



Clinical trial results:

A Multicenter Randomized Parallel Group Phase III Study Comparing the Bowel Cleansing Efficacy, Safety and Tolerability of NER1006 (a Low Volume Bowel Cleansing Solution) versus a Sodium Picosulfate and Magnesium Salt (SP+MS) Solution Using a Day Before-Only Dosing Regimen in Adults

Summary

EudraCT number	2014-002186-30
Trial protocol	GB DE NL ES PL
Global end of trial date	19 August 2015

Results information

Result version number	v1 (current)
This version publication date	04 September 2016
First version publication date	04 September 2016

Trial information

Trial identification

Sponsor protocol code	NER1006-03/2014
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02273141
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Norgine Limited
Sponsor organisation address	Norgine House, Widewater Place, Moorhall Road, Harefield, United Kingdom, UB9 6NS
Public contact	Director Clinical Operations, Clinical Development, Norgine Limited, 0044 01895826603, ClinicalTrials@norgine.com
Scientific contact	Director Clinical Operations, Clinical Development, Norgine Limited, 0044 01895826603, ClinicalTrials@norgine.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	21 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 August 2015
Global end of trial reached?	Yes
Global end of trial date	19 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the overall bowel cleansing efficacy and the 'Excellent plus Good' cleansing rate in the colon ascendens of a 1-day day before-only split-dosing regimen with NER1006 compared to a 1-day day before-only split-dosing regimen with SP+MS, graded according to the Harefield Cleansing Scale (HCS) in patients undergoing screening, surveillance or diagnostic colonoscopy.

Protection of trial subjects:

Screening/Randomisation visit and on the day of colonoscopy prior to the procedure:

- Medical history at the time of screening visit.
- Informed consent.
- Full physical examination, including height and body weight.
- Inclusion/exclusion.
- Orthostatic blood pressure, pulse rate and body temperature measurements.
- 12-lead ECG.
- Blood sample collection: hematology, coagulation profile and biochemistry analyses.
- Urinalysis.
- Pregnancy test (urine) for all female patients of child bearing potential.
- Concomitant medication documentation/review.
- Eligibility check.

After the colonoscopy procedure and recovery period:

- Arterial blood pressure and pulse rate measurements 1 to 2 hours (\pm 30 minutes) after colonoscopy.
- Physical examination, including body weight.
- Concomitant medication documentation to include medication or IV fluids during colonoscopy.
- Recording and review of adverse events.

Each patient discharged from the colonoscopy unit with an appointment for a follow-up visit. There are two follow up visits. The following assessments performed at each of those two follow up visits:

- Physical examination.
- Blood sample collection: Biochemistry and hematology analyses.
- Review of any outstanding adverse events.
- Concomitant medication review.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 November 2014
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	Netherlands: 28
Country: Number of subjects enrolled	Poland: 341
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Italy: 87
Worldwide total number of subjects	515
EEA total number of subjects	515

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)	413
From 65 to 84 years	102
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period : 12 NOV 2014 (first patient first visit) to 19 AUG 2015 (last patient last visit)
Territories : Germany, Italy, Poland, Netherlands, Spain and United Kingdom

Pre-assignment

Screening details:

Male or female outpatients and inpatients aged ≥ 18 to ≤ 85 years undergoing a screening, surveillance, or diagnostic colonoscopy were eligible for inclusion.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind ^[1]
Roles blinded	Data analyst, Assessor ^[2]

Arms

Are arms mutually exclusive?	Yes
Arm title	NER1006

Arm description:

NER1006 Powder for Oral Solution

Arm type	Experimental
Investigational medicinal product name	NER1006
Investigational medicinal product code	NER1006
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

NER1006 Powder for Oral Solution consisting of one sachet of Dose 1 and two sachets (A & B) for Dose 2.

Dosing regimen : 1-Day Split-Dosing. Self administered. Both doses (Dose 1 & Dose 2) taken in the evening of the day before the clinical procedure. Doses within 1-2 hour interval.

