Clinical trial results:
Colonic lesion staining and flagging efficacy of methylene blue administered as MMX® 25 mg modified release tablets to patients receiving a split dose regimen of bowel cleansing preparation for colonoscopy

Summary

EudraCT number	2017-003505-17
Trial protocol	IT
Global end of trial date	28 February 2019

Results information

Result version number	v1 (current)
This version publication date	29 December 2022
First version publication date	29 December 2022

Trial information

Trial identification

Sponsor protocol code	CB-17-01/15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cosmo Technologies Ltd
Sponsor organisation address	Riverside II, Sir John Rogerson’s Quay, Dublin, Ireland,
Public contact	Diego Scanniffio, CROSS Research SA, 0041 916300510, diego.scanniffio@croalliance.com
Scientific contact	Diego Scanniffio, CROSS Research SA, 0041 916300510, diego.scanniffio@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	28 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2019
Global end of trial reached?	Yes
Global end of trial date	28 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the colonic lesion staining and flagging efficacy of single 200 mg oral doses of Methylene Blue MMX® 25 mg tablets administered to patients undergoing colonoscopy, in association with a high volume split dose regimen of bowel preparation, or a low volume split dose regimen of bowel preparation. Bowel cleansing quality will also be evaluated according to the validated Boston Bowel Preparation Scale (BBPS) after the intake of the bowel cleansing preparation and of a total dose of 200 mg of Methylene Blue MMX® 25 mg tablets administered the day before the colonoscopy procedure, with bowel preparation or water indicated volumes.

Protection of trial subjects:

Subjects were followed for safety and tolerability assessments: adverse events, vital signs, and physical examination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 February 2018
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: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	65
From 65 to 84 years	35

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

According to the study plan, the investigator included in the study and randomised 100 subjects.

Pre-assignment

Screening details:

Outpatients scheduled for colonoscopy were informed about the aims, procedures, benefits and possible risks of the study prior to signing the informed consent form for inclusion in the trial.
Screening/Enrolment Visit window: Day -30 to Day -3.

Period 1

Period 1 title	Treatment Period - overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open trial and no masking procedure was applied.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A (Test treatment 1 - T1)

Arm description:

High volume split dose regimen bowel preparation (Selg-Esse®) along with 8 Methylene Blue MMX® 25 mg modified release tablets according to a 3+3+2 intake schedule.

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

Dosage and administration details:

An oral dose of 200 mg of Methylene Blue MMX® 25 mg modified release tablets was administered during bowel cleansing preparation administered the day before the colonoscopy procedure. IMP was administered according to a 3+3+2 intake schedule.

Investigational medicinal product name	4-L, PEG-based bowel cleansing preparation (Selg-Esse®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Dose: The content of 4 bags dissolved in 4L of water.
In the evening before the colonoscopy, the subjects receiving the high volume split dose drank 250 mL of solution (Selg-Esse®) every 15 min up to approximately 2 L (up to 1 h and 45 min from the start of the intake), according to the investigator's or deputy's instructions. Then the subjects drank the remaining volume of the bowel cleansing preparation (2 L) in the morning of the colonoscopy day at the same rate (i.e. approximately 250 mL/15 min) until they completed the intake of the whole volume.

Arm title	Group B (Test treatment 2 - T2)

Arm description:

High volume split dose regimen bowel preparation (Selg-Esse®) along with 8 Methylene Blue MMX® 25 mg modified release tablets according to a 4+4 intake schedule.

Arm type	Experimental

Investigational medicinal product name	Methylene Blue MMX® modified release tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

An oral dose of 200 mg of Methylene Blue MMX® 25 mg modified release tablets was administered during bowel cleansing preparation administered the day before the colonoscopy procedure. IMP was administered according to a 4+4 intake schedule.

Investigational medicinal product name	4-L, PEG-based bowel cleansing preparation (Selg-Esse®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Dose: The content of 4 bags dissolved in 4L of water.
In the evening before the colonoscopy, the subjects receiving the high volume split dose drank 250 mL of solution (Selg-Esse®) every 15 min up to approximately 2 L (up to 1 h and 45 min from the start of the intake), according to the investigator's or deputy's instructions. Then the subjects drank the remaining volume of the bowel cleansing preparation (2 L) in the morning of the colonoscopy day at the same rate (i.e. approximately 250 mL/15 min) until they completed the intake of the whole volume.

