Digestive and Liver Disease 51 (2019) 1671–1677

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Digestive Endoscopy

Improved high-quality colon cleansing with 1L NER1006 versus 2L polyethylene glycol + ascorbate or oral sulfate solution

Alessandro Repici[a], Emmanuel Coron[b], Prateek Sharma[c,d], Cristiano Spada[e], Milena Di Leo[a], Colin L. Noble[f], Jürgen Gschossmann[g], Ana Bargalló García[h,i], Daniel C. Baumgart[j,*]

[a] Humanitas University, Milan, Italy
[b] Centre Hospitalier Universitaire Hotel Dieu, Nantes, France
[c] Department of Gastroenterology and Hepatology, Veterans Affairs Medical Center, Kansas City, MO, USA
[d] Department of Gastroenterology and Hepatology, University of Kansas Medical Center, Kansas City, KS, USA
[e] Fondazione Policlinico Universitario A. Gemelli, Rome, Italy
[f] Western General Hospital, Edinburgh, UK
[g] Klinikum Forchheim, Forchheim, Germany
[h] Hospital de Sant Joan Despí Moisès Broggi, Sant Joan Despí, Spain
[i] Endos Medicina, Barcelona, Spain
[j] Division of Gastroenterology, University of Alberta, Edmonton, Alberta, Canada

ARTICLE INFO

Article history:
Received 10 May 2019
Accepted 30 June 2019
Available online 10 August 2019

Keywords:
Bowel preparation
Colonoscopy
Colorectal cancer
Endoscopy

ABSTRACT

Background & aims: Colonoscopy requires bowel cleansing for gut mucosa visualization; high-quality cleansing facilitates lesion detection. NER1006 is a 1L polyethylene glycol (PEG) bowel preparation. This post hoc analysis of two randomized trials investigated cleansing efficacy assessed, as in clinical practice, by site endoscopists.

Methods: Patients received NER1006, 2L PEG + ascorbate (2LPEG), or oral sulfate solution (OSS) as a 2-day evening/morning regimen (N2D) or NER1006 morning-only dosing (N1D). Treatment-blinded site endoscopists assessed cleansing using the Harefield Cleansing Scale (HCS). Analyses were conducted in a modified full analysis set, including (mFAS; n = 1378) or excluding (mFAS2; n = 1319) imputed failures, and in patients with 100% treatment adherence (mFAS100; n = 1047). Overall cleansing success (HCS grade A/B), overall high-quality cleansing (HCS grade A), and high-quality segments (HCS 3–4) per treatment population were analyzed.

Results: Overall cleansing success was higher with N2D than 2LPEG (92.7–97.5% vs. 87.9–93.0%), and more patients had overall high-quality cleansing with N2D and N1D than 2LPEG (68.0–72.1% and 64.0–68.4% vs. 50.7–56.0%). Without imputed failures, N2D delivered more overall high-quality cleansing than OSS (74.5–77.3% vs. 67.8–69.8%). More high-quality segments were demonstrated with N2D and N1D versus 2 LPEG (82.5–87.1% and 79.4–84.4% vs. 70.4–76.3%) and with N2D versus OSS (82.7–89.5% vs. 78.1–84.4%).

Conclusion: When assessed by site endoscopists, NER1006 delivers greater high-quality cleansing than 2LPEG or OSS.

1. Introduction

Colonoscopy for colorectal cancer (CRC) screening reduces CRC incidence and mortality and has been widely adopted as a means to reduce morbidity and mortality from CRC [1–3]. To ensure that pre-cancerous and cancerous lesions can be detected, full visualization of the colonic mucosa during colonoscopy is required. This depends on effective pre-procedural bowel preparation [4–7]. Bowel preparations typically balance cleansing efficacy and tolerability by volume adjustment; high volume has historically been considered most effective; however, it can be difficult to tolerate for some patients. An additional selection criterion for bowel preparations includes safeguarding the patient's nutritional status. The

* Corresponding author at: Division of Gastroenterology, Zeidler Ledcor Centre, 8540 112th Street NW, University of Alberta, Edmonton, Alberta, T6G 2X8, Canada.
E-mail address: baumgart@ualberta.ca (D.C. Baumgart).

https://doi.org/10.1016/j.dld.2019.06.026

time period for the overall bowel preparation process often requires dietary control and fasting, which can be harmful to frail patients [8]. Preference should, therefore, be given to effective cleansers that minimize fasting periods [8].