Arm title	CITRAFLEET
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Arm description:

Sodium Picosulfate and Magnesium Salt (SP+MS) Powder for Oral Solution

Arm type	Active comparator
Investigational medicinal product name	CITRAFLEET
Investigational medicinal product code	Sodium Picosulfate and Magnesium Salt (SP+MS)
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

CITRAFLEET Powder for Oral Solution

Dosing regimen : Patients allocated to SP+MS at randomisation self-administered Dose 1 of study drug the morning of the day before the procedure and Dose 2 of study drug 6-8 hours later.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: Assessor : Colonoscopist

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Data analyst : Central reader

Number of subjects in period 1	NER1006	CITRAFLEET
Started	258	257
Completed	233	240
Not completed	25	17
Consent withdrawn by subject	15	10
Personal reasons	-	1
Adverse event, non-fatal	1	-
Screen failure	-	1
Lost to follow-up	3	1
Met exclusion criteria	6	4

Baseline characteristics

Reporting groups

Reporting group title	NER1006
Reporting group description:	NER1006 Powder for Oral Solution
Reporting group title	CITRAFLEET
Reporting group description:	Sodium Picosulfate and Magnesium Salt (SP+MS) Powder for Oral Solution

Reporting group values	NER1006	CITRAFLEET	Total
Number of subjects	258	257	515
Age categorical			
Units: Subjects			
Adults (18-64 years)	204	207	411
From 65-84 years	54	50	104
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	54.6	52.9	-
standard deviation	± 11.64	± 13.35	-
Gender categorical			
Units: Subjects			
Female	168	174	342
Male	90	83	173

Subject analysis sets

Subject analysis set title	NER1006
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mFAS included all randomized patients with the exception of any patient who (i) was randomized but subsequently failed to meet entry criteria and (ii) in whom it was confirmed (from their patient diary) that the same patient did not receive any study drug.

The mFAS was used as the primary population for all efficacy analyses. Patients in this analysis set were summarized according to the treatment to which they were randomly assigned.

Patients who did not have their eligibility confirmed based on the entry criteria were included in the mFAS, regardless of whether they received any study drug.

Subject analysis set title	CITRAFLEET
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mFAS included all randomized patients with the exception of any patient who (i) was randomized but subsequently failed to meet entry criteria and (ii) in whom it was confirmed (from their patient diary) that the same patient did not receive any study drug.

The mFAS was used as the primary population for all efficacy analyses. Patients in this analysis set were summarized according to the treatment to which they were randomly assigned.

Patients who did not have their eligibility confirmed based on the entry criteria were included in the mFAS, regardless of whether they received any study drug.

Reporting group values	NER1006	CITRAFLEET	
Number of subjects	250	251	
Age categorical Units: Subjects			
Adults (18-64 years)	200	206	
From 65-84 years	50	45	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	54.3	52.4	
standard deviation	± 11.65	± 13.08	
Gender categorical Units: Subjects			
Female	162	172	
Male	88	79	

End points

End points reporting groups

Reporting group title	NER1006
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Reporting group description:

NER1006 Powder for Oral Solution

Reporting group title	CITRAFLEET
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Reporting group description:

Sodium Picosulfate and Magnesium Salt (SP+MS) Powder for Oral Solution

Subject analysis set title	NER1006
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The mFAS included all randomized patients with the exception of any patient who (i) was randomized but subsequently failed to meet entry criteria and (ii) in whom it was confirmed (from their patient diary) that the same patient did not receive any study drug.

The mFAS was used as the primary population for all efficacy analyses. Patients in this analysis set were summarized according to the treatment to which they were randomly assigned.

Patients who did not have their eligibility confirmed based on the entry criteria were included in the mFAS, regardless of whether they received any study drug.

Subject analysis set title	CITRAFLEET
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The mFAS included all randomized patients with the exception of any patient who (i) was randomized but subsequently failed to meet entry criteria and (ii) in whom it was confirmed (from their patient diary) that the same patient did not receive any study drug.

The mFAS was used as the primary population for all efficacy analyses. Patients in this analysis set were summarized according to the treatment to which they were randomly assigned.