Arm title	Group C (Test treatment 3 - T3)

Arm description:

Low volume split dose regimen bowel preparation 1 (Izinova®) along with 8 Methylene Blue MMX® 25 mg modified release tablets according to a 3+3+2 intake schedule.

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

Dosage and administration details:

An oral dose of 200 mg of Methylene Blue MMX® 25 mg modified release tablets was administered during bowel cleansing preparation administered the day before the colonoscopy procedure. IMP was administered according to a 3+3+2 intake schedule.

Investigational medicinal product name	Izinova®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Dose: The content of each bottle was diluted in water, using the cup provided, to a total volume of approximately 0.5 L for each bottle: one bottle for the evening administration (day 1) and one bottle for the morning administration (day 2). A total volume of 1 L of solution + 2 L of water was drunk.
In the evening before the colonoscopy, the subjects receiving the low volume split dose of bowel preparation 1 drank 250 mL of solution (Izinova®) every 15 min up to 0.5 mL, followed by 250 mL of water every 15 min up to an additional 1 L (1.5 L total liquid intake), according to the investigator's or deputy's instructions. The same regimen was followed in the morning of the colonoscopy day up to an overall solution/water volume of 3 L.

Arm title	Group D (Test treatment 4 - T4)

Arm description:

Low volume split dose regimen bowel preparation 2 (Moviprep®) along with 8 Methylene Blue MMX® 25 mg modified release tablets according to a 3+3+2 intake schedule.

Arm type	Experimental

Investigational medicinal product name	Methylene Blue MMX® modified release tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

An oral dose of 200 mg of Methylene Blue MMX® 25 mg modified release tablets was administered during bowel cleansing preparation administered the day before the colonoscopy procedure. IMP was administered according to a 3+3+2 intake schedule.

Investigational medicinal product name	Moviprep®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Dose: The content of 1 'sachet A' and 1 'sachet B' were dissolved together in water to make 1 L of solution. One (1) L was prepared for the evening (day 1) and 1 L for the morning (day 2) administration. A total volume of 2 L of solution + 250 mL of water were drunk.
In the evening before the colonoscopy, the subjects receiving the low volume split dose of bowel preparation 2 (Group D; T4) drank 250 mL of solution (Moviprep®) every 15 min up to 1 L, followed by 250 mL of water (1.25 L total liquid intake), according to the investigator's or deputy's instructions. The same regimen (but without the 250 mL of water) was followed in the morning of the colonoscopy day up to an overall solution/water volume of 2.25 L.

Number of subjects in period 1	Group A (Test treatment 1 - T1)	Group B (Test treatment 2 - T2)	Group C (Test treatment 3 - T3)
Started	25	25	25
Completed	22	25	25
Not completed	3	0	0
Consent withdrawn by subject	3	-	-
Non-compliance	-	-	-

Number of subjects in period 1	Group D (Test treatment 4 - T4)
Started	25
Completed	24
Not completed	1
Consent withdrawn by subject	-
Non-compliance	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period - overall study

Reporting group description: -

Reporting group values	Treatment Period - overall study	Total	
Number of subjects	100	100	
Age categorical Units: Subjects			
Adults (18-64 years)	65	65	
From 65-84 years	35	35	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	61.4		
standard deviation	± 7.5	-	
Gender categorical Units: Subjects			
Female	48	48	
Male	52	52	
Race Units: Subjects			
White	100	100	

End points

End points reporting groups

Reporting group title	Group A (Test treatment 1 - T1)
Reporting group description:	
High volume split dose regimen bowel preparation (Selg-Esse®) along with 8 Methylene Blue MMX® 25 mg modified release tablets according to a 3+3+2 intake schedule.	
Reporting group title	Group B (Test treatment 2 - T2)
Reporting group description:	
High volume split dose regimen bowel preparation (Selg-Esse®) along with 8 Methylene Blue MMX® 25 mg modified release tablets according to a 4+4 intake schedule.	
Reporting group title	Group C (Test treatment 3 - T3)
Reporting group description:	
Low volume split dose regimen bowel preparation 1 (Izinova®) along with 8 Methylene Blue MMX® 25 mg modified release tablets according to a 3+3+2 intake schedule.	
Reporting group title	Group D (Test treatment 4 - T4)
Reporting group description:	
Low volume split dose regimen bowel preparation 2 (Moviprep®) along with 8 Methylene Blue MMX® 25 mg modified release tablets according to a 3+3+2 intake schedule.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
all randomised patients, who received at least one dose of the IMP and had at least one post-randomisation assessment of the primary efficacy data. This analysis set was used for the primary efficacy analysis.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least one dose of the IMP. Patients who took only the bowel preparation were not included in the safety set. This analysis set was used for the safety analyses.	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
all randomised patients who fulfilled the study protocol requirements in terms of IMP intake and collection of primary efficacy data and with no major deviations that could affect study results. This analysis set was used for sensitivity analyses;	

