Title: Colon cleansing efficacy and safety with 1L NER1006 versus 2L polyethylene glycol + ascorbate: a randomized Phase 3 trial

Authors: Raf Bisschops,* Jonathan Manning,‡ Lucy B. Clayton,§ Richard Ng Kwet Shing,§ and Marco Álvarez-González† on behalf of the MORA Study Group

Affiliations: **KU Leuven, University Hospitals Leuven, Leuven, Belgium; ‡Borders General Hospital, NHS Borders, Melrose, Berwickshire, UK; §Clinical Development, Norgine Ltd, Harefield, UK; and †Hospital del Mar, Barcelona, Spain.*

Correspondence: Lucy Clayton, Clinical Development, Norgine Ltd, Norgine House, Moorhall Road, Harefield, Uxbridge UB9 6NS, United Kingdom. email: LClayton@norgine.com; tel: +44 (0)1895 826669; fax: +44 (0)1895 825865.

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study supervision. Richard Ng Kwet Shing: Study concept and design, analysis and interpretation of data; drafting of the manuscript: critical revision of the manuscript for important intellectual content; statistical analysis; administrative, technical, or material support. Marco Álvarez-González: Acquisition of data; critical revision of the manuscript for important intellectual content.

Abbreviations used in this paper: 2LPEG, 2L polyethylene glycol with ascorbate in evening/morning split-dosing administration; ADR, adenoma detection rate; BBPS, Boston Bowel Preparation Scale; FAS, full analysis set; GI, gastrointestinal; HCS, Harefield Cleansing Scale; LCL, one-sided 97.5% lower confidence limit for the difference between treatments; mFAS, modified full analysis set; mFAS(cr), modified full analysis set with readable colonoscopy videos for central readers; N1D, NER1006 in 1-day morning-only administration; N2D, NER1006 in 2-day evening/morning split-dosing administration; NNT, number needed to treat; PDR, polyp detection rate; PEG, polyethylene glycol; PP, per protocol; SD, standard deviation; TEAE, treatment-emergent adverse event.

Abstract

Background and study aims Polyethylene glycol (PEG)-based bowel preparations are effective cleansers but many require high volume intake. This Phase 3, randomized, blinded, multicenter, parallel-group, central reader-assessed study MORA assessed the 1L PEG NER1006 bowel preparation versus standard 2L PEG with ascorbate (2LPEG).

Patients and methods Patients undergoing colonoscopy were randomized (1:1:1) to receive NER1006, as an evening/morning (N2D) or morning-only (N1D) regimen, or evening/morning 2LPEG. Cleansing was assessed using the Harefield Cleansing Scale (HCS) and the Boston Bowel Preparation Scale (BBPS). Primary endpoints were overall bowel cleansing success and high-quality cleansing in the right colon. Modified full analysis set (mFAS) and per protocol (PP) analyses were performed. Mean cleansing scores were analyzed *post hoc.*

Results Of 849 randomized patients, efficacy was analyzed in the following patient numbers (mFAS/PP): total, 822/670; N2D, n=275/220; N1D, n=275/218; 2LPEG, n=272/232. mFAS established non-inferiority. PP showed superiority for N2D on overall success (97.3% versus 92.2%; P=0.014) and for N2D and N1D on right-colon high-quality cleansing (N2D: 32.3% versus 15.9%, P<0.001: N1D: 34.4% versus 15.9%, P<0.001). Using HCS, N2D and N1D attained superior segmental high-quality cleansing (P≤0.003 per segment). N2D showed superior mean segmental HCS scores (P≤0.007 per segment). Both N2D and N1D achieved superior mean overall (P<0.001 and P=0.006) and right-colon BBPS scores (P<0.001 and P=0.013).

N2D demonstrated superior right-colon polyp detection (*P*=0.024). Adherence, tolerability and safety were comparable between treatments.

Conclusions NER1006 is the first low-volume preparation to demonstrate superior colon cleansing efficacy versus standard 2LPEG with ascorbate, with comparable safety and tolerability.

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Introduction

Effective bowel preparation is critical for the diagnostic and therapeutic success and cost-effectiveness of colonoscopy.[1,2] Suboptimal cleansing can impede detection of colonic neoplasia, necessitating early repeat procedures and delaying intervention.[3,4] An adequate level of bowel cleansing is increasingly recognized as a prerequisite for adenoma detection.[5] However, excellent-grade bowel cleansing will also improve detection of sessile serrated polyps.[5] Since these flat lesions are often found in the right colon and cecum, and account for a disproportionate number of cancers diagnosed after colonoscopy,[6] improving cleansing of the right colon is now a preventive healthcare priority.