Patients who did not have their eligibility confirmed based on the entry criteria were included in the mFAS, regardless of whether they received any study drug.

Primary: To evaluate the overall bowel cleansing efficacy of NER1006 compared with SP+MS, graded according to the HCS in patients undergoing colonoscopy

End point title	To evaluate the overall bowel cleansing efficacy of NER1006 compared with SP+MS, graded according to the HCS in patients undergoing colonoscopy
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End point description:

The hypothesis for this endpoint was to demonstrate non-inferiority of NER1006 to SP+MS (10% margin).

End point type	Primary
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End point timeframe:

Visit 2, Day of colonoscopy

End point values	NER1006	CITRAFLEET		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	250	251		
Units: Harefield Cleansing Scale	155	135		

Statistical analyses

Statistical analysis title	Fisher's exact test
Statistical analysis description:	
The success rate was the number of patients with successful overall bowel cleansing as a proportion of the number of patients in each group. Missing data were imputed as failures. The treatment effect was the NER1006 success rate minus the SP+MS success rate. A Hochberg procedure was used to control Type I error. A closed testing procedure was used to evaluate superiority.	
Comparison groups	CITRAFLEET v NER1006
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	< 0.025
Method	Fisher exact

Notes:

[1] - The 97.5% 1-sided lower confidence interval (CI) for the difference between bowel preparation cleansing rates was determined using exact Clopper-Pearson confidence limits.

Primary: To evaluate the the "Excellent plus Good" cleansing rate in the colon ascendens of NER1006 compared with SP+MS, graded according to the HCS in patients undergoing colonoscopy

End point title	To evaluate the the "Excellent plus Good" cleansing rate in the colon ascendens of NER1006 compared with SP+MS, graded according to the HCS in patients undergoing colonoscopy
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End point description:

The hypothesis for this endpoint was to demonstrate non-inferiority of NER1006 to SP+MS (10% margin).

End point type	Primary
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End point timeframe:

Visit 2, Day of colonoscopy

End point values	NER1006	CITRAFLEET		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	250	251		
Units: Harefield Cleansing Scale	11	3		

Statistical analyses

Statistical analysis title	Fisher's exact test
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Statistical analysis description:

The success rate was the number of patients with successful colon ascendens cleansing as a proportion of the number of patients in each group. Missing data were imputed as failures. The treatment effect was the NER1006 success rate minus the SP+MS success rate. A Hochberg procedure used to control

Type I error. A closed testing procedure was used to evaluate superiority.

Comparison groups	CITRAFLEET v NER1006
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
P-value	< 0.025
Method	Fisher exact

Notes:

[2] - The 97.5% 1-sided lower confidence interval (CI) for the difference between bowel preparation cleansing rates was determined using exact Clopper-Pearson confidence limits.

Secondary: To assess NER1006 compared to SP+MS: 1) the adenoma detection rate (ADR) for the colon ascendens

End point title	To assess NER1006 compared to SP+MS: 1) the adenoma detection rate (ADR) for the colon ascendens
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End point description:

If at least one of the alternative primary endpoints were met, then key secondary endpoints were evaluated hierarchically in a pre-specified order. Non-inferiority was concluded if the 1-sided 97.5% CL for difference in proportion of events between 2 groups excluded a 10% or greater difference in favor of SP+MS. Formal testing was to proceed in the hierarchy if preceding key secondary endpoint had at least met non-inferiority.

End point type	Secondary
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End point timeframe:

Day of colonoscopy, Visit 2

End point values	NER1006	CITRAFLEET		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	250	251		
Units: Adenoma detection rate (ADR)	6	4		

Statistical analyses

Statistical analysis title	Fisher's exact test
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Statistical analysis description:

ADR was defined as the number of patients with at least one adenoma in the colon ascendens divided by the number of patients in the modified full analysis set.

Difference was calculated as NER1006 rate – CITRAFLEET rate.

1-sided P value was obtained from Fisher's exact test. The comparison was with the difference in rate between NER1006 and CITRAFLEET versus a hypothesized difference of zero.

