS score at Double-blind Maintenance Phase Week 0 and Week 8 responder status as covariates in the model.

• The percentage of subjects in remission (PUCAI <10) at Double-blind Maintenance Phase Week 26. This endpoint will be compared between treatment arms using a CMH test stratifying by Week 8 responder status.

Safety Endpoints

Adverse Events (AEs) will be coded using MedDRA. Treatment-emergent AEs (TEAEs) will be defined in the SAP. The number of events, incidence, and percentage of TEAEs will be presented by treatment arm (ie, low or high dose), and overall, by system organ class, and by preferred term. Treatment emergent adverse events will be further summarized by treatment arm for severity and relationship to investigational product. TEAEs related to investigational product, TEAEs leading to withdrawal, serious adverse events, and deaths will be summarized by treatment arm. Clinical laboratory tests and vital signs, and their changes from baseline will be summarized by treatment arm and visit.

Exploratory Efficacy Endpoints:

· The change in fecal calprotectin from baseline to Week 8 in the Double-blind

Acute Phase.

· The change in fecal calprotectin from Double-blind Maintenance Phase Week 0

to Week 26 in the Double-blind Maintenance Phase.

Study description

Background summary

Ulcerative colitis is a serious chronic inflammatory disease of the colon and rectum. The major clinical feature is bloody diarrhea. While an acute attack can occasionally be fatal, the characteristic course for most patients is one of remissions and exacerbations over a number of years. Life expectancy after recovery from a first attack is unchanged; however, morbidity can be long lasting and may be associated with various extra-intestinal and late complications.

MMX mesalamine/mesalazine is approved for both the induction of remission in adult patients with mild to moderate UC and for maintenance of remission of UC. No data are available on the use of MMX mesalamine/mesalazine in children and adolescents. Since most information pertaining to the use of 5-ASA is based upon adult studies, Shire proposes to evaluate the effect of MMX mesalamine/mesalazine in children and adolescents aged 5-17 years with mild to moderate UC or who are in remission.
Commercially available MMX mesalamine/mesalazine is a novel, high-strength formulation of 5-ASA (1.2g of mesalamine/mesalazine per tablet), which uses MMX technology designed to release 5-ASA throughout the colon. For the purpose of this study, 2 pediatric formulations (300mg and 600mg tablets) were developed, which are smaller than the commercially available product.

This study is a PREA post-approval commitment with the US FDA.

Study objective

Primary:
The primary objective of the Double-blind Acute Phase of the study is to assess clinical response to MMX mesalamine/mesalazine between a low and high dose in children and adolescents aged 5-17 years with mild to moderate UC.
The primary objective of the Double-blind Maintenance Phase of the study is to

assess clinical response to MMX mesalamine/mesalazine between a low and high dose in children and adolescents aged 5-17 years who are in remission.

Secondary:
Double-blind Acute Phase
• To assess clinical and endoscopic response to treatment with MMX mesalamine/mesalazine between a low and high dose in children and adolescents aged 5-17 years with mild to moderate UC in the Double blind Acute Phase
• To assess changes in the Daily Ulcerative Colitis Scale (DUCS) for children and caregivers between a low and high dose of MMX mesalamine/mesalazine in children and adolescents aged 5-17 years with mild to moderate UC in the Double-blind Acute Phase
• To assess improvement in Pediatric Ulcerative Colitis Activity Index (PUCAI) score between a low and high dose of MMX mesalamine/mesalazine in children and adolescents aged 5-17 years with mild to moderate UC in the Double-blind Acute Phase
Double-blind Maintenance Phase
• To assess clinical and endoscopic response to treatment with MMX mesalamine/mesalazine between a low and high dose in children and adolescents aged 5-17 years who are in remission in the Double blind Maintenance Phase
• To assess changes in the DUCS for children and caregivers between a low and high dose of MMX mesalamine/mesalazine in children and adolescents aged 5-17 years who are in remission in the Double-blind Maintenance Phase
• To assess remission using the PUCAI score between a low and high dose of MMX mesalamine/mesalazine in children and adolescents aged 5-17 years who are in remission in the Double-blind Maintenance Phase
Safety
To evaluate the safety and tolerability of a low and high dose MMX mesalamine/mesalazine in children and adolescents aged 5-17 years with mild to moderate UC, in the Double blind Acute Phase, the Open label Acute Phase, and the Double blind Maintenance Phase.

Exploratory Objectives:
To assess changes in fecal calprotectin in subjects between a low and high dose of MMX mesalamine/mesalazine in both the Double-blind Acute and Double-blind Maintenance Phases.