Among the available bowel lavage solutions, split-dose polyethylene glycol (PEG)-based preparations are traditionally viewed as the gold standard.[4,7,8] However, many PEG-based preparations require intake of high-volume solutions of up to 4L, which may reduce patients' adherence.[4,9] Development of a 2L PEG-based preparation was made possible by the addition of ascorbate, which contributes to the laxative effect and enables delivery of the solution in a smaller volume.[10] This combined formulation has previously demonstrated a high degree of efficacy and safety in pre-colonoscopy bowel cleansing.[9,10]

NER1006 is the first 1L (32 US fl oz) PEG bowel preparation. It is a taste-optimized combination of two different formulations, designed to maximize patient adherence and to work synergistically for bowel cleansing. NER1006 is dual-flavored: the two doses are mango (Dose 1) and fruit punch (Dose 2). The lower reconstituted volume of NER1006 is achieved with an increased ascorbate component, which is administered in the second dose only.[11] NER1006 has previously demonstrated pharmacodynamic potential, efficacy, and an acceptable

tolerability profile in a Phase 2 study in healthy subjects and patients undergoing screening colonoscopy.[11] Three Phase 3 studies – MORA[12] , NOCT,[13] and DAYB[14] – have been conducted to further evaluate the efficacy, safety, and tolerability of NER1006. These trials were designed as non-inferiority studies (consistent with regulatory guidance for evaluation of bowel preparations[15]), but also included pre-planned superiority testing if non-inferiority was attained.

Reported here are the results of the MORA study, which compared NER1006, administered as an evening/morning split-dosing or morning-only regimen, to the standard 2L PEG plus ascorbate preparation in patients undergoing colonoscopy.

Patients and methods

Study Design

This was a Phase 3, randomized, multicenter, colonoscopist- and central reader-blinded, non-inferiority study conducted at 29 clinics or hospitals with colonoscopy facilities in Belgium, France, Germany, Italy, Poland, Spain, and the UK (registration/protocol: EudraCT Number, 2014-002185-78; ClinicalTrials.gov, NCT02273167).

The study was conducted in accordance with the Declaration of Helsinki and received Independent Ethics Committee approval in all participating countries. Patients provided written informed consent.

Patients

Eligible patients were males and females aged 18–85 years undergoing screening, surveillance or diagnostic colonoscopy. Women of child-bearing potential

were required to have a negative pregnancy test and practice birth control during the study. Major exclusion criteria were: history of severe constipation, known or suspected ileus, gastrointestinal (GI) obstruction, gastric retention, bowel perforation, toxic colitis, or megacolon within the previous 12 months; prior significant GI surgery; severe acute inflammatory bowel disease; regular use of laxatives or colon motility-altering drugs; active intestinal bleeding; or clinically significant low hemoglobin level. Patients with severe renal insufficiency (glomerular filtration rate [GFR] <30mL/min/1.73m^2) were excluded, but mild-to-moderate renal impairment was allowed. Full exclusion criteria are provided in Supplementary Table 1. Eligibility criteria were similar to those of the trial establishing the efficacy and safety of the reference treatment (2LPEG).[9]

Treatment Allocation and Masking

Patients were randomly assigned (1:1:1) to receive NER1006 (PLENVU®; Norgine, Harefield, UK), administered as a 2-day evening/morning split-dosing (N2D) or 1-day morning-only (N1D) regimen, or the 2L PEG with ascorbate preparation (2LPEG; MOVIPREP®; Norgine, Harefield, UK), administered as a 2-day evening/morning split-dosing regimen. Randomization was blocked using a block size of six (codes created using SAS V9.2) and centrally conducted using an interactive web response system generated by the contract research organization Pharmaceutical Product Development (Wilmington, NC, USA). Patients were enrolled by the principal investigator or other study staff, who also gave patients their study medication. Site colonoscopists and central readers were blinded to treatment assignment. Patients and study site staff were reminded not to reveal treatment assignment to the colonoscopist.