The US Multi-Society Task Force recognizes that efficacy is of primary importance and recommends a benchmark of 85% adequate bowel preparation [9]. The European Society for Gastrointestinal Endoscopy recommends a minimum of ≥90% and a target of ≥95% adequate bowel preparation for colonoscopies [10]. No guidelines address high-quality cleansing, but a growing body of evidence now suggests that adenoma detection rates are associated with CRC rates and that detection of polyps, adenomas, and sessile or serrated polyps may increase with high-quality colon cleansing [6,11–17].

The Harefield Cleansing Scale (HCS) is a validated scale for bowel cleansing assessment [18]. Successful bowel preparation means that the least clean segment has, at most, only residual opaque liquid or semi-solid stool left that is fully removable with appropriate suction (score 2) [18]. Bowel preparation that results in visualization of the mucosal surface after appropriate suction is deemed adequate for the detection of adenomas and advanced adenomas [5,10]. The HCS includes two high-quality segmental cleansing scores, achievable only if no washing is required: score 3, which allows for clear liquid to be present, and score 4, which requires an empty and clean colon segment.

Switching to a better bowel preparation remains perhaps the easiest measure to undertake for rapid quality improvements in colonoscopy. NER1006 (PLENVU®, a registered trademark of the Norgine group of companies) is the first 1L polyethylene glycol (PEG) bowel preparation. It was recently approved in Europe and the USA. The low reconstituted volume of NER1006 is achieved by increasing the ascorbate components, relative to previous 2L PEG and ascorbate (2LPEG) preparations, and delivering them in the second dose only. The efficacy and safety of NER1006 were established in three Phase III clinical trials. Cleansing was assessed by site colonoscopists and treatment-blinded central readers using the HCS (assessors were trained on HCS scoring before the clinical trials began). Primary efficacy endpoints were based on the central readers' scores, thereby minimizing inter-reader assessment variability [19–22]. However, in real-world clinical practice, site endoscopists assess the level of bowel cleansing before making clinical decisions.

This post hoc analysis of two of the three NER1006 Phase III trials was conducted to examine the rates of successful and high-quality cleansing on the HCS, as scored by the treatment-blinded site endoscopists. This analysis better reflects the real-world cleansing performance of NER1006 versus current alternatives such as 2LPEG (MOVIPREP®, Norgine Ltd, Harefield, UK; assessed in the MORA trial) and oral sulfate solution (OSS; SUPREP®, Braintree Laboratories, Braintree, MA, USA; assessed in the NOCT trial). These two comparators are both widely used and known for their high cleansing efficacy [23–27]. For a robust assessment of comparative cleansing efficacy, three complementary efficacy measures were analyzed: first, the patient-level rates of standard HCS overall colon cleansing success; then, the patient-level rate of overall high-quality cleansing; finally, the rate of segments cleansed at high-quality across the patient population ('population-level').

2. Methods

2.1. Patients

Patients included in the MORA and NOCT trials were males and females aged 18–85 years who required a screening, surveillance, or diagnostic colonoscopy. Inclusion and exclusion criteria were near-identical across the trials and have been described previously [19,20]. The only difference was in the MORA trial in which patients with up to moderate renal insufficiency were permitted to participate due to the established safety of the PEG-based comparator product in such patients [23].

To facilitate comparisons with published primary trial results, the efficacy endpoints were first analyzed in the original primary analysis set called the modified full analysis set (mFAS), using the site endoscopists' HCS scores, as opposed to central readers. The mFAS included all randomized patients except those who failed to meet the eligibility criteria and also did not receive any study drug according to their patient diary. The second analysis was performed in a subset of the mFAS, the mFAS2, in patients with documented HCS grades (i.e., excluding patients with missing colonoscopy data who were imputed as failures). The mFAS2 reflects cleansing performance as seen by endoscopists in the clinic by only including patients who actually underwent a colonoscopy with bowel cleansing assessment. Thirdly, the efficacy analysis was refined in a further subset of mFAS patients, the mFAS100, with self-reported 100% treatment adherence (i.e., they took both bowel preparation doses and all additional clear fluids). These patients also had fully documented segmental HCS scores. As per the label, additional clear fluid intake was mandatory for NER1006 and OSS and strongly recommended for 2LPEG.

2.2. Study designs

The two trials were Phase III, multicenter, randomized, endoscopist- and central reader-blinded, actively controlled trials conducted in Europe and the US (MORA: NCT02273167; NOCT: NCT02254486) [19,20]. All patients provided written informed consent. In the MORA study, a total of 849 patients were randomly assigned in a 1:1:1 ratio to receive: (i) NER1006 as an evening/morning split-dosing regimen (N2D); (ii) NER1006 as a morning-only dosing regimen (N1D); (iii) 2LPEG administered as an evening/morning split-dosing regimen [20]. In NOCT, 621 patients were randomly assigned in a 1:1 ratio to receive either NER1006 or OSS, each administered as an evening/morning split-dosing regimen. The comparators were administered as per their labels: 2LPEG allowed for meals, including light dinner, on the day before the colonoscopy, but OSS permitted only breakfast the day prior to the procedure. Both NER1006 regimens permitted light breakfast and light lunch, and N1D permitted a light dinner.

2.3. Assessments

The HCS was used for efficacy endpoint assessments and post hoc analyses (Supplementary Table S1). Overall successful cleansing is an HCS grade of A or B, with all segments at a score 2 or higher on the HCS segmental score scale 0–4. High-quality, grade A on the HCS, requires all segments to be scored as 3 or 4. A failure is defined as an HCS grade C or D. In these post hoc analyses, the treatment-blinded site endoscopists' HCS scores were analyzed to determine first the rate of overall successful cleansing, and then the overall rate of high-quality cleansing achieved in the respective patient treatment groups. A further measure of high-quality cleansing was also analyzed: the rate of achievement of high-quality cleansing (HCS segmental score 3 or 4) at the segment population level. Each of these three endpoints was assessed in the mFAS, mFAS2, and mFAS100 for each study.

2.4. Statistics

All authors had access to the study data and have reviewed and approved the final manuscript. All analyses were carried out using the statistical package R v3.4.2 (The R Foundation, 2015). For each trial, patient- and segment-level data were extracted, and site endoscopists' HCS grades/scores were documented, according to

Table 1
Patient characteristics in mFAS100.

	MORA			NOCT	
	N2D	N1D	2LPEG	N2D	OSS
Patients, N	204	193	200	225	225
Sex, n (%)	*				
F	115 (56.4)	100 (51.8)	89 (44.5)	107 (47.6)	90 (40.0)
M	89 (43.6)	93 (48.2)	111 (55.5)	118 (52.4)	135 (60.0)
Age group, n (%)	*				
≤65	152 (74.5)	148 (76.7)	167 (83.5)	187 (83.1)	183 (81.3)
>65	52 (25.5)	45 (23.3)	33 (16.5)	38 (16.9)	42 (18.7)
Race, n (%)				*	
White or Caucasian	200 (98.0)	192 (99.5)	198 (99.0)	189 (84.0)	183 (81.3)
Black	3 (1.47)	1 (0.52)	0 (0)	30 (13.3)	22 (9.78)
Asian	0 (0)	0 (0)	2 (1.0)	6 (2.67)	15 (6.67)
Other	1 (0.49)	0 (0)	0 (0)	0 (0)	5 (2.22)
BMI, N:	203	193	198	225	225
Missing, n (%)	1 (0.49)	0 (0)	2 (1.0)	–	–
Mean (SD), (kg/m^2)	27.1 (4.63)	27.1 (4.20)	26.4 (4.0)	29.6 (5.51)	29.8 (6.21)
Colonoscopy indication, n (%)					
Screening	99 (48.5)	99 (51.3)	98 (49.0)	134 (59.6)	139 (61.8)
Surveillance	49 (24.0)	33 (17.1)	40 (20.0)	64 (28.4)	63 (28.0)
Diagnostic	56 (27.5)	61 (31.6)	62 (31.0)	27 (12.0)	23 (10.2)

N2D: 2-day evening/morning NER1006 regimen, N1D: morning-only NER1006 regimen, OSS: oral sulfate solution.
* The P value was <0.05 for NER1006 versus the comparator.

treatment group. The proportion of patients with overall successful or high-quality cleansing was calculated from documented overall HCS grades. The proportion of high-quality segments was calculated from documented segmental HCS scores. *P* values comparing NER1006 to the comparator bowel preparation were estimated using the one-sided Student's t-test. This test was also used to assess high-quality cleansing superiority of NER1006 versus comparator in patients with an overall cleansing failure. Cleansing success rates are reported as percentages. Missing overall efficacy data were conservatively imputed as failures in mFAS, and excluded in both mFAS2 and mFAS100. Missing segmental HCS scores were excluded in mFAS100.

3. Results

3.1. Patient characteristics and disposition

The baseline characteristics for the full analysis sets in the MORA and NOCT trials have been reported previously [19,20]. Baseline characteristics for the mFAS100 are presented in Table 1 and for the mFAS and mFAS2 in Supplementary Tables S2 and S3. In summary, baseline characteristics were comparable between the groups across the analysis populations, with the exception of N2D having 10.0–11.9% fewer men and 9.0–9.3% more elderly patients than 2LPEG in MORA. There were also minor imbalances in BMI and race between N2D and the comparators in MORA and NOCT, respectively, in mFAS2 and mFAS100. Patient disposition is presented in Fig. 1. The MORA trial mFAS100/mFAS ratios were 74% (204/275), 70% (193/275), and 74% (200/272) for N2D, N1D, and 2LPEG, respectively. In NOCT, the mFAS100/mFAS ratios were 82% (225/276) for N2D and 80% (225/280) for OSS.

