A Phase 2 Randomized Trial of DCL-101, a Novel Pill-Based Colonoscopy Prep, vs 4L Polyethylene Glycol-Electrolyte Solution

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INTRODUCTION: **DCL-101, a novel Pill Prep, is compositionally identical to standard 4L polyethylene glycol-electrolyte solution (PEG-ELS) and delivers the salt encapsulated, with PEG 3350 coadministered as a taste-free oral solution. The aim of this study was to compare the safety, taste, and tolerability of DCL-101 with 4L PEG-ELS in outpatients preparing for colonoscopy, with a secondary objective to assess efficacy.**

METHODS: **This was a multicenter, randomized, investigator-blinded, phase 2 clinical trial of 45 adult patients undergoing outpatient colonoscopy. Patients were randomized 2:1 to either DCL-101 (3L in cohort 1; 4L in cohort 2) or 4L PEG-ELS, each administered with split dosing. Safety was assessed over 3 post-treatment clinic visits. Tolerability was measured using the Lawrance Bowel-Preparation Tolerability Questionnaire and the Mayo Clinic Bowel Prep Tolerability Questionnaire. Efficacy was determined by expert central readers, blinded to treatment, using the Ottawa Bowel Preparation Quality Scale, Boston Bowel Preparation Scale, and Aronchick scale.**

RESULTS: **Both DCL-101 doses had superior taste and tolerability relative to 4L PEG-ELS. All adverse events were grade 1 with no significant differences in adverse events among the 3 regimens. There were no significant differences in efficacy among the 3 treatments as defined by the centrally read Ottawa Bowel Preparation Quality Scale, Boston Bowel Preparation Scale, or Aronchick scores. There were no inadequate preps as judged by the site endoscopist.**

DISCUSSION: **DCL-101 Pill Prep is a novel strategy that vastly improves the taste and tolerability of PEG-ELS solutions with safety and efficacy comparable with split-dose 4L PEG-ELS solutions.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A431; http://links.lww.com/CTG/A432; and http://links.lww.com/CTG/A433.

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INTRODUCTION

Poor tolerability, suboptimal safety, and imperfect efficacy compromise currently marketed colonoscopy preparation regimens (1). This study evaluates a novel, taste-free pill-based colonoscopy preparation, DCL-101, designed to improve tolerability while maintaining safety and efficacy.

Polyethylene glycol-electrolyte solution (PEG-ELS) is the gold standard for safety and efficacy among colonoscopy preparations (prep), but is poorly tolerated because of its salty taste and its large, 4L volume (2,3). In 2000, Aronchick et al. described a sodium phosphate tablet (Visicol; Salix Pharmaceuticals, Bridgewater, NJ) that achieved bowel cleansing comparable with sodium phosphate solution and was better tolerated than both PEG-ELS and sodium phosphate solution (4). However, reports of renal failure associated with sodium phosphate products led the US Food and Drug Administration (FDA) to place a black box warning on phosphate-based bowel purgatives in 2008 (5). Technology reviews by the American Society for Gastrointestinal Endoscopy and the European Society for Gastrointestinal

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Endoscopy recommend against its routine use because of the hazard to patients (1,6).

A recent meta-analysis demonstrated that PEG-ELS remains the most efficacious product for colonic cleansing before colonoscopy, despite a number of newer low-volume products introduced to the market (3). Recent guidelines for colonoscopy prep recommend that patients with risk factors for a poor prep or with renal or congestive heart failure receive 4L PEG-ELS rather than a low-volume prep (7). A split-dose regimen has decreased complaints about the volume of PEG-ELS, but complaints about the unpleasant taste persist (8,9).