Bowel Cleansing Schedules and Dietary Restrictions

Study treatment compositions are shown in Supplementary Table 2. Patients in the N2D and 2LPEG groups self-administered the first and second doses at approximately 6 p.m. on the day before and approximately 6 a.m. on the day of colonoscopy (Figure 1). Patients in the N1D group self-administered the first and second doses at approximately 5 a.m. and 7 a.m. on the day of colonoscopy. A window of ±2 hours of the start time was acceptable. For outpatients, administration of bowel preparation normally took place at home.

The day before colonoscopy, patients had either a light breakfast (NER1006 groups) or normal breakfast (2LPEG) and light lunch (all groups), followed by clear soup and/or plain yoghurt for dinner (N1D and 2LPEG groups only). Patients could consume clear fluids *ad libitum* from starting the first dose, until 2 hours (NER1006 groups) or 1 hour (2LPEG) before the start of colonoscopy. Dietary restrictions for 2LPEG were aligned with the Summary of Product Characteristics. Colonoscopy was recommended for morning or early afternoon (N2D and 2LPEG) or for early afternoon (N1D).

Assessments and Endpoints

Experienced site colonoscopists conducted and recorded the colonoscopies and applied colon landmarks to the videos. Bowel-cleansing efficacy was assessed by the site colonoscopists, and by independent central readers (six experienced and trained colonoscopists) blinded to site scores, based on video review, using the Harefield Cleansing Scale [16] (HCS; for primary endpoints); central reader scores

were used for the efficacy analysis. Representative images of HCS scores are provided in Supplementary Figure 1. Central readers also assessed bowel cleansing efficacy using the Boston Bowel Preparation Scale [17] (BBPS; supportive secondary endpoint). Both scales are validated for assessing the quality of bowel preparation [16–18] and are summarized in Supplementary Table 3.

The two alternative primary endpoints were: overall bowel cleansing success rate (grades A and B on the HCS) and high-quality cleansing rate (score 4 [excellent] plus score 3 [good] on the HCS, i.e. fully visualized mucosa without any cleaning during colonoscopy) in the right colon (the ascending colon and cecum)[16]. Key secondary endpoints included polyp detection rate (PDR) in the right colon and overall colon (assessed by the site colonoscopist), and adenoma detection rate (ADR) in the right colon and overall colon (assessed by pathological review of polyp biopsies). Lesion detection rates were calculated as the percentage of patients with at least one adenoma (for ADR) or polyp (for PDR) in the analyzed population. Tolerability, acceptability, and adherence (defined as taking 75% or more of each dose) were assessed using patient diaries. Safety was monitored through adverse event reporting, clinical laboratory evaluation, vital signs, physical examinations, and electrocardiograms. Mean overall and segmental cleansing scores, and efficacy in the elderly were analyzed *post hoc*.

Statistics

Statistical analyses were conducted using SAS Version 9.2 (SAS Institute, Cary, NC, USA). Alpha of 0.05 was split across the two primary endpoints, providing a significance threshold of $P<0.025$ (one-sided). Assuming overall cleansing success rates of 90% for all three groups, and with a non-inferiority margin of 10%, a sample

size of 245 patients per group provided at least 90% power to demonstrate non-inferiority of each NER1006 group versus 2LPEG. To accommodate comparison of two NER1006 groups with the control, a hierarchical testing approach was used whereby N2D was assessed first and, if successful, then N1D was evaluated (each versus 2LPEG). In each case, non-inferiority was proven if the one-sided 97.5% lower confidence limit (LCL) for the difference between treatments was ≥-10%. If non-inferiority was met for either primary endpoint, that endpoint was assessed for superiority using Fisher's exact test, and key secondary endpoints were tested using the following hierarchy: ADR in the right colon; ADR in the overall colon; PDR in the right colon; PDR in the overall colon. In *post hoc* analyses, increases in primary endpoint attainment were expressed as numbers needed to treat (NNTs), calculated as the inverse of the absolute rate difference.

The full analysis set (FAS) was defined as all randomized patients in the study. The modified FAS (mFAS) excluded any patient who failed screening and for whom the patient diary confirmed that the patient did not take any study drug. The mFAS was used as the primary population for all efficacy analyses. Missing efficacy data were imputed as failures. The mFAS(cr) population included patients with readable colonoscopy videos for central readers. The per protocol (PP) set included patients without major protocol deviations, who met eligibility criteria, who took ≥75% of each bowel preparation dose, and who had available data for at least one of the primary endpoints. The safety set comprised all patients for whom it could not be ruled out that they received the study medication at least once (based on patient diary).