Study design

This is a prospective study with an 8-week Double-blind Acute Phase, and a 26-week Double-blind Maintenance Phase. Each phase includes 2 arms, and subjects will be randomized to 1 of 2 doses (low or high) of MMX mesalamine/mesalazine (900-4800mg/day, given once daily) at the beginning of each phase. Randomization will be in a 1:1 ratio stratified by body weight group. There is an additional 8-week, Open-label Acute Phase for subjects who do not achieve a clinical response or who have withdrawn from the Double-blind Acute Phase after a minimum of 2 weeks and, in the investigator*s opinion, have

not benefited from treatment in the Double-blind Acute Phase. Clinical response is defined as partial UC DAI <=1 (rectal bleeding=0, stool frequency <=1, and PGA=0) at the end of the Double-blind Acute Phase. In this Open-label Acute Phase, subjects are treated with the high dose of MMX mesalamine/mesalazine for their weight group.
At the Baseline Visit (Visit 2):
• Subjects with partial Ulcerative Colitis Disease Activity Index (UC-DAI) >=2 (a combined rectal bleeding and stool frequency score >=1 and PGA=1 or 2) will be randomized into the Double-blind Acute Phase.
• Subjects with partial UC-DAI <=1 (rectal bleeding=0, stool frequency <=1, and PGA=0) will be randomized into the Double-blind Maintenance Phase.
Subjects with a clinical response after completion of treatment in either the Double-blind Acute Phase or the Open-label Acute Phase will be eligible to enter the Double-blind Maintenance Phase.
Subjects without a clinical response after completion of acute treatment in the Open-label Acute Phase must be withdrawn.
All subjects will have a Screening Visit (Visit 1), and screened subjects who are eligible will proceed to the Baseline Visit (Visit 2). Study visits occur at the following time points after the Baseline Visit (Visit 2), dependent on the subject*s partial UC-DAI score:
Double-blind Acute Phase: Week 2, Week 4, Week 8 (Double-blind Acute Phase Withdrawal)
Open-label Acute Phase: Week 2, Week 4, Week 8 (Open-label Acute Phase Withdrawal)
Double-blind Maintenance Phase: Weeks 2-4 (investigational product dispensation only), Week 13, Week 26 (Double-blind Maintenance Phase Withdrawal)

Intervention

MMX mesalamine/mesalazine, administered orally, randomized in a 1:1 ratio stratified by body weight group to the following doses:
900mg/day or 1800mg/day for subjects weighing 18 to <= 23kg
1200mg/day or 2400mg/day for subjects weighing >23 to <= 35kg
1800mg/day or 3600mg/day for subjects weighing >35 to <= 50kg
2400mg/day or 4800mg/day for subjects weighing >50 to <= 90kg

MMX mesalamine/mesalazine tablet strengths 300, 600, and 1200mg with matching placebos to maintain the blind between low and high dose groups

Study burden and risks

See question E9.

It is possible that some of the topics in the questionnaires may be sensitive or embarrassing. The investigators will ensure that the consultations take

place in a private environment and will make every effort to make the trial subject/parent/caregiver as relaxed and comfortable as possible.

What is the potential for benefit to trial subjects?
There is no guaranteed benefit to the trial subjects from taking part in this study. If treatment works it may help to control the disease. The investigator will assess the balance of risks and benefits of continuing to participate in the study. Even if the research participants do not benefit personally from the study, the information gained may facilitate the development of better treatment for other (pediatric) patients with Ulcerative Colitis.

At the end of the study, the lower doses (300 and 600mg) IMP will not be available to patients. The 1200mg tablets are commercially available. The investigator will discuss alternative treatment options with the subject/parents/caregivers for subject's future care.

Contacts

Public
Shire Development LLC

Shire Way 300
Lexington 02421
US
Scientific
Shire Development LLC

Shire Way 300
Lexington 02421
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

General:
1. Ability to voluntarily provide written, signed, and dated (personally or via a legally authorized representative [LAR]) informed consent or assent as applicable to participate in the study.
2. Subject*s parent/LAR demonstrates an understanding, ability, and willingness to fully comply with study procedures and restrictions.
3. Male and female children and adolescents aged 5-17 years, inclusive, at the Baseline Visit (Visit 2).
4. Body weight 18-90 kg at the Screening Visit (Visit 1) and the Baseline Visit (Visit 2).
5. Male, or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential.
6. Diagnosed with mild to moderate UC, established by sigmoidoscopy or colonoscopy with compatible histology. Screened subjects may also have an unconfirmed diagnosis of mild to moderate UC* however the diagnosis of mild to moderate UC must have been established by sigmoidoscopy or colonoscopy with compatible histology prior to the Baseline Visit (Visit 2).
7. Subject is able to swallow the investigational product whole.
Doubleblind Acute Phase:
8. Partial UCDAI
score >=2 (a combined rectal bleeding and stool frequency score >=1 and PGA=1 or 2) at the Baseline Visit (Visit 2), for which 5ASA would be used as part of normal treatment.
9. If the subject is on 5ASA treatment prior to study entry, then the dose must be stable. Stable therapy is defined as no change in dose, or no initiation of 5ASA, from the onset of the current acute flare through discontinuation of therapy (required at the Baseline Visit [Visit 2]). Please see exclusion criterion 29 for an additional 5ASA dose related requirement.
Doubleblind Maintenance Phase:
10. Partial UCDAI <=1 (rectal bleeding=0, stool frequency <=1 and PGA=0) at the Baseline Visit (Visit 2).

