# 2 SYNOPSIS

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| Name of Sponsor/Company: Norgine Ltd | Individual Study Table Referring to Part of the Dossier<br>Volume:<br>Page: | *(For National Authority Use Only)* |
| Name of Finished Product: MOVIPREP Orange® (NRL0706) | | |
| Names of Active Ingredients: Ascorbic acid, PEG3350, sulphate and electrolytes | | |

**Title of the Study:**
Open study to assess the tolerability, safety and efficacy of an adapted 2 litre gut cleansing solution (NRL0706) in routine colon cleansing prior to colonoscopies for colon tumour screening

**Coordinating Investigator:**
[redacted]
Klinikum Aschaffenburg
[redacted]
Germany
Tel: [redacted]
Fax: [redacted]

**Study Centres:**
The study was a multi-centre study and was conducted in 5 centres in Germany:

- [redacted] Gastroenterologische Praxis, Hof
- [redacted] Internistische Gemeinschaftspraxis, Ludwigshafen
- [redacted], Klinikum Aschaffenburg, Medizinische Klinik II, Aschaffenburg
- [redacted] Gastroenterologische Praxis, Freising
- [redacted], Praxis Gastroenterologie am Max Weber Platz, München

**Publication (Reference):**
Not applicable

| **Studied Period:** | **Phase of Development:** |
|---|---|
| 22 Mar 2010 (date of first subject enrolled)<br>24 Aug 2010 (date of last subject completed) | Phase II |

**Objectives:**
To assess the tolerability, acceptability, safety and efficacy of the flavour-modified 2 litre gut cleansing solution (NRL0706; trade name MOVIPREP Orange®) in routine colon cleansing prior to screening colonoscopies

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**Methodology:**
This was a single-country, multi-centre, open, phase II study in male and female subjects aged 40 to 75 years, undergoing colonoscopy for colon cancer screening to assess the tolerability, safety and efficacy of NRL0706. Gut cleansing was performed using the established standard split dosing intake for 2 litres of MOVIPREP®.

**Number of Subjects:**

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| Planned: | 120 screened subjects<br>100 evaluable subjects |
| Actual: | Enrolled: 121 subjects<br>Safety: 118 subjects<br>Intention-to-treat (ITT): 118 subjects<br>Per protocol (PP): 115 subjects |

**Diagnosis and Main Criteria for Inclusion:**
The subjects' written informed consent had to be obtained prior to inclusion. Study subjects had to satisfy the following inclusion criteria:

1. Male or female ambulatory subjects aged between 40 and 75 years
2. No history of significant gastrointestinal diseases, including gastrointestinal obstruction and perforation or acute symptoms requiring a colonoscopy procedure
3. Willing to undergo a complete colonoscopy for colon cancer screening
4. Willing, able and competent to complete the entire procedure and to comply with study instructions

Females of childbearing potential had to employ an adequate method of contraception.

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**Test Product, Dose and Mode of Administration, Batch Number:**

IMP: NRL0706

The ingredients of NRL0706 were contained in two separate sachets to be reconstituted in water to obtain a 1-litre gut cleansing solution.

**Sachet A** contained the following active substances:

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| Polyethylen glycol (PEG) 3550 | 100.000 g |
| Sodium sulphate anhydrous | 7.500 g |
| Sodium chloride | 2.691 g |
| Potassium chloride | 1.015 g |

**Sachet B** contained the following active substances:

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| Ascorbic acid | 4.700 g |
| Sodium ascorbate | 5.900 g |
| Other ingredients: | Orange flavour and sweetener |

Pharmaceutical form: Powder for oral solution (per 1 litre) in two sachets

Route of administration: Oral

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| Posology: | The treatment (1 pack) consisted of 2 litres NRL0706. One pack contained four sachets (2 x PEG+E/'A' + 2 x ascorbic acid/ascorbate/'B') of NRL0706. Two sachets (1 x 'A' plus 1 x 'B') were dissolved in water to obtain a 1-litre gut cleansing solution. Each litre was to be drunk within 1 to 1.5 h followed by at least 0.5 litre of any additional clear fluid which might have included water, clear soup, fruit juice without pulp, soft drinks, tea and/or coffee (without milk). | |
| Batch Number: | MOVIPREP Orange® sachet A: | Batch Number 160709 |
| | MOVIPREP Orange® sachet B: | Batch Number 101693 |
| | Combined IMP Pack: | Batch Number 210709 |

