



## 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 |
|-----------------------|-----------------|

##### 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:

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**Results analysis stage**

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|  |                |
|--|----------------|
| 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:

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**General information about the trial**

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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.

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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.

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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:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                    |
|--------------------------------------|--------------------|
| 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:

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**Subjects enrolled per age group**

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|   |     |
|---|-----|
| 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  $\geq 18$  to  $\leq 85$  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 <sup>[1]</sup>           |
| Roles blinded                | Data analyst, Assessor <sup>[2]</sup> |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | 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.

|                  |            |
|------------------|------------|
| <b>Arm title</b> | CITRAFLEET |
|------------------|------------|

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

| <b>Number of subjects in period 1</b> | 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:<br>NER1006 Powder for Oral Solution                                       |            |
| Reporting group title  | CITRAFLEET |
| Reporting group description:<br>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<br>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<br>Units: years        |         |            |       |
| arithmetic mean                       | 54.6    | 52.9       |       |
| standard deviation                    | ± 11.64 | ± 13.35    | -     |
| Gender categorical<br>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.

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

## End points

### End points 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

|                            |         |
|----------------------------|---------|
| 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.

### 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 |
|-----------------|---|

End point description:

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

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

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

|  |                                |
|--|--------------------------------|
| <b>Statistical analysis title</b>  | Fisher's exact test            |
| Statistical analysis description:<br>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 <sup>[1]</sup> |
| 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 |
|-----------------|--|

End point description:

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

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

End point timeframe:

Visit 2, Day of colonoscopy

|                                  |                      |                      |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| <b>End point values</b>          | 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

|                                   |                     |
|-----------------------------------|---------------------|
| <b>Statistical analysis title</b> | Fisher's exact test |
|-----------------------------------|---------------------|

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 <sup>[2]</sup> |
| 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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|----------------------------|---------------------|

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 <sup>[3]</sup> |
| 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) |
|-----------------|--|

## 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 |
|----------------|-----------|

## 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 |
|----------------------------|---------------------|

## 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 <sup>[4]</sup> |
| 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 |
|-----------------|---|

## 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 |
|----------------|-----------|

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 |
|----------------------------|---------------------|
|----------------------------|---------------------|

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 <sup>[5]</sup> |
| 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) |
|-----------------|--|

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 |
|----------------|-----------|

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

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 <sup>[6]</sup> |
| 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 |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.0   |

### 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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 16 September 2014 | Protocol amendment :<br>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:<br>-Implementation of paper rather than electronic diaries and Patient Reported Outcome measures.<br>-Changes to Visit 3 and Visit 4 for monitoring patients for any potential kidney injury.<br>-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".<br>-For clarification, word "known" added to Exclusion Criteria "Patients with known liver disease of grades B and C according to the Child Pugh classification".<br>-More precise definition for 'post-menopausal and surgically sterile' included in Inclusion Criterion.<br>-Advice given for contraception amended.<br>-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.<br>-Clarification regarding capturing site colonoscopist's experience and personal Adenoma Detection Rate.<br>-Clarification regarding conduct of colonoscopy and scoring.<br>-'Thrombin Time' has been removed from the 'Coagulation' profile.<br>-Genitourinary system deleted as not a requirement under "Physical Examination" for purpose of conducting colonoscopy.<br>-Clarification added to ensure patients have recovered sufficiently from the colonoscopy procedure prior to discharge from clinic.<br>-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.<br>-Clarifications in Biochemistry panel: "Urea" same as "Blood Urea Nitrogen".<br>-In line with the Sponsor Company's policy "Management of Product Quality Complaints relating to IMP", reporting requirement included.<br>-Change of company/contact details : "Statistical Expertise".<br>-Confidence limit relating to key secondary endpoints amended.<br>-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