The disagreeable taste of PEG-ELS results from the electrolyte component of the product. By contrast, the PEG 3350 component of the product is nearly tasteless. DCL-101 is an investigational combination product for colonic cleansing intended for use before colonoscopy and is made of the same components as PEG-ELS. DCL-101 addresses the unpleasant taste of PEG-ELS by encapsulating the 38.31 g of salts into 48 size 0 capsules (size 0 capsules measure 21.6-mm long by 7.6-mm diameter, comparable with a Tylenol 500-mg gel cap) and coadministering the 236 g of PEG 3350 as a dilute, essentially taste-free, 4L solution. Thus, patients are not required to drink 4 L of a poorly palatable salty solution before colonoscopy, but rather consume 36 capsules with 3 L of a solution that is practically indistinguishable from water (or 48 capsules with 4 L). Split dosing of DCL-101 requires the patient to take 18 capsules and 1.5 L (or 24 capsules and 2 L) of the taste-free liquid on 2 consecutive days.

The primary objective of this phase 2 study was to compare the safety of 3L and 4L split-dose DCL-101 to split-dose 4L PEG-ELS in patients preparing for colonoscopy, with secondary objectives to assess tolerability and bowel cleansing efficacy.

METHODS

Study design

This was a phase 2a, multicenter, investigator-blinded, randomized, active comparator, noninferiority trial designed to assess the safety, tolerability, and efficacy of split-dose 3L or 4L DCL-101, as compared to split-dose 4L PEG-ELS (GoLYTELY; Braintree Laboratories, Braintree, MA) in healthy outpatients preparing for elective colonoscopy. Patients were recruited from 5 independent practices in California and North Carolina with organized clinical research programs. Cohort 1 of the study comprised 15 patients assessing the safety of 3L DCL-101 compared with control, and cohort 2 comprised 30 patients assessing the safety of 4L DCL-101 compared with control. A Data Safety Monitoring Board (DSMB), composed of 3 independent medical professionals with experience in drug safety evaluation, was assembled for reviews after cohort 1 and after cohort 2. The Western Institutional Review Board provided its initial approval on July 1, 2016.

In cohort 1, 15 patients were randomized 2:1 using concealed allocation through an Interactive Web Response System to either split-dose 3L DCL-101 or standard split-dose 4L PEG-ELS. After a successful DSMB review, an additional 30 patients (cohort 2) were randomized 2:1 using the same process to either split-dose 4L DCL-101 or standard split-dose 4L PEG-ELS (Figure 1). A third cohort was planned, to assess efficacy further, using the centrally read Ottawa Bowel Preparation Quality Scale (OBPQS) as the primary endpoint. The study was not extended to a third cohort because of concerns with the accuracy of the OBPQS in a centrally read format.

The total study duration for all cohorts was up to 60 days. There was a 3- to 30-day screening and randomization phase, a 2-day treatment phase, and a 7-day follow-up phase. An additional follow-up clinic visit was required 30 days after the study colonoscopy for any patient with an ongoing treatment-related adverse event at the end of the 7-day follow-up.

Study population

All participants provided informed consent before any study procedures. The study enrolled healthy adult outpatients aged 18–75 years requiring routine colonoscopy for the indication of colon cancer screening or surveillance. Exclusion criteria included ileus or suspected bowel obstruction, bowel perforation, previous alimentary tract surgery, significant gastroparesis or gastric outlet obstruction, acute colitis, toxic megacolon, inflammatory bowel disease, congestive heart failure, pregnant or lactating women, clinically significant electrolyte abnormalities, renal or hepatic insufficiency,