Comparison groups	CITRAFLEET v NER1006
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
P-value	< 0.025
Method	Fisher exact

Notes:

[3] - 10% Non-inferiority margin

Secondary: To assess NER1006 compared to SP+MS: 2) the overall adenoma detection rate (ADR)

End point title	To assess NER1006 compared to SP+MS: 2) the overall adenoma detection rate (ADR)
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End point description:

If at least one of the alternative primary endpoints were met, then key secondary endpoints were evaluated hierarchichally in a pre-specified order. Non-inferiority was concluded if the 1-sided 97.5% CL for difference in proportion of events between 2 groups excluded a 10% or greater difference in favor of SP+MS. Formal testing was to proceed in the hierarchy if preceding key secondary endpoint had at least met non-inferiority.

End point type	Secondary
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End point timeframe:

Day of colonoscopy, Visit 2

End point values	NER1006	CITRAFLEET		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	250	251		
Units: Adenoma detection rate (ADR)	22	19		

Statistical analyses

Statistical analysis title	Fisher's exact test
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Statistical analysis description:

ADR was defined as the number of patients with at least one adenoma in the overall colon divided by the number of patients in the modified full analysis set.

Difference was calculated as NER1006 rate – CITRAFLEET rate.

1-sided P value was obtained from Fisher's exact test. The comparison was with the difference in rate between NER1006 and CITRAFLEET versus a hypothesized difference of zero.

Comparison groups	NER1006 v CITRAFLEET
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
P-value	< 0.025
Method	Fisher exact

Notes:

[4] - 10% Non-inferiority margin

Secondary: To assess NER1006 compared to SP+MS: 3) the polyp detection rate (PDR) with NER1006 for the colon ascendens

End point title	To assess NER1006 compared to SP+MS: 3) the polyp detection rate (PDR) with NER1006 for the colon ascendens
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End point description:

If at least one of the alternative primary endpoints were met, then key secondary endpoints were evaluated hierarchichally in a pre-specified order. Non-inferiority was concluded if the 1-sided 97.5% CL for difference in proportion of events between 2 groups excluded a 10% or greater difference in favor of SP+MS. Formal testing was to proceed in the hierarchy if preceding key secondary endpoint had at least met non-inferiority.

End point type	Secondary
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End point timeframe:

Day of colonoscopy, Visit 2

End point values	NER1006	CITRAFLEET		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	250	251		
Units: polyp detection rate (PDR)	12	8		

Statistical analyses

Statistical analysis title	Fisher's exact test
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Statistical analysis description:

PDR was defined as the number of patients with at least one polyp in the colon ascendens divided by the number of patients in the modified full analysis set.

Difference was calculated as NER1006 rate – CITRAFLEET rate.

1-sided P value was obtained from Fisher's exact test. The comparison was with the difference in rate between NER1006 and CITRAFLEET versus a hypothesized difference of zero.

Comparison groups	CITRAFLEET v NER1006
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[5]
P-value	< 0.025
Method	Fisher exact

Notes:

[5] - 10% Non-inferiority

Secondary: To assess NER1006 compared to SP+MS: 3) the overall polyp detection rate (PDR)

End point title	To assess NER1006 compared to SP+MS: 3) the overall polyp detection rate (PDR)
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End point description:

If at least one of the alternative primary endpoints were met, then key secondary endpoints were evaluated hierarchically in a pre-specified order. Non-inferiority was concluded if the 1-sided 97.5% CL for difference in proportion of events between 2 groups excluded a 10% or greater difference in favor of SP+MS. Formal testing was to proceed in the hierarchy if preceding key secondary endpoint had at least met non-inferiority.

End point type	Secondary
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End point timeframe:

Day of colonoscopy, Visit 2

End point values	NER1006	CITRAFLEET		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	250	251		
Units: polyp detection rate (PDR)	39	36		

Statistical analyses

Statistical analysis title	Fisher's exact test
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Statistical analysis description:

PDR was defined as the number of patients with at least one polyp in the overall colon divided by the number of patients in the modified full analysis set.

Difference was calculated as NER1006 rate - CITRAFLEET rate.