**Duration of Treatment:**

Each subject recruited into the study was treated with a single treatment of NRL0706. The subjects underwent the gut cleansing prior to the colonoscopy starting the evening before the procedure, according to the presently recommended intake instructions for the split dose intake of MOVIPREP® over two days with a nocturnal break. The recruited subjects received the investigational medicinal product (IMP) at the screening visit and were given detailed intake instructions. The scheduled colonoscopy was performed within 30 days of the screening visit. The end-of-treatment (EOT) assessment was conducted after completion of the colonoscopy procedure when the subject was ready to leave the endoscopy unit.

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**Reference Therapy, Dose and Mode of Administration, Batch Number:**
Not applicable

**Criteria for Evaluation:**
**Primary Endpoint:**
The subject's Visual Analogue Scale (VAS (100 mm)) ratings for the overall tolerance of the intake of NRL0706 and the overall acceptance of the NRL0706 gut preparation

**Secondary Endpoints:**

- Tolerance assessment
  a) 5-point Verbal Rating Scale (VRS) per litre intake of NRL0706 and overall
  b) 3-point VRS to assess the degree of difficulty of drinking the gut cleansing solution
  c) 5-point VRS on the overall tolerance rating
  d) Assessment of the pre-defined symptoms (nausea, vomiting, abdominal discomfort and abdominal pain) per litre during the NRL0706 intake
- Taste evaluation
  a) VAS (100 mm) taste evaluation after the intake of each litre of NRL0706
  b) 3-point VRS on the overall taste evaluation
- Acceptability
  a) Compliance with the intake using the documentation of the intake of NRL0706 and clear liquid
  b) 4-point VRS to assess the ease of drinking of NRL0706 following the intake instructions
  c) VAS (100 mm) to assess the overall satisfaction with the gut cleansing procedure
- Efficacy
  a) Degree of cleansing using a 5-grade scale for each of the pre-defined colon areas
  b) Final grading of the overall quality of the gut preparation (A or B 'success' versus C or D 'failure') using the Harefield Cleansing Scale™
  c) 5-point VRS for the overall judgement of the investigator of the colon preparation

**Safety Parameters:**

- Subject documentation forms (SDFs) were used to assess the clinical tolerance using the pre-defined symptoms (e.g. nausea, vomiting)
- Monitoring of spontaneous adverse events (AEs) and clinically significant symptoms from the SDF questionnaire
- Cardiovascular parameters blood pressure and pulse rate were documented (pre/post preparation and pre/post colonoscopy)
- Body weight (pre/post preparation)

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**Statistical Methods:**
A PP and an ITT analysis were carried out. The primary analysis used the defined ITT as well as the PP population for analysis. The tolerance, acceptability, safety and efficacy parameters of the study were assessed using descriptive statistic methods and compared descriptively, where available, to a historic previous MOVIPREP® study, conducted in an almost identical manner in the same target population (NRL994-01/2004).

**SUMMARY – CONCLUSIONS**

**EFFICACY RESULTS:**

**Primary variable:**
The primary variable of this study was to assess the tolerance of intake of the flavour-modified 2-litre cleansing solution NRL0706 (MOVIPREP Orange®) and the overall acceptance of the gut preparation used prior to selective tumour screening colonoscopies. These parameters were assessed by the subjects using a 100-mm VAS. For the overall tolerance of the subjects in the ITT population, a mean value of 72.7 (SD = 22.91) mm was calculated and a mean value of 68.7 (SD = 24.18) mm for the overall acceptance. The latter parameter was also assessed in a similar study with an identical target population with NRL994 (study NRL994-01/2004) as a historic control group. The mean value for NRL994 was 75.6 (SD = 15.00) mm for the overall acceptance.

