



Clinical trial results:

Effect of oral administration of Methylene Blue MMX® tablets on double-stranded DNA damage assessed by H2AX analysis of colon biopsy samples

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2013-000634-35 |
| Trial protocol | IT |
| Global end of trial date | 09 December 2014 |

Results information

| | |
|-----------------------------------|---------------------------|
| Result version number | v1 (current) |
| This version publication date | 29 August 2021 |
| First version publication date | 29 August 2021 |
| Summary attachment (see zip file) | Article (Repici 2018.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | CB-17-01/08 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-----------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02295774 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Study protocol : CRO-13-113 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Cosmo Technologies Ltd |
| Sponsor organisation address | Riverside 2, 49 Sir John Rogerson's Quay, Grand Canal Dock, Dublin,, Dublin, Ireland, D02 KV60 |
| Public contact | Study Management Unit, CROSS S.A., +41 916300510, corporate@croalliance.com |
| Scientific contact | Study Management Unit, CROSS S.A., +41 916300510, corporate@croalliance.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 17 April 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 December 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 December 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the effect of a total oral dose of 200 mg of Methylene Blue MMX® tablets on colonic epithelial double-stranded DNA during a full chromoendoscopy in comparison with a standard white light colonoscopy without use of Methylene Blue MMX®.

Protection of trial subjects:

The colonoscopic exam will be performed according to the standard procedure protocols of the clinic. Blood samples will be collected at Visits 1 and 2 for renal and liver function measurement (creatinine, urea, AST, γ-GT, ALT, total bilirubin, haemoglobin). For patients with abnormal hepatic and renal function post-colonoscopy, a follow-up blood sample will be collected within two weeks after colonoscopy.

Background therapy:

NA

Evidence for comparator:

NA

| | |
|---|---------------|
| Actual start date of recruitment | 15 April 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Italy: 13 |
| Worldwide total number of subjects | 13 |
| EEA total number of subjects | 13 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 6 |

| | |
|---------------------|---|
| From 65 to 84 years | 7 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 10 patients were planned to be included in the study. The investigator included 13 subjects in the study. After inclusion, 10 subjects took the study treatment and were considered in the analyses of safety and efficacy, whilst the remaining 3 subjects discontinued the study before taking the IMP.

Pre-assignment

Screening details:

Visit 1; 1st colonoscopy; day -14/-2-outpatients scheduled for screening or surveillance colonoscopy at the clinical site will be informed about the aims, procedures, benefits and possible risks of the study prior to signing the informed consent form for inclusion in the trial. Their medical history and demographics and reason for colonoscopy.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | Enrolment (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable

Arms

| | |
|-----------|----------------|
| Arm title | Methylene Blue |
|-----------|----------------|

Arm description:

Single centre, open label, safety study.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Methylene blue MMX® modified release tablets |
| Investigational medicinal product code | MB-MMX |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The patients will receive a 4-L PEG-based bowel cleansing preparation, following the instructions enclosed with the product, starting in the afternoon before the 2nd colonoscopy. The patients, who will receive the bowel cleansing preparation according to a full dose regimen, will start the intake in the afternoon before the colonoscopy day and shall drink at least 250 mL of solution every 15 min, so that the intake is complete 4 h after.

The subjects, who will receive the bowel cleansing preparation according to a split dose regimen, will start to drink 250 mL of solution every 15 min in the evening before the colonoscopy day up to approximately 2 or 3 L according to the investigator instructions. The remaining quantity of bowel cleansing preparation will be then drunk in the morning of the colonoscopy day at the same rate, until the intake is complete.

During the intake of the bowel cleansing preparation, a total oral dose of 200 mg will be taken by each subject.

| Number of subjects in period 1 | Methylene Blue |
|---------------------------------------|----------------|
| Started | 13 |
| Completed | 10 |
| Not completed | 3 |
| Consent withdrawn by subject | 2 |
| laboratory tests were altered | 1 |

Baseline characteristics

Reporting groups

| | |
|---|-----------|
| Reporting group title | Enrolment |
| Reporting group description: | |
| The investigator included in the study 13 subjects. inclusion, 10 subjects took the study treatment, whilst the remaining 3 subjects discontinued the study before taking the IMP. The 10 subjects, who received the study treatment, also completed the study. | |

| Reporting group values | Enrolment | Total | |
|--|-----------|-------|--|
| Number of subjects | 13 | 13 | |
| Age categorical | | | |
| Age: 18-75 years old inclusive | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 13 | 13 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Out-patients of both sexes scheduled for a screening or surveillance colonoscopy and identified as having the clinical requirement for a second colonoscopy within 2 weeks of the initial colonoscopy. | | | |
| Units: Subjects | | | |
| Female | 3 | 3 | |
| Male | 10 | 10 | |

Subject analysis sets

| | |
|---|------------------|
| Subject analysis set title | Safety set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Safety Set: all subjects who will receive at least one dose of the IMP. This analysis set will be used for safety analyses. | |
| Subject analysis set title | FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Full Analysis Set (FAS): all included subjects, who will receive at least one dose of the IMP and will have at least one biopsy for the evaluation of the level of γ H2AX. This analysis set will be used for the primary analysis | |
| Subject analysis set title | Per Protocol Set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Per Protocol Set (PP): all included subjects who will fulfil the study protocol requirements in terms of IMP intake and collection of primary analysis data and without major deviations that may affect study results. This analysis set will be used for sensitivity analyses | |
| Subject analysis set title | Enrolled Set |

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Enrolled Set: all screened subjects. This analysis set will be used for demographic, baseline and background characteristics

| Reporting group values | Safety set | FAS | Per Protocol Set |
|--|------------|-----|------------------|
| Number of subjects | 10 | 10 | 10 |
| Age categorical | | | |
| Age: 18-75 years old inclusive | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 10 | 10 | 10 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical | | | |
| Out-patients of both sexes scheduled for a screening or surveillance colonoscopy and identified as having the clinical requirement for a second colonoscopy within 2 weeks of the initial colonoscopy. | | | |
| Units: Subjects | | | |
| Female | 3 | 3 | 3 |
| Male | 7 | 7 | 7 |

| Reporting group values | Enrolled Set | | |
|--|--------------|--|--|
| Number of subjects | 13 | | |
| Age categorical | | | |
| Age: 18-75 years old inclusive | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 13 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Gender categorical | | | |
| Out-patients of both sexes scheduled for a screening or surveillance colonoscopy and identified as having the clinical requirement for a second colonoscopy within 2 weeks of the initial colonoscopy. | | | |
| Units: Subjects | | | |
| Female | 3 | | |
| Male | 7 | | |

End points

End points reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Methylene Blue |
|-----------------------|----------------|

Reporting group description:

Single centre, open label, safety study.

| | |
|----------------------------|------------|
| Subject analysis set title | Safety set |
|----------------------------|------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Safety Set: all subjects who will receive at least one dose of the IMP. This analysis set will be used for safety analyses.

| | |
|----------------------------|-----|
| Subject analysis set title | FAS |
|----------------------------|-----|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Full Analysis Set (FAS): all included subjects, who will receive at least one dose of the IMP and will have at least one biopsy for the evaluation of the level of γ H2AX. This analysis set will be used for the primary analysis

| | |
|----------------------------|------------------|
| Subject analysis set title | Per Protocol Set |
|----------------------------|------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Per Protocol Set (PP): all included subjects who will fulfil the study protocol requirements in terms of IMP intake and collection of primary analysis data and without major deviations that may affect study results. This analysis set will be used for sensitivity analyses

| | |
|----------------------------|--------------|
| Subject analysis set title | Enrolled Set |
|----------------------------|--------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Enrolled Set: all screened subjects. This analysis set will be used for demographic, baseline and background characteristics

Primary: The effect of a total oral dose of 200 mg of Methylene Blue MMX® tablets on colonic epithelial double-stranded DNA in colonic biopsy samples collected during chromoendoscopy

| | |
|-----------------|---|
| End point title | The effect of a total oral dose of 200 mg of Methylene Blue MMX® tablets on colonic epithelial double-stranded DNA in colonic biopsy samples collected during chromoendoscopy |
|-----------------|---|

End point description:

Evaluation, by histone γ H2AX analysis, of the effect of a total oral dose of 200 mg of Methylene Blue MMX® tablets on colonic epithelial double-stranded DNA in colonic biopsy samples collected during chromoendoscopy as compared to control biopsies collect. At both colonoscopies, the γ H2AX assay was negative for all the colonic regions, for all the analysed subjects (N=10, safety set). The occurrence of any DNA double strand damage could be excluded at each of the performed colonoscopies on the basis of the γ H2AX analysis result.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Following the colonoscopy.

| End point values | Methylene Blue | Safety set | | |
|-----------------------------|-------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 10 ^[1] | 10 | | |
| Units: 10 | | | | |
| Negative | 10 | 10 | | |
| Positive | 0 | 0 | | |

Notes:

[1] - 3 Patients were discontinued before starting the treatment

Statistical analyses

| Statistical analysis title | SAS version 9.3 (TS1M1). |
|----------------------------|--------------------------|
|----------------------------|--------------------------|

Statistical analysis description:

The statistical analysis was performed using SAS® version 9.3 (TS1M1). The data documented in this trial and the clinical parameters measured were described using classic descriptive statistics for quantitative variables and frequencies for qualitative variables.

| | |
|---|-----------------------------|
| Comparison groups | Methylene Blue v Safety set |
| Number of subjects included in analysis | 20 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | ≥ 0.2 ^[3] |
| Method | Chi-squared |

Notes:

[2] - The data documented in this study and the parameters measured will be evaluated and compared using classic descriptive statistics, i.e mean, SD, CV (%), minimum, median and maximum values for quantitative variables, and frequencies for qualitative variables.

[3] - The comparison between Visit 2 and Visit 1 using the Mc Nemar's Chi Square test was NOT APPLICABLE because there is no change between visits

Secondary: To evaluate the staining quality obtained with oral Methylene Blue MMX® tablets.

| | |
|-----------------|--|
| End point title | To evaluate the staining quality obtained with oral Methylene Blue MMX® tablets. |
|-----------------|--|

End point description:

On average, the staining quality of the colonic mucosa was acceptable (i.e. at least the 50% of colon mucosa is stained=score 3) in the ascending, transverse and descending colon both in terms of mean and of median SC. On average, the staining quality of rectosigmoid was detectable (i.e. at least the 25% of colon mucosa is stained=score 2). The majority of subjects (40.0% of the subjects) had NSA of 2 regions. The frequency of NSA of 3 or 4 regions was 20.0% (2 subjects each). TSC had a mean ± SD of 11.0±3.4.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Following the colonoscopy

| End point values | Methylene Blue | FAS | Per Protocol Set | |
|-----------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 10 | 9 | 9 | |
| Units: 10 | 10 | 9 | 9 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the study

Adverse event reporting additional description:

No serious AEs (SAEs) occurred throughout the study. Eight (8) out of the 10 subjects (80%) in the safety set experienced at least one TEAE, for a total of 13 TEAEs. The investigator judged only one of the 13 reported TEAEs as unrelated to the treatment in 1 subject (10%). One PTAE occurred during the study.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

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|-----------------------|---------------------------------------|
| Reporting group title | Pre-Treatment-emergent adverse events |
|-----------------------|---------------------------------------|

Reporting group description:

PTAEs: all AEs occurring before the dose of the IMP and not worsening after the dose of the IMP.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Treatment Emergent Adverse Event |
|-----------------------|----------------------------------|

Reporting group description:

TEAEs: all AEs occurring or worsening after the dose of the

| Serious adverse events | Pre-Treatment-emergent adverse events | Treatment Emergent Adverse Event | |
|---|---------------------------------------|----------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 10 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Pre-Treatment-emergent adverse events | Treatment Emergent Adverse Event | |
|---|--|----------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 8 / 10 (80.00%) | |
| Nervous system disorders | | | |
| Headache | Additional description: Headache was a mild and transient episode. The investigator judged the episode of headache as unrelated to the treatment. The subject took 200 mg of ibuprofen PRN as therapeutic countermeasure | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |

| | | | |
|-----------------------------|---|----------------|-----------------|
| Faeces discoloured | Additional description: Four (4) of the subjects, who reported chromaturia, suffered also from discolouration of the faeces. Faeces discolouration lasted from 4 to 7 days. | | |
| | subjects affected / exposed | 0 / 13 (0.00%) | 4 / 10 (40.00%) |
| | occurrences (all) | 0 | 1 |
| Renal and urinary disorders | | | |
| Chromaturia | Additional description: out of 10 subjects suffered from chromaturia after the intake of methylene blue. The investigator judged that all 8 reported episodes were related TEAEs. Indeed, chromaturia is a well-known and expected untoward effect of methylene blue. | | |
| | subjects affected / exposed | 0 / 13 (0.00%) | 8 / 10 (80.00%) |
| | occurrences (all) | 0 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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|---|
| Study results did not evidence any effect of Methylene Blue MMX® tablets on the colonic epithelial double-stranded DNA, measured by γ H2AX, as compared to a previous white light colonoscopy without Methylene Blue MMX®. |
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Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29906809>