Exclusion criteria

General:
1. Severe UC (defined by PGA=3) at the Baseline Visit (Visit 2).
2. Crohn*s disease, bleeding disorders, active peptic ulcer disease, or UC known to be confined to the rectum
(isolated rectal proctitis).
3. Asthma, only if known to be 5 ASA sensitive.
4. Positive stool culture for enteric pathogens (including Salmonella, Shigella, Yersina, Aeromonas, Plesiomonas, or
Campylobacter). Clostridium difficile toxin, ova, or parasites present.

5. Previous colonic surgery.
6. Any history of hepatic impairment, in the opinion of the investigator.
7. Moderate to severe renal impairment, in the opinion of the investigator
8. Immediate or significant risk of toxic megacolon, in the opinion of the investigator.
9. History of pancreatitis.
10. History of Reyes syndrome.
11. Systemic or rectal corticosteroid use within 4 weeks prior to the Screening Visit (Visit 1). Topical, intranasal, or inhaled use is not exclusionary.
12. Immunomodulator (6mercaptopurine, azathioprine) use within 6 weeks prior to the Screening
Visit (Visit 1).
13. History of biologic (e.g., antitumor necrosis factor agents, integrin receptor antagonists) use at
any time.
14. Antibiotic use within 7 days prior to the Screening Visit (Visit 1).
15. Any anti-inflammatory drugs, not including 5ASA treatment but including non-steroidal anti-inflammatory drugs such as aspirin, COX2 inhibitors or ibuprofen, within 7 days prior to the Screening Visit (Visit 1) unless used at over-the-counter levels for <3 days. However, prophylactic use of a stable dose of aspirin up to 325mg/day for cardiac
disease is permitted.
16. Prebiotic/probiotic use within 7 days prior to the Screening Visit (Visit 1). Yogurt products are
permitted.
17. Oral anticoagulant use (with the exception of subjects who have been on a stable dose of Vitamin K antagonists such as warfarin for at least 90 days prior to the Screening Visit [Visit 1] and who are medically stable).
18. Treatment with antidiarrheals and/or antispasmodics within 3 days prior to the Screening Visit (Visit 1).
19. Vaccination/immunization within 14 days prior to the Screening Visit (Visit 1).
20. Predisposed to the development of myo- or pericarditis.
21. Previously been screened or randomized into this study and withdrawn.
22. Current or recurrent disease that could affect the action, absorption, or disposition of the investigational product, or could effect clinical or laboratory assessments.
23. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment, including surgery, or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures.
24. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations) that could affect (improve or worsen) the condition being studied, or could affect the action, absorption, or disposition of the investigational product(s), or clinical or laboratory assessment. (Current use is defined as use within 14 days of the Screening Visit [Visit 1].)
25. Known or suspected intolerance or hypersensitivity to the investigational product(s) (aminosalicylates [5 ASA]), closely related compounds (including but not limited to salicylates), or any of the stated ingredients.
26. Known history of alcohol or other substance abuse within the last year.
27. Within 30 days prior to the first dose of investigational product:

Have used an investigational product
Have been enrolled in a clinical study (including vaccine studies) that, in the investigator*s opinion, may impact this study.
Doubleblind Acute Phase:
28. Normal mucosal appearance (defined by endoscopic score=0) based on central reading or local reading (if central reading is not available) at the Screening Visit (Visit 1) or Baseline Visit (Visit 2).
29. Current relapse on a 5ASA dose higher than the low dose tested in the study (900mg for subjects weighing 18 to 23kg, 1200mg for subjects weighing >23 to 35kg, 1800mg for subjects weighing >35 to 50kg, and 2400mg for subjects weighing >50 to 90kg).
30. Acute flare with onset >6 weeks prior to the Baseline Visit (Visit 2) if being treated with 5ASA
for the flare. There is no limit to the onset of flare prior to the Baseline Visit (Visit 2) if the flare is untreated.
Doubleblind Maintenance Phase:
31. Mucosal appearance (endoscopic score)=2 or 3 based on central reading or local reading (if central reading is not available) at the Screening Visit (Visit 1) or Baseline Visit (Visit 2).;Re-randomization: Subjects with a clinical response i.e., partial UC-DAI <= 1 (rectal bleeding=0, stool frequency <=1, and PGA=0) after completion of treatment in either the Double-blind or the Open-label Acute Phases will be eligible for re-randomization into the Double-blind Maintenance
Phase provided they still meet all Baseline (Visit 2) inclusion and exclusion criteria (where re-assessed). Subjects may be re-randomized into the Double-blind Maintenance Phase if they turned 18 during participation in either Acute Phase of the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-12-2014
Enrollment:	16

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mezavant XL (but only the 1.2 g product for use in adults)
Generic name:	MMX Mesalamine/Mesalazine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-08-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-03-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-08-2016

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
Other	NCT02093663
EudraCT	EUCTR2013-001744-65-NL
CCMO	NL48356.078.14