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 γH2AX. 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 γH2AX. 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 γH2AX 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 γH2AX 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 γH2AX 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

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

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.

Study results did not evidence any effect of Methylene Blue MMX® tablets on the colonic epithelial double-stranded DNA, measured by γH2AX, as compared to a previous white light colonoscopy without Methylene Blue MMX®.

Notes:

Online references

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