The safety and efficacy of Methylene Blue MMX® modified release tablets administered to subjects undergoing screening or surveillance colonoscopy.

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Evaluation of the histologically proven adenoma or carcinoma detection rate in patients undergoing a full colonoscopy with and without mucosal contrast enhancement, obtained with 200 mg of Methylene Blue MMX® tablets. The lack of mucosal contrast,…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON41630

Source
ToetsingOnline

Brief title
Efficacy of Methylene Blue for screening/surveillance colonoscopy

Condition

- Gastrointestinal neoplasms benign

Synonym
Polyp and adenoma detection during colonoscopy. Abnormal growth of tissue detection during colonoscopy

Research involving
Human

Sponsors and support

Primary sponsor: Cosmo Technologies Ltd
Source(s) of monetary or material Support: Farmaceutical

Intervention

Keyword: Efficacy, Safety, Screening colonoscopy, Surveillance colonoscopy

Outcome measures

Primary outcome

Primary end-point: The primary end-point of this study is to assess the detection efficacy of chromoendoscopy performed with 200mg Methylene Blue MMX® 25 mg tablets versus placebo tablets (white light endoscopy) in terms of the percentage of subjects with at least one histologically proven adenoma or carcinoma.

Adenoma is defined as the histological Vienna Grade 3 to 4.2. Histologically proven carcinoma is defined as Vienna Grade 4.3 to 5b.

The Vienna Classification will be made by blinded central laboratory pathologists who will review slides prepared from an additional tissue section of each paraffin embedded specimen prepared at the local site laboratory in accordance with the histology charter.

Secondary outcome

Secondary end-points:

The secondary endpoints will be evaluated in all study groups, e.g. 200mg,

100mg MMX and placebo groups.

Secondary end-points of this study are the following:

- False positive rate between treatment and placebo control arms; the rate being defined as the proportion of patients with no histologically confirmed adenoma or carcinoma within any of the subjects excised lesions and the subject having undergone at least one excision (see 16.3)
- Number of histologically proven adenomas (Vienna categories 3, 4.1 and 4.2) and carcinomas (Vienna categories 4.3, 4.4, 5.a and 5.b) detected per subject.
- Number of histologically proven serrated lesions (traditional serrated adenomas, sessile serrated adenomas, hyperplastic polyps, fibroblastic polyps and mixed polyps) detected per subject;
- Adverse events;
- Vital signs during colonoscopy (Systolic blood pressure, Diastolic blood pressure, Heart rate and Oxygen saturation);
- Renal and liver function tests (Creatinine, Urea, AST, GGT, ALT and Total Bilirubin

Exploratory end-points:

The exploratory endpoints will be evaluated in all treatment groups.

The exploratory endpoints in the study are:

- Proportion of subjects with at least one polypoid lesion;

- Number of polypoid lesions detected per subject;

- Proportion of subjects with at least one non polypoid lesion;

- Number of non polypoid lesions detected per subject;

- Number of histologically proven carcinomas (Vienna categories 4.3, 4.4, 5.a and 5.b) detected per subject;

- Proportion of subjects with at least one histologically proven serrated lesion;

- Number of histologically proven adenomas or carcinomas detected in the right colon (i.e. caecum and ascending colon) per subject;

- Number of excised or biopsied polypoid lesions detected in the right colon (i.e. caecum and ascending colon) per subject;

- Number of non polypoid lesions detected in the right colon (i.e. caecum and ascending colon) per subject;

- Number of histologically proven serrated lesions (traditional serrated adenomas, sessile serrated adenomas, hyperplastic polyps, fibroblastic polyps and mixed polyps) detected in the right colon (i.e. caecum and ascending colon) per subject;

- Lesion size (total number of lesions < 5mm, lesions * 5 mm and < 10 mm and lesions * 10 mm);

- Boston Bowel Preparation Score for bowel cleansing preparation quality;

- Measures of colonoscopy performance:

* Time to reach the caecum

* Withdrawal time from the caecum to exit, excluding interventional time if any

- Consensus between local and central reading of the endoscopy video with

regards to the need for excision of the identified lesions.

Study description

Background summary

It is generally accepted that cancer screening reduces the number of deaths from cancer.

One type of cancer screening is colonoscopy. This involves a doctor inserting a camera via a tube into the colon and looking for any abnormal growths or polyps in the wall of the colon.

Bowel polyps are not usually cancerous, although they need to be removed as some will eventually turn into cancer if left untreated. The goal of the colonoscopy is to find all the polyps that a patient has.

It is generally accepted that the removal of polyps found during colonoscopy reduces the incidence of cancer for all patients.

Methylene Blue MMX is a tablet containing a blue dye that is taken the night before a colonoscopy. The tablets are taken along with the laxative drink that is used to clear the colon so the doctor has a clear view of the colon wall during the colonoscopy. Some polyps are flat and not easily seen. The blue dye in the tablets turns the colon wall blue temporarily. The blue stain shows up normal and abnormal tissue differently and improves the contrast between the two.
This improves the doctor*s ability to find polyps and to tell what type they may be.

The scientific justification for this research is that Methylene Blue MMX tablets offer a potential way to increase the number of polyps found during colonoscopy, and to reduce the incidence of colorectal cancer as a result.

Study objective

Evaluation of the histologically proven adenoma or carcinoma detection rate in patients undergoing a full colonoscopy with and without mucosal contrast enhancement, obtained with 200 mg of Methylene Blue MMX® tablets. The lack of mucosal contrast, obtained with placebo tablets is equivalent to a standard white light colonoscopy endoscopic procedure- the current standard of care.

Study design

This is double blind at randomisation, placebo controlled parallel group study

Intervention

Dose regimen

The subjects will be randomized 2:2:1 into three groups:

Group One will receive an oral dose of 200 mg of Methylene Blue MMX® 25 mg tablets: 3 Methylene Blue MMX® 25 mg tablets (75 mg) after the first 2 litres of bowel preparation, 3 Methylene Blue MMX® 25 mg tablets (75 mg)after a total of 3 litres of bowel preparation and, finally, 2 Methylene Blue MMX® 25 mg tablets (50mg) after a total of 4 litres of bowel preparation have been consumed.

Group Two will receive an oral dose of matching placebo tablets: 3 tablets after the first 2 litres of bowel preparation, 3 tablets after a total of 3 litres of bowel preparation and, finally, 2 tablets after a total of 4 litres of bowel preparation have been consumed.

Group Three will be included only for masking purposes in order to reduce the acquisition bias due to the lack of investigator and subject blinding between placebo and Methylene Blue MMX® 200 mg groups. This unpowered masking group will be treated with 100 mg Methylene Blue MMX® 25 mg tablets: 1 tablet (25mg) of Methylene Blue MMX® 25mg tablets and two placebo tablets after the first 2 litres of bowel preparation, additional 2 tablets (50 mg) of Methylene Blue MMX® 25mg tablets and one placebo tablet after a total of 3 litres of bowel preparation, and, finally, 1 tablet (25 mg) of Methylene Blue MMX® 25 mg tablet, and one placebo tablet after a total of 4 litres of bowel preparation solution have been consumed.

Investigational drug products will be dispensed as individual clinical supplies (a blister pack) containing the indicated amount of Methylene Blue MMX® 25 mg tablets or matching placebo tablets and the standard amount of bowel prep solution.

A member of study site staff will dispense the individual clinical supplies at randomisation and issue each patient with instructions for preparing for the colonoscopy and intake of the study drug.

Study burden and risks

Potential risks of single oral dose administrations of Methylene Blue MMX® to patients are expected to be limited to known side effects of Methylene Blue as reported for the products available on the market. Methylene Blue MMX® in the Phase 1 and 2 studies was well tolerated and adverse events are expected not to

surpass in frequency the AEs previously reported in the safety, bioavailability and efficacy studies of Methylene Blue. See the Investigators Drug Brochure for a summary of available data. Methylene Blue is not expected to change the risk profile of colonoscopy and indeed may lower the risk as greater delineation of the lesions is expected.