Results

Patient Disposition and Characteristics

Patients were enrolled between October 2014 and June 2015, with follow-up completed in August 2015. The study ended when sufficient evaluable patients had been recruited. The FAS comprised 849 patients, of whom 822 (96.8%) were included in the mFAS (Figure 2). The most common reason for exclusion from the mFAS was ineligibility based on screening laboratory tests. The mFAS included 13, 5 and 12 patients in the N2D, N1D, and 2LPEG groups, respectively, for whom missing efficacy data were imputed as failures.

Overall, demographic characteristics were well-balanced between groups (Table 1). A renal function consistent with mild to moderate renal insufficiency (GFR 30–90 mL/min/1.73m^2) was present in 70–74% of patients. In the FAS, similar proportions of patients in the N2D, N1D, and 2LPEG groups underwent colonoscopy for screening (50–51%), surveillance (22–24%) or diagnosis (26–28%). Most patients were outpatients (92–94% across treatment groups). The time between completion of bowel preparation (and additional clear fluid) and the start of colonoscopy was recorded (Supplementary Table 4). Colonoscopy was started in most patients within 6 hours of completing intake of the bowel preparation in each group (N2D, 60.4%; N1D, 75.6%; 2LPEG, 73.9%).

Bowel Cleansing Efficacy

Overall colon

Both NER1006 regimens achieved non-inferiority versus 2LPEG for both alternative primary endpoints of successful overall bowel cleansing and high-quality

cleansing in the right colon (Figure 3A). High rates of overall bowel cleansing success were achieved in all three groups (N2D, 92.0%; N1D, 89.1%; 2LPEG, 87.5%). N2D and N1D were non-inferior to 2LPEG for overall bowel cleansing (LCL for the difference: -4.0% and -6.9%, respectively). Among patients in the PP set, higher rates of overall bowel cleansing success were achieved, which reached superiority for the N2D group compared to 2LPEG (N2D, 97.3%; N1D, 92.7%; 2LPEG, 92.2%, *P*=0.014 for N2D vs 2LPEG) (Figure 3B). Consistent results were also obtained in the FAS (Supplementary Figure 2). Cleansing success in the overall colon that was assessed using the BBPS reflected and supported the cleansing success that was assessed using the HCS (Figure 3C). Rates of overall successful bowel cleansing in the mFAS were 90.5% with N2D, 88.4% with N1D and 85.3% with 2LPEG, and the mean overall BBPS scores in the mFAS(cr) were higher with both N2D (6.7 ± 1.22; *P*<0.001) and N1D (6.6 ± 1.46; *P*=0.006) versus 2LPEG (6.3 ± 1.25) (Figure 3D).

Among patients aged ≤65 years, rates of overall bowel cleansing success were similar across treatment groups, whereas the rate appeared higher in the N2D group than in the other two groups in patients aged >65 years (Supplementary Figure 3).

Right colon

High-quality bowel preparation in the right colon was achieved by 31.6% (87/275) of patients in the N2D group, 33.8% (93/275) in the N1D group, and 15.1% (41/272) in the 2LPEG group (Figure 3A). Non-inferiority was demonstrated for N2D and N1D compared to 2LPEG (LCL for the difference: 8.1% and 10.3%,

respectively). Furthermore, high-quality cleansing rates with both N2D and N1D reached statistical superiority compared to 2LPEG (P<0.001 for both comparisons). Corresponding NNTs were 6.0 and 5.3, respectively. Significantly improved rates of high-quality cleansing in the right colon were also seen in the PP set for both N2D and N1D (P<0.001 for both comparisons) (Figure 3B), in the FAS (P<0.001 for both comparisons) (Supplementary Figure 2), in the right colon using the BBPS (P<0.001 and P=0.002 respectively) (Figure 3C) and in the mFAS(cr) when using mean segmental scores (BBPS: P<0.001 and P=0.013 respectively, Figure 3D;HCS: P<0.001 for both comparisons, Figure 3E). Significantly (P≤0.006) higher rates of high-quality cleansing of the right colon were also attained with both NER1006 regimens versus 2LPEG in patients aged ≤65 years and in those aged >65 years (Supplementary Figure 3).

Other colon segments

With the HCS, both NER1006 groups showed significantly (P≤0.003) greater rates of high-quality cleansing success than 2LPEG in all other bowel segments (transverse colon, descending colon, sigmoid colon, and rectum) (Figure 3A). With the BBPS, N2D and N1D attained superior high-quality cleansing in the transverse colon (P=0.004 and P=0.001).