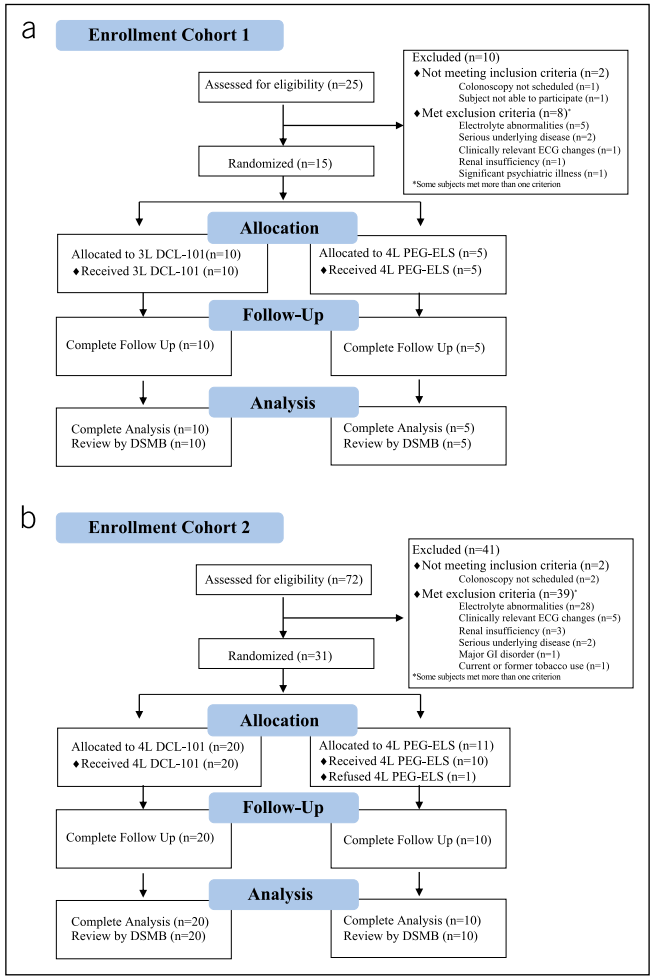

Figure 1. CONSORT diagram for (**a**) cohort 1 and (**b**) cohort 2. ECG, electrocardiogram; GI, gastrointestinal; PEG-ELS, polyethylene glycol-electrolyte solution.

Table 1. Study demographics

	Cohort 1		Cohort 2	
	DCL-101 3L	PEG-ELS 4L	DCL-101 4L	PEG-ELS 4L
n	10	5	20	11
Gender, n (%)				
Female	5 (50)	4 (80)	12 (60)	7 (63.6)
Male	5 (50)	1 (20)	8 (40)	4 (36.4)
Age (y)				
Mean (SD)	53.3 (8.49)	56.0 (4.95)	56.0 (7.88)	59.6 (7.67)
Median (IQR)	53.5 (50.5–56.5)	56.0 (53.0–58.0)	56.0 (50.8–60.5)	58.0 (55.0–63.0)
Race, n (%)				
Asian	0 (0.0)	1 (20)	1 (5)	0 (0.0)
Black or African American	1 (10)	0 (0.0)	3 (15)	2 (18.2)
White	9 (90)	4 (80)	16 (80)	9 (81.8)
Ethnicity, n (%)				
Hispanic or Latino	3 (30)	1 (20)	1 (5)	0 (0.0)
Not Hispanic or Latino	7 (70)	4 (80)	19 (95)	11 (100)
Weight (kg)				
Mean (SD)	78.2 (17.97)	68.4 (7.41)	87.2 (19.04)	86.1 (19.8)
Median (IQR)	73.5 (65.3–88.9)	65.3 (65.3–67.6)	85.1 (76.4–102)	81.2 (76.0–89.8)
BMI				
Mean (SD)	27.5 (4.84)	25.5 (3.19)	30.8 (7.82)	31.4 (6.01)
Median (IQR)	26.6 (23.5–30.6)	26.9 (23.3–27.2)	29.4 (26.8–33.5)	30.7 (26.7–34.1)
Highest level of education, n (%)				
High school diploma/GED	0 (0.0)	0 (0.0)	4 (20.0)	1 (9.1)
Some college	5 (50.0)	2 (40.0)	5 (25.0)	2 (18.2)
Associate degree	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)
College diploma	3 (30.0)	1 (20.0)	4 (20.0)	0 (0.0)
Bachelor degree	0 (0.0)	2 (40.0)	2 (10.0)	3 (27.3)
Graduate degree	2 (20.0)	0 (0.0)	5 (25.0)	3 (27.3)

BMI, body mass index; GED, General Educational Development certification; IQR, interquartile range; PEG-ELS, polyethylene glycol-electrolyte solution.

impaired gag reflex, and those predisposed to aspiration. Former or current smoking was an exclusion criterion because cigarette smoking can affect taste, a component of the tolerability endpoint.

Treatments, dosage, and administration

All colon preparations were self-administered by patients over 2 days (split dosing) and based on specific printed and video instructions provided. All patients were instructed to consume a low-residue breakfast the day before colonoscopy followed by a clear liquid diet for lunch and to begin the colonoscopy prep at 6 PM. Prep solution was to be consumed at a rate of 1 L per hour. Patients could consume water or sugar-free clear liquid if they felt thirsty during the process up until 2 h before their colonoscopy, consistent with clinical practice. Patients kept a treatment diary noting when they took their study treatment, their compliance with low-residue/clear liquid diet, whether they read the included Frequently Asked Questions (FAQ) sheet, and whether they watched the instructional video. Subjects also recorded all symptoms and adverse events throughout the study. Patients were required to bring their patient diary to each study visit along with all used and unused study treatment containers.

Study outcome measures

Safety was the primary endpoint of this study and was assessed over the course of multiple patient clinic visits including screening, the day of colonoscopy, 1–2 days after colonoscopy, and 7 days after colonoscopy. Data collected at each clinic visit included vital signs with orthostatic blood pressure measurement, blood chemistries, and urinalysis. An electrocardiogram recording was performed at screening, on the day of colonoscopy and 7 days after receiving study drug. Patient diaries were reviewed at each clinic visit. Adverse events were graded on the Common Terminology Criteria for Adverse Events, a 5-point severity scale with grade 1 equal to

Table 2. Adverse events

	Cohort 1			Cohort 2		
Adverse event, n (%)	DCL-101 3L (n = 10)	PEG-ELS 4L (n = 5)	*P* value[a]	DCL-101 4L (n = 20)	PEG-ELS 4L (n = 10)	*P* value[a]
Abdominal cramps	4 (40.0)	3 (60.0)	0.61	2 (10.0)	3 (30.0)	0.30
Abdominal distension	0 (0.0)	0 (0.0)	N/A	2 (10.0)	2 (20.0)	0.58
Abdominal pain	0 (0.0)	0 (0.0)	N/A	0 (0.0)	1 (10.0)	0.33
Bloating	4 (40.0)	4 (80.0)	0.28	4 (20.0)	5 (50.0)	0.12
Chills	0 (0.0)	0 (0.0)	N/A	2 (10.0)	0 (0.0)	0.54
Dehydration	0 (0.0)	0 (0.0)	N/A	1 (5.0)	0 (0.0)	1.00
Dizziness	0 (0.0)	2 (40.0)	0.10	1 (5.0)	1 (10.0)	1.00
Dread	0 (0.0)	0 (0.0)	N/A	0 (0.0)	1 (10.0)	0.33
Elevated anion gap	0 (0.0)	0 (0.0)	N/A	1 (5.0)	1 (10.0)	1.00
Elevated creatine kinase	1 (10.0)	0 (0.0)	1.00	0 (0.0)	1 (10.0)	0.33
Elevated calcium	0 (0.0)	0 (0.0)	N/A	1 (5.0)	1 (10.0)	1.00
Elevated potassium	0 (0.0)	0 (0.0)	N/A	1 (5.0)	0 (0.0)	1.00
Elevated sodium	0 (0.0)	0 (0.0)	N/A	2 (10.0)	1 (10.0)	1.00
Elevated total bilirubin	0 (0.0)	0 (0.0)	N/A	0 (0.0)	1 (10.0)	0.33
Elevated uric acid	0 (0.0)	0 (0.0)	N/A	0 (0.0)	1 (10.0)	0.33
Excessive thirst	3 (30.0)	3 (60.0)	0.33	4 (20.0)	2 (20.0)	1.00
Foggy feeling in head	0 (0.0)	0 (0.0)	N/A	1 (5.0)	0 (0.0)	1.00
Gas	0 (0.0)	0 (0.0)	N/A	1 (5.0)	3 (30.0)	0.10
Gastric fullness	3 (30.0)	1 (20.0)	1.00	5 (25.0)	5 (50.0)	0.23
Gurgling in stomach	0 (0.0)	0 (0.0)	N/A	1 (5.0)	0 (0.0)	1.00
Headache	1 (10.0)	2 (40.0)	0.24	2 (10.0)	3 (30.0)	0.30
Heartburn	0 (0.0)	0 (0.0)	N/A	1 (5.0)	0 (0.0)	1.00
Nausea	3 (30.0)	2 (40.0)	1.00	14 (70.0)	7 (70.0)	1.00
Sleep disturbance	5 (50.0)	2 (40.0)	1.00	4 (20.0)	5 (50.0)	0.12
Unpleasant taste	2 (20.0)	4 (80.0)	0.09	4 (20.0)	6 (60.0)	0.04
Vomiting	0 (0.0)	0 (0.0)	N/A	4 (20.0)	0 (0.0)	0.27
Weakness	0 (0.0)	0 (0.0)	N/A	1 (5.0)	0 (0.0)	1.00

N/A, not applicable; PEG-ELS, polyethylene glycol-electrolyte solution.
[a]*P* value from the Fisher exact test.

"mild" and grade 5 equal to "death." Serious adverse events were defined as events that are life-threatening, lead to hospitalization, or cause permanent injury or death.

Secondary endpoints included tolerability and efficacy. Tolerability was measured using 2 validated colonoscopy preparation tolerability scales, the Bowel-Preparation Tolerability Questionnaire by Lawrance et al. (Lawrance Instrument) and the Mayo Clinic Bowel Prep Tolerability Questionnaire (Mayo Instrument) (10,11). The Lawrance Instrument is a validated questionnaire asking patients to score 9 symptoms during bowel preparation on a 5-point Likert scale. These Symptom Scores are summed for all 9 symptoms to arrive at an aggregate tolerability score (ATS), with a lower ATS indicating better tolerability (10). The range of published ATS values is a mean of 8.0–8.5 for PEG-ELS and a mean of 5.2–5.7 for sodium picosulfate-magnesium citrate solution (10,12).

The Mayo Instrument is a validated questionnaire containing 8 items addressing tolerability, ability to consume the entire dose, and willingness to use again. Patients are also asked to score 7 symptoms during bowel preparation on a 4-point Likert scale, which are averaged to determine a Symptom Score. The median published Symptom Score is 1.7 (interquartile range [IQR] 1.4–2.1), with higher Symptom Scores indicating poorer tolerability. The authors of the Mayo Instrument did not find evidence of differences in Symptom Scores according to the type of prep used among patients taking PEG-ELS, 2L PEG-ELS with ascorbic acid (Moviprep; Norgine, Amsterdam, the Netherlands), and PEG 3350 (Miralax; Bayer Pharmaceuticals, Berlin, Germany) (11).

Apprehension about the bowel prep is a significant barrier to patient compliance with screening colonoscopy; so, a small panel of exploratory survey questions assessed patient perceptions of taste and dread as measures of tolerability (13,14).

Table 3. Median Lawrance Tolerability Scores

	Cohort 1			Cohort 2		
	DCL 3L (n = 10)[a]	PEG-ELS 4L (n = 5)[a]	*P* value[b]	DCL 4L (n = 20)[a]	PEG-ELS 4L (n = 10)[a]	*P* value[b]
Unpleasant taste	0 (0–0)	2 (2–3)	0.0050	0 (0–0.5)	2 (1–2)	<0.0001
Excessive thirst	0 (0–2)	1 (0–1)	1.00	0 (0–1)	1.5 (0–2)	0.07
Nausea	0 (0–1)	0 (0–2)	0.62	0 (0–1)	0 (0–1)	0.51
Vomiting	0 (0–0)	0 (0–0)	1.00	0 (0–0)	0 (0–0)	0.38
Bloating	0 (0–1)	1 (1–2)	0.05	0 (0–1)	1.5 (1–2)	0.026
Abdo pain/cramps	0 (0–1)	1 (0–1)	0.58	0 (0–0)	1 (0–2)	0.030
Headache	0 (0–1)	1 (0–2)	0.27	0 (0–1.5)	0 (0–2)	0.78
Dizziness	0 (0–0)	0 (0–1)	0.10	0 (0–0)	0 (0–0)	1.00
Sleep disturbance	0 (0–1)	0 (0–0)	0.51	0 (0–1)	1.5 (0–3)	0.11
Aggregate Tolerability Score (ATS) (lower ATS is better)	1 (1–6)	5 (4–10)	0.06	4.5 (0.5–7.5)	8 (4–14)	0.037
Did you miss work because of the preparation?			1.00			1.00
Yes	2 (20%)	1 (20%)		5 (25%)	2 (20%)	
No	8 (80%)	4 (80%)		15 (75%)	8 (80%)	
If you required a future colonoscopy, would you be willing to use the same bowl preparation again?			0.33			1.00
Yes	10 (100%)	4 (80%)		19 (95%)	9 (90%)	
No	0 (0%)	1 (20%)		1 (5%)	1 (10%)	

Scores for individual items are 0 = none, 1 = very mild, 2 = mild, 3 = moderate, and 4 = severe. Total score is the sum of the individual item scores.
PEG-ELS, polyethylene glycol-electrolyte solution.
[a]Data are presented as the sample median (interquartile range; 25th percentile–75th percentile).
[b]Data for individual items and total score were analyzed using the Wilcoxon rank-sum test. Data from the bottom 2 questions were analyzed using the Fisher exact test.

Efficacy was measured by central readers blinded to treatment, using the Aronchick scale, the Boston Bowel Preparation Scale (BBPS) (total score and dichotomized scores), and the OBPQS (4,15,16).

Statistical methods

As a phase 2a study, our primary objective was to obtain data on safety and tolerability of multiple dose levels of the investigational product. Efficacy was a secondary objective. After review of previous early-phase trials of this and other bowel preparation products, and considering the expected rate of tolerability and adverse events with the investigational product and traditional PEG-based bowel preparation, the final sample size was reviewed with the FDA and agreed on.

A modified intention-to-treat analysis was followed such that all patients who received any of the study preparation and had at least 1 postrandomization efficacy assessment were included in the analysis set. None of the included patients in cohorts 1 and 2 had any major deviations from the protocol. The Fisher exact test was used for categorical data, and the Wilcoxon rank-sum test was used for ordinal data. All P values <0.05 were considered statistically significant.

The protocol is compliant with the US Federal Policy for the Protection of Human Subjects. The Western Institutional Review Board provided its initial approval on July 1, 2016. The ClinicalTrials.gov identifier assigned for this study is NCT02910440.

RESULTS

Baseline characteristics and demographics

A total of 46 patients were randomly assigned to one of the bowel preparations. One patient withdrew after being randomized to receive PEG-ELS. Forty-five patients received study drug and completed the study in cohorts 1 and 2 (Figure 1). Enrollment began in January 2017 and was completed by October 2017. There were no clinically important differences in baseline characteristics or demographics between patients in the DCL-101 and PEG-ELS treatment groups, in either cohort 1 or cohort 2 (Table 1).

Safety

All patients were able to self-administer DCL-101 without difficulty. There were no serious adverse events. All adverse events were adjudicated as grade 1. There were no episodes of orthostatic hypotension. No significant differences were seen in adverse events among the 3 treatment regimens (Table 2). The independent DSMB gave approval for ongoing study after review of both cohorts 1 and 2.