Expected untoward effects of Methylene Blue include nausea, vomiting, diarrhoea, abdominal and praecordial pain, dizziness, headache, profuse sweating, mental confusion and the formation of methaemoglobin. In few cases, episodes of fever, haemolytic anaemia, bladder irritation and blood pressure alterations occurred. Bluegreen discolouration of urine, faeces, skin and sclera is recorded but is a completely reversible effect. Patients with glucose6phosphate deficiency and NADPH reductase deficiency are known to be at particular risk of adverse events and are excluded from the study

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

* Males or females, aged between 50 and 75.
* A female is eligible to enter and participate in this study if she is: of non-childbearing potential including pre-menopausal females with documented (medical report verification) hysterectomy or double oophorectomy or postmenopausal.Or of child bearing potential, has a negative serum pregnancy test at screening and urine pregnancy test prior to start the study drug, and abstain completely from sexual intercourse or agrees to using highly effective contraceptive methods (e.g. intrauterine device, hormonal contraceptive drug, tubal ligation) during the study until completion of the follow-up procedures).
* Outpatients scheduled for screening or surveillance colonoscopy for polyps or colorectal cancer.
* Able to comprehend the full nature and purpose of the study, including possible risks and side effects.
* Able to co-operate with the investigator and to comply with the requirements of the entire study.
* Signed written informed consent prior to inclusion in the study.
* Patients taking psychiatric medications which could possibly interact with methylene blue are not to be included in the study if they have been taken up to 2 weeks prior to enrolment. Prozac is prohibited up to 5 weeks prior to enrolment.
* Patients will be included in accordance with the opinion of the countrywide screening committee.

Exclusion criteria

* Patients at high risk of colorectal cancer e.g. ulcerative colitis
* Pregnancy or lactation.
* Previous medical history of, or suspected hypersensitivity to, the Methylene Blue and/or formulations' ingredients.
* Previous medical history of, or suspected hypersensitivity to, the PEG based bowel cleansing preparation and/or bowel cleansing formulations' ingredients.
* Previous medical history of gastrointestinal obstruction or perforation, toxic megacolon, major colonic resection, severe diverticulitis, heart failure (Class III or IV), serious cardiovascular disease, ulcerative colitis or Crohn*s disease.
* ALT, AST, GGT, Bilirubin, Creatinine or Urea greater than 2.5 x the upper limit for normal range, based on local laboratory testing.
* The presence of serious cardiovascular disease, including very large abdominal aortic aneurysms (particularly if they are symptomatic), patients who are immediately postoperative, and patients who have suffered recent myocardial infarction (within 3 weeks), pulmonary embolism, or are currently hemodynamically unstable.
* The presence of liver disease with coagulopathy
* A history of anaemia (previously recorded haemoglobin of less than 10mg/dL) within the last 30 days prior to enrollment.

* Known or suspected deficiency of glucose-6-phosphate dehydrogenase,
* Known or suspected deficiency of NADPH reductase
* Treatment within 5 weeks prior to randomisation with Fluoxetine (Prozac).
* Concurrent treatment, or previous treatment within 2 weeks with any of the prohibited psychiatric medications that may interact with Methylene Blue as listed under Prohibited medications; Selective Serotonin Reuptake Inhibitors (SSRI), Serotonin-Norepinepherine Reuptake Inhibitors (SNRI*s), listed Tricyclic anti-depressants or Monoamine oxidase A inhibitors.
* Current enrollment in any other clinical trial, or previous enrollment in a clinical trial within the last 30 days.
* Other medical condition that in the investigators opinion would make the administration of the study drug or procedures hazardous to the subject.
* Men and women, between 50-75 years of age, who have accepted invitation to enrol in the national bowel cancer screening programme.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-06-2014
Enrollment:	272
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Methylene Blue MMX®

Generic name:	Not Applicable

Ethics review

Approved WMO Date:	31-10-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2012-003983-32-NL
CCMO	NL45956.018.13