Primary: Colonic lesion staining and flagging efficacy of Methylene Blue MMX® 25 mg modified release tablets

End point title	Colonic lesion staining and flagging efficacy of Methylene Blue MMX® 25 mg modified release tablets[1]
End point description:	
To evaluate the colonic lesion staining and flagging efficacy of Methylene Blue MMX® 25 mg modified release tablets after a total oral dose of 200 mg in association with a high volume or a low volume split dose regimen of bowel cleansing preparation or a low volume split dose regimen of bowel cleansing preparation or water. Staining quality observed in each region on the 0-4 scale.	
End point type	Primary
End point timeframe:	
Evaluated on Day 2 (Day of Colonoscopy)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Could not be entered

End point values	Group A (Test treatment 1 - T1)	Group B (Test treatment 2 - T2)	Group C (Test treatment 3 - T3)	Group D (Test treatment 4 - T4)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	24	24	24
Units: Score				
arithmetic mean (standard deviation)				
Ascending Colon	2.05 (± 1.32)	1.58 (± 1.18)	1.63 (± 1.17)	1.57 (± 1.12)
Transverse Colon	2.00 (± 1.22)	1.75 (± 2.33)	1.63 (± 1.21)	1.61 (± 1.34)
Descending Colon	1.95 (± 1.16)	2.33 (± 1.24)	1.67 (± 1.46)	2.05 (± 1.33)
Rectosigmoid	2.43 (± 1.16)	3.00 (± 1.10)	2.04 (± 1.46)	2.27 (± 1.42)

Statistical analyses

No statistical analyses for this end point

Primary: Bowel cleansing quality according to the validated Boston Bowel Preparation Scale (BBPS)

End point title	Bowel cleansing quality according to the validated Boston Bowel Preparation Scale (BBPS)[2]

End point description:

To evaluate the bowel cleansing quality according to the validated Boston Bowel Preparation Scale (BBPS) after the intake of the high volume or the low volume split dose regimen bowel cleansing preparation and of a total dose of 200 mg of Methylene Blue MMX® 25 mg modified release tablets administered during the intake of the bowel cleansing preparation or water.

End point type	Primary

End point timeframe:

Evaluated at D2 (Colonoscopy Day)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Could not be entered

End point values	Group A (Test treatment 1 - T1)	Group B (Test treatment 2 - T2)	Group C (Test treatment 3 - T3)	Group D (Test treatment 4 - T4)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	24	24	24
Units: Score				
arithmetic mean (standard deviation)				
Right	2.18 (± 0.39)	2.21 (± 0.51)	2.21 (± 0.51)	2.17 (± 0.38)
Transverse	2.14 (± 0.35)	2.42 (± 0.50)	2.25 (± 0.44)	2.08 (± 0.28)
Left	2.09 (± 0.29)	2.29 (± 0.46)	2.21 (± 0.41)	2.09 (± 0.29)
Total BBPS	6.41 (± 0.96)	6.92 (± 1.28)	6.67 (± 1.09)	6.25 (± 0.99)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Group A (Test treatment 1 - T1)
Reporting group description: -	
Reporting group title	Group B (Test treatment 2 - T2)
Reporting group description: -	
Reporting group title	Group C (Test treatment 3 - T3)
Reporting group description: -	
Reporting group title	Group D (Test treatment 4 - T4)
Reporting group description: -	

Serious adverse events	Group A (Test treatment 1 - T1)	Group B (Test treatment 2 - T2)	Group C (Test treatment 3 - T3)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Group D (Test treatment 4 - T4)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group A (Test treatment 1 - T1)	Group B (Test treatment 2 - T2)	Group C (Test treatment 3 - T3)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
Renal and urinary disorders			

Chromaturia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Group D (Test treatment 4 - T4)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 24 (8.33%)		
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		

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

None reported