1-sided P value was obtained from Fisher's exact test. The comparison was with the difference in rate between NER1006 and CITRAFLEET versus a hypothesized difference of zero.

Comparison groups	NER1006 v CITRAFLEET
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[6]
P-value	< 0.025
Method	Fisher exact

Notes:

[6] - 10% Non-inferiority margin

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored continuously and were reported to the Investigator by the patient for the duration of the study (This definition includes events occurring from the time of informed consent until 28 days after last patient last visit).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	NER1006
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Reporting group description:

NER1006 Powder for Oral Solution

Reporting group title	CITRAFLEET
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Reporting group description:

Sodium Picosulfate and Magnesium Salt (SP+MS) Powder for Oral Solution

Serious adverse events	NER1006	CITRAFLEET	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 235 (0.43%)	0 / 241 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Ovarian abscess			
subjects affected / exposed	1 / 235 (0.43%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	NER1006	CITRAFLEET	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 235 (17.02%)	24 / 241 (9.96%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 235 (1.70%)	4 / 241 (1.66%)	
occurrences (all)	5	4	
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	8 / 235 (3.40%) 8	3 / 241 (1.24%) 3	
Nausea subjects affected / exposed occurrences (all)	6 / 235 (2.55%) 6	2 / 241 (0.83%) 2	
Vomiting subjects affected / exposed occurrences (all)	11 / 235 (4.68%) 11	0 / 241 (0.00%) 0	
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	3 / 235 (1.28%) 3	0 / 241 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2014	Protocol amendment : Use of Citra Fleet in patients with rhabdomyolysis is contraindicated. This was erroneously omitted in the exclusion criteria of the study protocol and was included in line with the Summary Product Characteristics (SPC).
19 December 2014	Protocol amendment: -Implementation of paper rather than electronic diaries and Patient Reported Outcome measures. -Changes to Visit 3 and Visit 4 for monitoring patients for any potential kidney injury. -Exclusion criterion "Regular use of laxatives or colon motility altering drugs in the last month (i.e. more than 2-3 times per week)" changed to "last 28 days" prior to Screening Visit instead "last month". -For clarification, word "known" added to Exclusion Criteria "Patients with known liver disease of grades B and C according to the Child Pugh classification". -More precise definition for 'post-menopausal and surgically sterile' included in Inclusion Criterion. -Advice given for contraception amended. -To reflect clinical practice and enable flexibility, sites will be allowed to schedule the IMP intake +/- 2 hrs before or after the suggested approx. time in the protocol. -Clarification regarding capturing site colonoscopist's experience and personal Adenoma Detection Rate. -Clarification regarding conduct of colonoscopy and scoring. -'Thrombin Time' has been removed from the 'Coagulation' profile. -Genitourinary system deleted as not a requirement under "Physical Examination" for purpose of conducting colonoscopy. -Clarification added to ensure patients have recovered sufficiently from the colonoscopy procedure prior to discharge from clinic. -Clarification to Exclusion Criteria "known hypersensitivity to PEG, ascorbic acid and sulfates or any other component of IMP or comparator" does not include those with sulfa/sulpha drug allergy/intolerance. -Clarifications in Biochemistry panel: "Urea" same as "Blood Urea Nitrogen". -In line with the Sponsor Company's policy "Management of Product Quality Complaints relating to IMP", reporting requirement included. -Change of company/contact details : "Statistical Expertise". -Confidence limit relating to key secondary endpoints amended. -Assessment Schedule updated to clarify Physical Examination.
30 March 2015	Protocol amendment to document due to a planned increase in the number of patients to be randomised to account for a 20% drop out as opposed to 10% stated in the previous version of the protocol. Further amendments were made to incorporate additional information for site logistical purposes, alignment with the Statistical Analysis Plan and general clarification.
25 June 2015	Protocol amendment following statistical input recommending three distinct population analyses on the data, namely the Full Analysis Set (FAS), the modified Full Analysis Set (mFAS), and the Per Protocol (PP) set. In addition, one administrative amendment was made relating to a change to the Sponsor's Project Manager.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported