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Investigation aimed to evaluate the blood levels and the safety of Methylene Blue MMX® 25 mg modified-release tablets administered to healthy volunteers receiving two different bowel cleaning preparation for colonoscopy

Submission date 10/07/2020	**Recruitment status** No longer recruiting	[ ] Prospectively registered [ ] Protocol
Registration date 15/09/2020	**Overall study status** Completed	[ ] Statistical analysis plan [ ] Results
Last Edited 15/09/2020	**Condition category** Digestive System	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Currently, methylene blue is used in human and veterinary medicine for a number of therapeutic (treatment) and diagnostic procedures. Chromoendoscopy is a technique in which different dyes are applied to the gastrointestinal mucosa (the inner surface of the digestive system) in order to highlight specific structural changes. This staining method allows doctors to see features that would otherwise not be visible and improves the accuracy of the examination. The study sponsor, Cosmo Technologies Ltd, has developed Methylene Blue MMX® 25 mg modified-release tablets. The aim of this study is to evaluate the blood levels and safety of Methylene Blue MMX® 25 mg modified-release tablets given to healthy volunteers receiving two different bowel cleaning preparations for colonoscopy.

Who can participate?
Healthy male and female volunteers aged 50-65

What does the study involve?
Participants receive the same dose, i.e. a total dose of 200 mg of Methylene Blue MMX® 25 mg modified-release tablets, along with a bowel cleansing preparation as a full dose in one period and a split dose in the other period or vice versa. In the afternoon of Day 1, the participants allocated to the full dose bowel preparation will drink the whole dose of the bowel cleansing preparation. The participants allocated to the split-dose will drink part of the volume of the bowel cleansing preparation in the evening of Day 1 and part of the volume in the morning of Day 2. In the evening of Day 1 in each period, a total oral dose of 200 mg of Methylene Blue MMX® tablets will be given to all the participants.

What are the possible benefits and risks of participating?
Chromoendoscopy with Methylene Blue dye is considered a safe treatment. In this study the

adverse effects will be collected and classified. For comparison, the most common adverse reactions of any severity reported in the Phase III trials occurred in at least 1% of participants in the Methylene Blue MMX® 200 mg dose group and at a frequency higher than in the placebo group. Urine and feces discoloration are expected reactions after oral intake of methylene blue. Since the product is always taken along with a bowel cleansing preparation, nausea and vomiting might also occur. Less common adverse reactions (<1%) reported more frequently than placebo included: polyuria (urinating more than usual), dysuria (painful or difficult urination), migraine, abdominal discomfort, diarrhea, hematemesis (vomiting blood), cough, anemia, pain, chills and blue sclera discoloration (bluish coloration of the whites of the eyes). Intake of the bowel cleansing preparation is necessary for colon preparation before colonoscopy and is part of the standard of care. Possible adverse effects related to the intake of the bowel cleansing preparations are nausea, abdominal fullness and bloating. Abdominal cramps, vomiting and anal irritation occur less frequently. Diagnostic colonoscopy is normally a safe procedure. Only in exceptional cases, complications, even severe, such as perforation (0.1-0.3%), hemorrhage (0.1-0.5%), cardiorespiratory problems (0.4%) or other not foreseeable complications could occur. Normally if these rare events occur, they are related to the presence of associated pathologies. Potentially, the participants could benefit from the better procedural results thanks to the oral intake of Methylene Blue MMX® modified-release tablets and from the colonoscopy as a screening test. Many local and international guidelines for the prevention of colorectal cancer recommend a suitable screening test should be applied in the asymptomatic population from the 50th year of age. No other benefits are foreseen to volunteers participating in this study.

Where is the study run from?
CROSS Research S.A. (Switzerland)

When is the study starting and how long is it expected to run for?
February 2018 to June 2019

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

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Study CRO-PK-18-327 - Sponsor code CB-17-01/17

Study information

Scientific Title
Bioavailability and safety of Methylene Blue MMX® 25 mg modified-release tablets administered to healthy volunteers receiving a full and a split-dose regimen of bowel cleansing preparation for colonoscopy, according to a randomized cross-over design

Study objectives
In the present study, the PK profile and the bioavailability of methylene blue will be investigated in healthy male and female volunteers receiving the same dose, i.e. a total dose of 200 mg of Methylene Blue MMX® 25 mg modified-release tablets, along with a bowel cleansing preparation taken according to a split dose and a full dose regimen according to a randomized cross-over design. As secondary study endpoints, all the study volunteers will undergo one colonoscopy during study period 2 in order to evaluate the bowel cleansing quality and technical aspects of the colonoscopy performance, i.e. the time to reach the caecum and withdrawal time.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 27/02/2018, independent ethics committee (Comitato Etico Cantonale, Canton Ticino, c/o Ufficio di sanità, Via Orico 5, 6501 Bellinzona, Switzerland; +41 (0)91 814 30 57; dss-ce@ti.ch), ref: 3329, 2018-00274, 2018DR1040

Study design
Open-label randomized cross-over safety and bioavailability descriptive study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Diagnostic

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Bowel cleansing preparation

Interventions
According to the randomized cross-over design, the subjects will receive, in addition to the 8 Methylene Blue MMX® tablets, the AxMP according to a full dose regimen in one period and to a split-dose regimen in the other or vice versa. Both regimens are approved and described in the patient information leaflet of the product.