3.2. Overall bowel cleansing success

The rates of endoscopist-assessed successful overall bowel cleansing across treatment groups and analysis sets are presented in Table 2. Compared to the mFAS, in mFAS2, exclusion of data imputed as failures resulted in increased rates of overall bowel cleansing success. In the mFAS2 of the MORA study, 97.0% (255/263) overall bowel cleansing success was achieved for the N2D group. The rate of successful overall bowel cleansing was significantly higher for the N2D group compared to 2LPEG in both the mFAS (92.7% [255/275] vs. 87.9% [239/272]; $P = 0.028$) and mFAS2 (97.0% [255/263] vs. 90.9% [239/263]; $P = 0.002$), whereas overall cleansing efficacy did not differ significantly between N1D and 2LPEG in either mFAS (89.5% [246/275] vs. 87.9% [239/272]; $P = 0.280$) or mFAS2 (91.1% [246/270] vs. 90.9% [239/263]; $P = 0.462$). In NOCT, there was no significant difference in overall cleansing success between N2D and OSS in the mFAS (87.3% [241/276] vs. 88.6% [248/280]; $P = 0.675$) or mFAS2 (93.1% [241/259] vs. 93.9% [248/264]; $P = 0.660$). For the MORA mFAS100, 97.5% (199/204), 93.3% (180/193), and 93.0% (186/200) of patients in N2D, N1D, and 2LPEG, respectively, achieved successful overall bowel cleansing ($P = 0.016$ N2D vs. 2LPEG). In the NOCT mFAS100, successful overall bowel cleansing was achieved by 93.8% (211/225) and 93.3% (210/225) of patients in the N2D and OSS groups, respectively, ($P = 0.424$).

Treatment-specific overall bowel cleansing failure rates indicated that N2D delivered the numerically lowest treatment group failure rates in each trial: 2.5% (5/204) in MORA and 6.2% (14/225) in NOCT. These very low failure rates were not compared statistically.

3.3. Overall high-quality bowel cleansing success

The rates of endoscopist-assessed overall high-quality bowel cleansing (grade A on the HCS) across the treatment groups and analysis sets are presented in Table 3. In MORA, the attainment of high-quality cleansing was significantly greater in both the N2D (68.0%; 187/275) and N1D (64.0%; 176/275) groups compared to 2LPEG (50.7%; 138/272) in the mFAS ($P < 0.001$ for both comparisons). Similarly, in mFAS2, 71.1% (187/263; $P < 0.001$) patients on N2D and 65.2% (176/270; $P = 0.001$) patients on N1D achieved overall high-quality cleansing success compared to 2LPEG (52.5%; 138/263). In NOCT, the rate of high-quality cleansing with N2D was significantly greater than with OSS in the mFAS2 (74.5% [193/259] vs. 67.8% [179/264]; $P = 0.045$). In the MORA mFAS100, significantly more patients achieved overall high-quality cleansing success with N2D (72.1% [147/204]; $P < 0.001$) and N1D (68.4% [132/193]; $P = 0.006$), versus 2LPEG (56.0% [112/200]). Significantly higher rates of overall high-quality cleansing were also observed with N2D versus OSS (77.3% [174/225] vs. 69.8% [157/225]; $P = 0.035$) in the NOCT mFAS100. Across both studies, when data imputed as failures were excluded, the N2D group consistently achieved rates of overall high-quality cleansing of >70%.

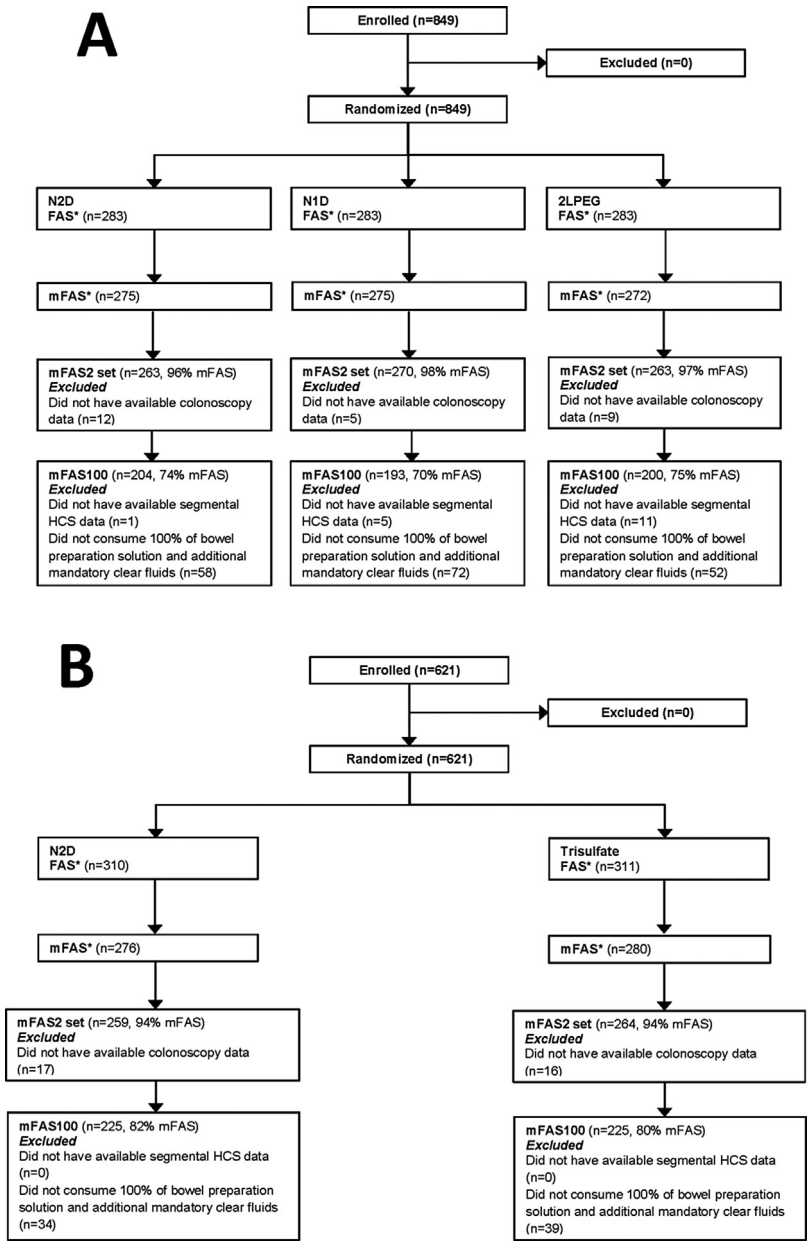

Fig. 1. Patient disposition in the MORA (A) and NOCT (B) trials.

Table 2
Overall bowel cleansing success.

	MORA			NOCT	
	N2D	N1D	2LPEG	N2D	OSS
mFAS					
%	92.7	89.5	87.9	87.3	88.6
n/N	255/275	246/275	239/272	241/276	248/280
P^*	0.028	0.28	–	0.675	–
mFAS2					
%	97.0	91.1	90.9	93.1	93.9
n/N	255/263	246/270	239/263	241/259	248/264
P^*	0.002	0.462	–	0.66	–
mFAS100					
%	97.5	93.3	93	93.8	93.3
n/N	199/204	180/193	186/200	211/225	210/225
P^*	0.016	0.459	–	0.424	–

mFAS: modified full analysis set.
mFAS2: modified full analysis set excluding imputed failures.
mFAS100: mFAS2 with segmental scorings and 100% treatment adherence.
* All *P* values are for NER1006 versus the comparator in the same trial.

Table 3
Overall high-quality bowel cleansing success.

	MORA			NOCT	
	N2D	N1D	2LPEG	N2D	OSS
mFAS					
%	68.0	64.0	50.7	69.9	63.9
n/N	187/275	176/275	138/272	193/276	179/280
P[*]	<0.001	<0.001	–	0.067	–
mFAS2					
%	71.1	65.2	52.5	74.5	67.8
n/N	187/263	176/270	138/263	193/259	179/264
P[*]	<0.001	0.001	–	0.045	–
mFAS100					
%	72.1	68.4	56	77.3	69.8
n/N	147/204	132/193	112/200	174/225	157/225
P[*]	<0.001	0.006	–	0.035	–

mFAS: modified full analysis set.
mFAS2: modified full analysis set excluding imputed failures.
mFAS100: mFAS2 with segmental scorings and 100% treatment adherence.
[*] All *P* values are for NER1006 versus the comparator in the same trial.

Table 4
High-quality segmental cleansing.

	MORA			NOCT	
	N2D	N1D	2LPEG	N2D	OSS
mFAS					
%	82.5	79.3	70.4	82.7	78.1
n/N	1134/1375	1091/1375	958/1360	1141/1380	1093/1400
P[*]	<0.001	<0.001	–	0.001	–
NNT	1.7	2.2	–	4.3	–
mFAS2					
%	86.6	82.3	74.8	88.1	82.8
n/N	1134/1310	1091/1325	958/1280	1141/1295	1093/1320
P[*]	<0.001	<0.001	–	<0.001	–
NNT	1.7	2.7	–	3.8	–
mFAS100					
%	87.1	84.4	76.3	89.5	84.4
n/N	888/1020	814/965	763/1000	1007/1125	950/1125
P[*]	<0.001	<0.001	–	<0.001	–
NNT	1.9	2.5	–	3.9	–

mFAS: modified full analysis set.
mFAS2: modified full analysis set excluding imputed failures.
mFAS100: mFAS2 with segmental scorings and 100% treatment adherence.
NNT: number needed to treat.
[*] All *P* values are for NER1006 versus the comparator in the same trial.

3.4. Segments with high-quality cleansing

The overall number of high-quality segments as a proportion of the total number of segments scored in each treatment group and analysis set is presented in Table 4. In the MORA trial, N2D and N1D achieved a significantly greater number of segments with high-quality cleansing than 2LPEG in both the mFAS (82.5% [1134/1375] and 79.3% [1091/1375] vs. 70.4% [958/1360]; $P<0.001$ for both) and mFAS2 populations (86.6% [1134/1310] and 82.3% [1091/1325] vs. 74.8% [958/1280]; $P<0.001$ for both). The N2D group had the highest number of segments that were scored three or four. In the mFAS100, the MORA N2D and N1D populations achieved 87.1% (888/1020) and 84.4% (814/965) segments with high-quality cleansing, while 2LPEG achieved 76.3% (763/1000)($P<0.001$ for both vs. 2LPEG).

Similarly in NOCT, N2D achieved significantly greater numbers of high-quality segments than OSS in both the mFAS (82.7% [1141/1380] vs. 78.1% [1093/1400]; $P=0.001$) and mFAS2 (88.1% [1141/1295] vs. 82.8% [1093/1320]; $P<0.001$) populations. In the mFAS100 of NOCT, the N2D group achieved 89.5% (1007/1125) segments with high-quality cleansing, while in OSS, it was 84.4% (950/1125; $P<0.001$).

4. Discussion

We analyzed the relative colon-cleansing efficacy of the 1L NER1006 versus two alternatives that are known for their high cleansing efficacy. This post hoc analysis explored the attainment of overall and high-quality bowel cleansing success at the patient and segment population levels. Bowel cleansing success in the mFAS population was comparable to that of the central readers in this analysis set, which has been reported previously [19,20]. In the current analysis, while overall cleansing success rates were high for all treatments in both trials, N2D distinguished itself with a higher overall success rate versus 2LPEG in all three analysis sets. While the lack of significance with N1D versus 2LPEG may appear surprising, the result is consistent with clinical guidelines; same-day dosing is typically less effective than overnight split dosing [28]. Even so, N1D still improved high-quality cleansing versus 2LPEG.

Overall high-quality cleansing efficacy (HCS grade A) was also notably higher in patients receiving N2D versus 2LPEG or OSS. The difference reached significance versus OSS when imputed failures were excluded, as in mFAS2, and it was even more marked in the 100% adherence group, mFAS100. N1D demonstrated significantly improved high-quality cleansing efficacy vs. 2LPEG in all three populations, mFAS, mFAS2, and mFAS100. In both trials, in the 100%

adherence group, N2D achieved greater than 70% HCS grade A success, a level that was not achieved by 2LPEG or OSS. In MORA, N1D achieved 68% HCS grade A success, significantly higher than the 56% achieved by 2LPEG. The greater high-quality cleansing efficacy of both N2D and N1D vs. comparators was also reflected at the segmental level for all analyses.

User-friendliness was not a focus for the current analysis, however, on the day before the colonoscopy, N2D may present an increased patient benefit compared to OSS by permitting both breakfast and lunch; N1D also allowed for a light dinner. Apart from convenience, avoidance of unnecessary fasting periods may be beneficial to groups of patients who have difficulty tolerating extended fasting [8].

This post hoc analysis presented cleansing quality assessment by site endoscopists, rather than by central readers as in the primary analyses. Central readers score cleansing quality more strictly than site endoscopists, which is useful for academic and regulatory purposes [29]. However, central readers are not used routinely in clinical practice; therefore, this analysis may better reflect the real-world performance of the respective treatments.

These post hoc analyses have several strengths. Based on two randomized Phase III clinical trials with near-identical study design, these analyses evaluated comparative efficacy in refined data sets; for instance, all patients in the mFAS100 had documented segmental cleansing scores and 100% adherence rates. This enabled a true comparative efficacy analysis between bowel preparations when used as per the label.

The limitations of the analyses presented here include their post hoc nature as well as the potential for greater variability, in terms of inter-reader assessments, for site endoscopists compared to central readers [22]. In addition, imbalances in certain baseline patient characteristics in the N2D group versus comparator bowel preparations were observed in both the trials; with observed differences in MORA in the gender and age grouping of patients and differences in race observed in NOCT. Another limitation is the different meals the patients received in the NOCT trial. This may have been expected to disadvantage the cleansing performance of NER1006 as the food was permitted closer to the initiation of bowel preparation dosing. The time-lapse from the end of treatment to start of colonoscopy was monitored and documented, but not controlled, and was not a factor in these post hoc analyses.

In conclusion, in patients with HCS scores assessed by site endoscopists, NER1006 delivered more overall high-quality, HCS grade A, cleansing successes than 2LPEG or OSS. This difference was most evident at 100% treatment adherence, indicating a dose-dependent response. Such compelling results encourage future clinical trial assessment of a formal hypothesis on high-quality cleansing superiority of NER1006 versus 2LPEG or OSS. Among patients who took N2D, more than 7 out of 10 patients achieved overall high-quality cleansing — reproducibly in two randomized controlled trials. NER1006 delivered more high-quality colon segments than 2LPEG or OSS. NER1006 thus effectively supports cleansing success, facilitating lesion detection, in patients undergoing colonoscopy.

Conflict of interest statement

AR has received research grants from Norgine. EC has served as a consultant for Fujifilm, Mauna Kea Technologies, and Medtronic, and has received speaker's fees from Cook, Moly-Spindler, Olympus, and Norgine. PS has served as a consultant for Boston Scientific and received grants from CDx Labs, US Endoscopy, Medtronic. CS has served as a consultant for Medtronic, Norgine, Alfa Sigma, Corporate Health, and NISO Biomed. MDL has no relevant disclosures. CN has received support for attending the conference from Norgine. JG has been on the speaker list for Norgine and has served on Norgine advisory boards. ABG has no relevant disclosures. DB has no conflicts of interest to disclose regarding this manuscript.

Funding

The studies reported in this publication were funded by Norgine. ClinicalTrials.gov: NCT02273167 and NCT02254486.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.06.026.

References

[1] Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. BMJ 2014;348:g2467.
[2] Lin OS, Kozarek RA, Cha JM. Impact of sigmoidoscopy and colonoscopy on colorectal cancer incidence and mortality: an evidence-based review of published prospective and retrospective studies. Intest Res 2014;12:268–74.
[3] Nishihara R, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095–105.
[4] Oh CH, Lee CK, Kim JW, Shim JJ, Jang JY. Suboptimal bowel preparation significantly impairs colonoscopic detection of non-polypoid colorectal neoplasms. Dig Dis Sci 2015;60:2294–303.
[5] Clark BT, Protiva P, Nagar A, Imaeda A, Ciarleglio MM, Deng Y, et al. Quantification of adequate bowel preparation for screening or surveillance colonoscopy in men. Gastroenterology 2016;150:396–405, quiz e14–15.
[6] Clark BT, Laine L. High-quality bowel preparation is required for detection of sessile serrated polyps. Clin Gastroenterol Hepatol 2016;14:1155–62.
[7] Anderson JC, Butterly LF, Robinson CM, Goodrich M, Weiss JE. Impact of fair bowel preparation quality on adenoma and serrated polyp detection: data from the New Hampshire colonoscopy registry by using a standardized preparation-quality rating. Gastrointest Endosc 2014;80:463–70.
[8] Nunes G, Barata AT, Santos CA, Patita M, Fonseca J. Nutritional deficiency during colonoscopy preparation: the forgotten iatrogeny. Rev Esp Enferm Dig 2018;110:285–91.
[9] Johnson DA, Barkun AN, Cohen LB, Dominitz JA, Kaltenbach T, Martel M, et al. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the U. S. multi-society task force on colorectal cancer. Gastrointest Endosc 2014;80:543–62.
[10] Kaminski MF, Thomas-Gibson S, Bugajski M, Bretthauer M, Rees CJ, Dekker E, et al. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) quality improvement initiative. Endoscopy 2017;49:378–97.
[11] Pontone S, Hassan C, Maselli R, Pontone P, Angelini R, Brighi M, et al. Multiple, zonal and multi-zone adenoma detection rates according to quality of cleansing during colonoscopy. United Eur Gastroenterol J 2016;4:778–83.
[12] Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370:1298–306.
[13] Kaminski MF, Wieszczy P, Rupinski M, Wojciechowska U, Didkowska J, Kraszewska E, et al. Increased rate of adenoma detection associates with reduced risk of colorectal cancer and death. Gastroenterology 2017;153:98–105.
[14] Fischbach W, Elsome R, Amlani B. Characteristics of right-sided colonic neoplasia and colonoscopy barriers limiting their early detection and prognosis: a review of the literature. Expert Rev Gastroenterol Hepatol 2018;12:585–96.
[15] Hassan C, Bisschops R, Heimanson Z, Amlani B, Epstein M. Tu1074 Impact of cleansing quality using the Harefield Cleansing Scale and polyp and adenoma detection rates: a post hoc analysis of three phase 3 randomized trials. Gastrointest Endosc 2018;87:AB521–2.
[16] Hassan C, Manning J, Amlani B, Epstein M. High-quality colon cleansing improves polyp and adenoma detection rates: post hoc analysis of 1749 patients in 3 randomized phase 3 clinical trials: 2017 Presidential Poster Award: 255. Am J Gasteroenterol 2017;112:S140–1.
[17] Hassan C, Manning J, Halonen J, Amlani B, Epstein M. High-quality cleansing improves lesion detection during colonoscopy compared to adequate cleansing: post hoc analysis of 1170 central-reader assessed patients in three randomised phase 3 trials. Endoscopy 2018;50:S87–8.
[18] Halphen M, Heresbach D, Gruss HJ, Belsey J. Validation of the Harefield Cleansing Scale: a tool for the evaluation of bowel cleansing quality in both research and clinical practice. Gastrointest Endosc 2013;78:121–31.
[19] DeMicco MP, Clayton LB, Pilot J, Epstein MS. Novel 1 L polyethylene glycol-based bowel preparation NER1006 for overall and right-sided colon cleansing: a randomized controlled phase 3 trial versus trisulfate. Gastrointest Endosc 2018;687:e3.