Similarly, with the HCS, N2D demonstrated significantly (P≤0.007) higher mean segmental cleansing scores in every colon segment compared to 2LPEG, while N1D achieved significantly (P≤0.029) higher performance in all segments except the sigmoid colon (mFAS(cr), Figure 3E).

Lesion Detection

The ADR and PDR in the right colon and in the overall colon were non-inferior for both N2D and N1D versus 2LPEG (Figure 3F). The overall colon ADR was 26.5% with N2D and 27.6% with N1D versus 26.8% with 2LPEG (*P*=0.569 and *P*=0.455, respectively). In the right colon the ADR was 11.6% each for N2D and N1D versus 8.1% for 2LPEG (*P*=0.106 for both comparisons). The PDR in the overall colon was 44.0% with N2D and 45.1% with N1D, versus 44.5% with 2LPEG (*P*=0.579 and *P*=0.478, respectively). In the right colon, the PDR was superior for N2D versus 2LPEG (23.3% vs 16.2%, *P*=0.024).

Tolerability, Acceptability, and Adherence

Based on patient diary responses, tolerability and acceptability of the bowel preparations were similar across the three treatment groups (Figure 4A). The self-reported adherence was around 90% or higher across all treatment groups (Figure 4B). A total of 93.1% N2D and 89.6% N1D patients completed their bowel preparation process without significant interference with normal daily activities, compared to 88.5% of 2LPEG patients.

Safety

Treatment-emergent adverse events (TEAEs) that were considered treatment-related were reported for 11.5%, 14.9%, and 7.6% of patients in the N2D, N1D, and 2LPEG groups, respectively. They were mild or moderate and of a gastrointestinal nature (Table 2). The two most-frequent and potentially related TEAEs for NER1006 were nausea and vomiting, and for 2LPEG, nausea and

abdominal pain. Overall adherence was high (87.5%) among all patients with TEAEs of vomiting and the majority of these patients attained successful overall bowel cleansing.

Two patients discontinued the study drug due to treatment-related TEAEs: one with vomiting in the N1D group, and one with nausea and vomiting in the 2LPEG group. There were no deaths or related serious TEAEs. In general, median changes from baseline in hematology, clinical chemistry, and urinalysis parameters were not considered clinically significant, and there were no clinically significant differences between groups. The incidence of shifts in electrolytes from normal at baseline to high at post-baseline visits is provided in Supplementary Table 5.

Discussion

In the mFAS population, both dosing regimens of NER1006 were non-inferior to standard 2LPEG in overall bowel cleansing. As seen in Figure 3, overall cleansing success rates were high in all three groups, whether using the HCS or BBPS. N2D achieved 92.7% of patients with successful bowel cleansing, exceeding the minimum standards of 85% set by the US Multi-Society Task Force on Colorectal Cancer [19] and 90% set by the European Society of Gastrointestinal Endoscopy (ESGE) [20] for reaching adequate level cleansing.

Statistically superior overall colon cleansing efficacy was demonstrated by N2D versus 2LPEG in the PP set, in which both N2D and N1D clearly exceeded US and European minimum adequate level standards; N2D even exceeded the new high 95% target level set recently by ESGE.[20]

Overall cleansing superiority was also demonstrated by both NER1006 dosing regimens versus 2LPEG on mean overall BBPS scores. N2D further demonstrated superior mean segmental cleansing scores (HCS) in all individual colon segments, as did N1D in most segments, including the right colon. Finally, both NER1006 dosing regimens achieved segmental high-quality cleansing superiority on the HCS in every colon segment versus 2LPEG.

Both NER1006 regimens demonstrated both non-inferior and statistically superior (P<0.001, mFAS) high-quality cleansing in the right colon versus 2LPEG. This superiority was repeated in the PP set, and in two out of three colon segments when using the BBPS definition of high-quality cleansing. Both NER1006 regimens also achieved superior mean right colon BBPS cleansing scores compared to 2LPEG. NER1006 thus has the potential to help increase the ADR and thereby reduce colorectal cancer. [21–25]

The high efficacy of both NER1006 and 2LPEG was consistent with results obtained in other studies.[9,10,13] Improved right-sided colon cleansing with NER1006 may help detection of high-risk sessile serrated polyps (SSPs) that require high-quality bowel preparation for detection.[5] This is the first bowel preparation study to specify right-sided cleansing as a primary endpoint. While SSPs were not directly assessed in this study, N2D demonstrated superior cleansing and PDR in the right colon versus 2LPEG (P<0.001 and P=0.024 respectively). Enhanced osmotic activity may enable NER1006 to achieve its high level of cleansing in the right colon.