In the afternoon of Day 1, the volunteers allocated to the full dose bowel preparation will drink the whole dose of the AxMP. Water intake is free. The participants allocated to the split-dose regimen will drink part of the volume of the AxMP in the evening of Day 1 and part of the volume in the morning of Day 2. Water intake is free.

In the evening of Day 1 in each period, a total oral dose of 200 mg of Methylene Blue MMX® tablets will be administered to all the participants. Along with both bowel cleansing preparation dose regimens, the IMP will be taken, as follows:
1. First dose of the IMP (tablets 1, 2 and 3) after the intake of at least one liter of AxMP
2. Second dose of IMP (tablets 4, 5 and 6) 1 hour ± 5 min after the first dose of the IMP (tablets 1, 2 and 3)
3. Third dose of IMP (tablets 7 and 8) 1 hour ± 5 min after the second dose of the IMP (tablets 4, 5 and 6)

In both periods, the intake of the whole dose (200 mg) of IMP will be completed the evening of day 1. The volunteers will accompany the intake of the tablets of IMP drinking the bowel cleansing preparation or still mineral water/clear liquids.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Methylene Blue MMX® 25 mg modified-release tablets

Primary outcome measure
Pharmacokinetic profile and kinetic parameters of methylene blue measured using a fully validated LC-MS/MS. The PK parameters were calculated at the following timepoints: post-dose starting from the intake of the last tablet at 4, 5, 6, 7, 8, 9, 10, 12, 16, 20, 24, 36 h

Secondary outcome measures
1. Bowel cleansing quality evaluated according to the validated Boston Bowel Preparation Scale (BBPS) during a colonoscopy
2. Safety and tolerability of Methylene Blue MMX® modified-release tablets, assessed by evaluating treatment-emergent adverse events, vital signs, physical examinations, laboratory tests and ECG throughout the whole study

Overall study start date
09/02/2018

Completion date
14/06/2019

Eligibility

Key inclusion criteria
1. Informed consent: signed written informed consent before inclusion in the study
2. Sex and age: men and women, 50-65 year old inclusive
3. Body Mass Index (BMI): 18.5-30 kg/m2 inclusive
4. Vital signs: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90
bpm, measured after 5 min at rest in the sitting position
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. Fertility (women only): in post-menopausal status for at least 1 year

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
24 healthy volunteers

Total final enrolment
24

Key exclusion criteria
1. Electrocardiogram (12-leads, supine position): clinically significant abnormalities
2. Physical findings: clinically significant abnormal physical findings which could interfere with the objectives of the study

3. Laboratory analyses: clinically significant abnormal laboratory values indicative of physical illness
4. Allergy: ascertained or presumptive hypersensitivity to methylene blue 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
5. Diseases: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, hematological, endocrine, psychiatric or neurological diseases that may interfere with the aim of the study and in particular asthma, anemia, deficiency of glucose-6-phosphate dehydrogenase and NADPH reductase or abnormal intestinal function, history of colorectal cancer or polyps; fecal occult blood positive patients
6. Medications: medications, including over the counter (OTC) medications and herbal remedies for 2 weeks before the start of the study. Concurrent or previous treatment, within 2 weeks before screening, with any of the prohibited psychiatric medications that may interact with methylene blue as listed in the drug safety alert
published by the US FDA, which include selective serotonin reuptake inhibitors (SSRI), serotoninnorepinephrine reuptake inhibitors (SNRI), tricyclic anti-depressants or monoamine oxidase A inhibitors and other psychiatric drugs. Previous or concomitant treatment with fluoxetine within 5 weeks prior to screening, and/or previous or concomitant treatment with anticoagulants or antiaggregant agents inducing an international normalized ratio (INR) > 1.5
7. Investigative drug studies: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study
8. Blood donation: blood donations for 3 months before this study
9. Drug, alcohol, caffeine, tobacco: history of drug, alcohol (>1 drink/day for females and >2 drinks/day for males, defined according to the USDA Dietary Guidelines 2015), caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥6 cigarettes/day)
10. Drug test: positive result at the abuse drug test at screening or day -1
11. Alcohol test: positive alcohol breath test at day -1
12. Diet: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians
13. Pregnancy (females only): positive or missing pregnancy test at screening
14. Previous study of methylene blue: subject enrolled in a previous study of methylene blue

Date of first enrolment
14/09/2018

Date of final enrolment
10/11/2018

Locations

Countries of recruitment
Switzerland

Study participating centre
CROSS Research SA
Via FA Giorgioli 14
Arzo

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6864

Sponsor information

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Sponsor type
Industry

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Funder(s)

Funder type
Industry

Funder Name
Cosmo Technologies Ltd.,

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
28/02/2021

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from Clinical Trial Project Manager at Cosmo, Cristina Gabriela Banyai (cbanyai@cosmopharma.com).

IPD sharing plan summary

Available on request