**Secondary variables:**
1. Tolerance

As a secondary variable, the tolerance of intake of the first and second litre of the IMP as rated by the subjects was analysed. The majority of subjects in the ITT population rated the tolerance of the intake of the first litre (NRL0706: 113 subjects (95.8%), NRL994: 237 subjects (97.9%)) as well as of the second litre (NRL0706: 106 subjects (89.8%), NRL994: 226 subjects (93.4%)) as acceptable or better (good/very good). No difference to the previously tested NRL994 could be observed.
In addition, the subjects documented the degree of difficulty of drinking of the gut cleansing solution with the help of a 3-point VRS. The majority of subjects stated having no problems drinking the gut cleansing solution (NRL0706: 82 subjects (69.5%) which was similar to NRL994: 182 subjects (75.2%)).
After completion of the intake, the subjects rated the overall tolerance of the gut cleansing solution. The majority of subjects rated the overall tolerance as good or very good (NRL0706: 81 subjects (68.6%) compared to the results with NRL994: 183 subjects (75.6%)).
The majority of subjects experienced no pre-defined symptoms during the intake of the first (NRL0706: 86 subjects (72.9%)) and the second litre (NRL0706: 87 subjects (73.7%)). The most frequently observed pre-defined symptoms were abdominal pain (NRL0706:14 subjects (11.9%)) and nausea (NRL0706: 14 subjects (11.9%)) during the intake of the first litre and nausea (NRL0706: 22 subjects (18.6%)) during the intake of the second litre.

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2. Taste evaluation

The taste of the first litre of the IMP was assessed with a mean value of 55.0 (SD = 22.00) mm (NRL0706) and that of the second litre with a mean value of 52.7 (SD = 23.25) mm (NRL0706) on a 100-mm VAS.

The majority of subjects in the ITT population rated the overall taste as okay or good (NRL0706: 93 subjects (78.8%).

3. Acceptability

To address the compliance with the intake instructions, the mean duration of the first intake was recorded as 1.81 (SD = 1.766) h, that of the second intake as 1.13 (SD = 0.664) h.

The majority of subjects in the ITT population rated the drinking of the IMP as easy or very easy (NRL0706: 109 subjects (92.4%)).

The overall satisfaction was assessed with a mean value of 73.3 (SD = 22.08) mm (NRL0706) which was similar to the results after using NRL994 (73.2 (SD = 16.42) mm).

4. Efficacy

For each of the 6 pre-defined colon areas, in the majority of cases the degree of cleansing by NRL0706 was rated as grade 3 (good).

In study NRL0706-01/2009, the investigator rated the majority of cases (88 subjects (74.6%) as a good preparation based on the assessment of all colon segments with grade 3 or 4. Similar results were previously seen for NRL994 where the investigator rated the majority of cases as well prepared with all colon segments with grade 3 or 4 (173 subjects (71.5%)).

For study NRL0706-01/2009, the majority of the colon preparations were assessed as successful preparations (114 subjects (96.6%)) by the investigator. In comparison, after the NRL994 treatment the investigator also rated the majority as successful preparations (230 subjects (95.0%)).

**SAFETY RESULTS:**

In total, for 12 subjects (10.2%) in the safety population of study NRL0706-01/2009 (N = 118) 21 treatment-emergent AE (TEAE) episodes were reported during the course of the study of which 6 (28.6%) were assessed as unrelated, 9 (42.9%) were assessed as possibly related and 6 (28.6%) as probably related to the intake of the IMP by the investigator.

Overall, the intensity of the TEAE symptoms was mild in 20 cases (95.2%) and severe in 1 case (4.8%) during study NRL0706-01/2009.

During the course of study NRL0706-01/2009, 1 treatment-emergent serious AE (SAE) occurred in 1 subject (0.8%) and was assessed as unrelated to the intake of the IMP by the investigator (detection of cancer). There was no TEAE leading to premature discontinuation. For none of the TEAEs during study NRL0706-01/2009, an action was taken regarding the IMP.

According to the current version of the SmPC for MOVIPREP®, gastrointestinal disorders (very common: abdominal pain, nausea, abdominal distension and anal discomfort) are well known side effects. The same was the case in study NRL0706-01/2009.

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Vital signs and body weight showed only minor, non-relevant changes after dosing of the IMP.
In vital signs, body weight and physical examinations, none of the parameters assessed showed systematically or relevant changes during the course of study NRL0706-01/2009.

**CONCLUSION:**
In conclusion, the treatment of the subjects with NRL0706 was well tolerated and safe. The observed cleansing results of the colon are similar to the previously documented results with NRL994 (MOVIPREP®), indicating that the flavour modification has no effect on the acceptability, tolerance, safety and efficacy of the MOVIPREP® cleansing solution.

Date of the Report: 25 Mar 2011