All three groups showed high self-reported adherence with intake of both the bowel preparation doses and additional clear fluids. The self-reported patient diary responses indicated that all treatments were well-tolerated and acceptable.

Differences in tolerability/acceptability between NER1006 and 2LPEG were not detected in this study. This may be because the tolerability of 2LPEG is already high.

The overall safety profile of NER1006 was comparable to that of 2LPEG. Treatment-related TEAEs were generally gastrointestinal and mild or moderate in severity, which reflected the expected safety profiles of PEG-based bowel preparations. Although vomiting occurred more commonly with NER1006, rates were low and there was no indication this impacted on efficacy or adherence.

The consistent efficacy, acceptability, adherence, and safety between the two NER1006 treatment regimens (N2D and N1D) supports the flexible dosing according to physician and patient preference, and planned timing of colonoscopy.

This study has potential limitations. Eligible patients without primary endpoint data were imputed as failures, which diluted success rates in the mFAS sets. Within-group and between-group differences in the interval between completion of bowel preparation and the colonoscopy could underestimate the true efficacy of the treatment groups. The ‘smallest groups first’ analysis hierarchy of secondary endpoints reduced the power to identify lesion detection rate differences between groups. Inclusion of patients undergoing colonoscopy for reasons other than screening (~50% of the mFAS set) may limit comparisons with reports focused on screening colonoscopy patients. Self-reported patient diaries with variable response rates may not be as reliable as validated patient-reported outcome questionnaires or objective measures. Finally, results may not be generalizable to patients with severe constipation, who were excluded from the study.

The study has many strengths. This study had a randomized, multicenter design and large sample sizes. All site colonoscopists were blinded to the treatment

allocation and cleansing efficacy was assessed by treatment-blinded central readers and validated cleansing scales. Both primary endpoints were evaluated using the HCS, supported by assessments using the BBPS. The hierarchical testing procedure avoided type I error associated with testing of both two experimental groups and two primary endpoints. The results of this study are also clinically relevant. High-quality cleansing in the HCS is obtained only if no additional cleaning of the colon is required during colonoscopy (in contrast to the BBPS) and may therefore facilitate the endoscopic procedure. In addition, the higher cleansing efficacy observed with the lower volume preparation is beneficial for the patient to receive a higher-quality colonoscopy.

Conclusion

In patients undergoing colonoscopy, the new 1L PEG-based bowel preparation NER1006 (PLENVU®) demonstrated a very high bowel-cleansing efficacy, which was also well-tolerated for flexible evening/morning split-dosing or morning-only dosing. Evening/morning split-dosing NER1006 provided superior overall colon cleansing versus 2LPEG in the PP population. Both NER1006 dosing regimens provided significantly higher rates of segmental high-quality cleansing, which potentially reduces the need for additional cleaning during colonoscopy.

NER1006 is the first 1L PEG-based bowel preparation, and the first low-volume bowel preparation to have demonstrated superior colon cleansing efficacy versus standard split-dosing 2L PEG + ascorbate.

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Competing interests

Raf Bisschops has received honoraria from Norgine for speaking and Advisory Board attendance. **Jonathan Manning** has received honoraria from Norgine for speaking and for Investigator Advisory Board attendance. **Lucy Clayton** and **Richard Ng Kwet Shing** are employees of Norgine. **Marco Antonio Álvarez-González** has received honoraria from Norgine for Advisory Board attendance and from Casen-Recordati for speaking and teaching. This study was funded by Norgine Ltd (Harefield, UK).

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Figures and Tables

Figure 1. Study plan

Figure 2. Patient disposition

Figure 3. Bowel cleansing efficacy according to
(A) the HCS (mFAS)
(B) the HCS (PP set)
(C) the BBPS (mFAS)
(D) mean overall and right colon BBPS scores (mFAS(cr))
(E) mean segmental HCS scores (mFAS(cr))
(F) lesion detection rates (mFAS)

Legend: LCL, one-sided 97.5% lower confidence limit for the difference between treatments.