[20] Bisschops R, Manning J, Clayton LB, Ng Kwet Shing R, Álvarez-González M. Colon cleansing efficacy and safety with 1 L NER1006 versus 2 L polyethylene glycolÁ+Áascorbate: a randomized phase 3 trial. Endoscopy 2019;51:60–72.
[21] Schreiber S, Baumgart DC, Drenth JPH, Filip RS, Clayton LB, Hylands K, et al. Colon cleansing efficacy and safety with 1 L NER1006 versus sodium picosulfate with magnesium citrate: a randomized phase 3 trial. Endoscopy 2019;51:73–84.
[22] Kane SV, Ananthakrishnan AN. Toward reducing bias in clinical trials: central readers for endoscopic endpoints. Gastrointest Endosc 2016;83:198–200.
[23] Hassan C, Bretthauer M, Kaminski MF, Polkowski M, Rembacken B, Saunders B, et al. Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2013;45:142–50.
[24] Pohl J, Halphen M, Kloess HR, Fischbach W. Impact of the quality of bowel cleansing on the efficacy of colonic cancer screening: a prospective, randomized, blinded study. PLoS One 2015;10:e0126067.
[25] Moon CM, Park DI, Choe YG, Yang DH, Yu YH, Eun CS, et al. Randomized trial of 2-L polyethylene glycol + ascorbic acid versus 4-L polyethylene glycol as bowel cleansing for colonoscopy in an optimal setting. J Gastroenterol Hepatol 2014;29:1223–8.
[26] Rex DK, DiPalma JA, McGowan J, Cleveland Mv. A comparison of oral sulfate solution with sodium picosulfate: magnesium citrate in split doses as bowel preparation for colonoscopy. Gastrointest Endosc 2014;80:1113–23.
[27] Kim B, Lee SD, Han KS, Kim BC, Youk EG, Nam MJ, et al. Comparative evaluation of the efficacy of polyethylene glycol with ascorbic acid and an oral sulfate solution in a split method for bowel preparation: a randomized, multicenter phase III clinical trial. Dis Colon Rectum 2017;60:426–32.
[28] ASGE Standards of Practice Committee, Saltzman JR, Cash BD, Pasha SF, Early DS, Muthusamy VR, et al. Bowel preparation before colonoscopy. Gastrointest Endosc 2015;81:781–94.
[29] Ell C, Fischbach W, Bronisch HJ, Dertinger S, Layer P, Rünzi M, et al. Randomized trial of low-volume PEG solution versus standard PEG + electrolytes for bowel cleansing before colonoscopy. Am J Gastroenterol 2008;103:883–93.