Figure 4. Tolerance and acceptability of (A); and adherence to (B) bowel preparations among respondents to the questions in the patient diary (mFAS)

Legend: Adherence defined as ≥75% of both doses of bowel preparation taken.

Table 1. Baseline characteristics (FAS)

Table 2. Safety summary (safety set)

Table 1. Baseline characteristics (FAS)

Characteristic	**N2D (n=283)**	**N1D (n=283)**	**2LPEG (n=283)**
Sex, n (%)			
Male	120 (42.4)	131 (46.3)	144 (50.9)
Female	163 (57.6)	152 (53.7)	139 (49.1)
Age			
Years, mean (SD)	56.3 (12.0)	54.9 (13.2)	54.3 (12.5)
≤65 years, n (%)	209 (73.9)	219 (77.4)	235 (83.0)
>65 years, n (%)	74 (26.1)	64 (22.6)	48 (17.0)
Race, n (%)			
White or Caucasian	275 (97.2)	279 (98.6)	280 (98.9)
Other	8 (2.8)	4 (1.4)	3 (1.1)
BMI			
N	280	282	279
mean (SD)	27.3 (4.7)	27.1 (4.5)	26.4 (4.1)
Renal insufficiency			
N	281	281	282
Mild to moderate (creatinine clearance ≥30 – <90mL/min)	204 (72.6%)	208 (74.0%)	198 (70.2%)
None (creatinine clearance ≥90mL/min)	77 (27.4%)	73 (26.0%)	84 (29.8%)
Indication for colonoscopy			
Screening	141 (49.8)	143 (50.5)	140 (49.5)[a]

Surveillance	68 (24.0)	62 (21.9)	66 (23.3)
Diagnostic	74 (26.1)	78 (27.6)	76 (26.9%)
In-/outpatient status, n (%)			
Outpatient on Day 1	260 (91.9)	266 (94.0)	260 (91.9)
Outpatient on Day 2	260 (91.9)	264 (93.3)	259 (91.5)
Inpatient on Day 1	3 (1.1)	4 (1.4)	4 (1.4)
Inpatient on Day 2	3 (1.1)	6 (2.1)	5 (1.8)
No record of in-/outpatient status	20 (4.6)	13 (7.1)	19 (6.7)

[a]One patient in the 2LPEG group lacked data on indication for colonoscopy.

SD, standard deviation.

Table 2. Safety summary (safety set)*

	N2D (n=262)	N1D (n=269)	2LPEG (n=263)
Total number of related TEAEs, n	50 (P=0.186†)	67 (P=0.026†)	33
Patients with related TEAEs, n (%)	30 (11.5) (P=0.140‡)	40 (14.9) (P=0.009‡)	20 (7.6)
Patients with specific related TEAEs[a], n (%)			
Vomiting	10 (3.8) (P=0.054‡)	17 (6.3) (P=0.002‡)	3 (1.1)
Nausea	12 (4.6) (P=0.514‡)	13 (4.8) (P=0.515‡)	9 (3.4)
Abdominal pain[b]	2 (0.8) (P=0.450‡)	4 (1.5) (P=0.749‡)	5 (1.9)
Thirst	2 (0.8) (P=1.000‡)	5 (1.9) (P=0.450‡)	2 (0.8)
Dehydration	1 (0.4) (P=1.000‡)	4 (1.5) (P=0.373‡)	1 (0.4)
Dry mouth	3 (1.1) (P=0.124‡)	2 (0.7) (P=0.499‡)	0
Headache	0 (P=0.249‡)	2 (0.7) (P=0.683‡)	3 (1.1)
Feeling cold	0 (P=0.249‡)	1 (0.4) (P=0.368‡)	3 (1.1)
Patients with related severe TEAEs, n (%)	0	0	0
Patients with related serious TEAEs, n (%)	0	0	0

Deaths, n (%)	0	0	0

[a]Most frequently reported TEAEs (≥3 patients in any treatment group) judged ‘possibly’ or ‘probably’ related to study medication by the investigator; Medical Dictionary for Regulatory Activities preferred terms.

[b]Includes all preferred terms that contain ‘Abdominal pain’.

*P-values obtained in a post-hoc analysis: †2-sided P-value from negative binomial model fitted to the number of TEAEs the subject experienced and including treatment as a fixed effect: ‡2-sided P-value from Fisher's exact test for the difference between treatment groups.

TEAE, treatment-emergent adverse event.