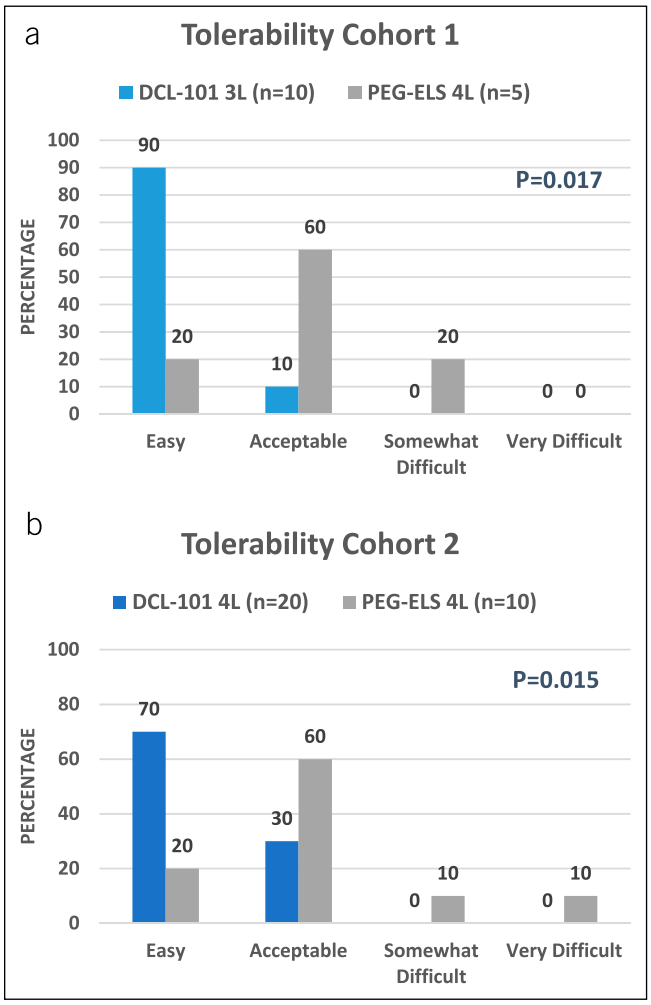

Figure 2. Mayo Questionnaire Tolerability Scores for (**a**) cohort 1 and (**b**) cohort 2. DCL-101 at both doses has superior tolerability than PEG-ELS 4L. PEG-ELS, polyethylene glycol-electrolyte solution.

Tolerability

Superior tolerability was demonstrated. In this study, the Lawrance Instrument median ATS for split-dose PEG-ELS (8.0, IQR 4–14) was comparable with previously published scores for PEG-ELS (mean 8.0–8.5) (10,12). Split-dose 4L DCL-101 had a significantly better median ATS of 4.5 (IQR 0.5–7.5; $P = 0.037$) (Table 3), lower than any previously published ATS. The median ATS for split-dose 3L DCL-101 was 1.0, but with the small size of cohort 1, it did not reach statistical significance ($P = 0.06$).

The median Mayo Instrument Symptom Score for split-dose PEG-ELS was 1.83 in each cohort, whereas the median Symptom Score for split-dose 3L DCL-101 was 1.58 and for split-dose 4L DCL-101 was 1.67 (see Table, Supplementary Digital Content 1, http://links.lww.com/CTG/A431, Mayo Bowel Prep Tolerability Scores). These differences did not reach statistical significance. DCL-101 performed significantly better than PEG-ELS on individual items in the Mayo Instrument that assessed overall tolerability (Figure 2) and willingness to use again (Figure 3). All patients receiving DCL-101 rated the tolerability of DCL-101 as acceptable or better (Figure 2). In the Mayo Instrument validation study, just 17% of patients found the prep easy to tolerate, and similarly, just 20% of patients in this study found PEG-ELS easy to tolerate (11). Conversely, 90% of patients reported 3L DCL-101 easy to tolerate ($P = 0.017$) and 70% of patients reported 4L DCL-101 easy to tolerate ($P = 0.015$) (Figure 2). In the original Mayo Instrument validation study, 55% of patients were mostly willing to use the same prep again. Similarly, 50% of patients receiving PEG-ELS in this study were mostly willing to take PEG-ELS. By contrast, 95% of patients taking 4L DCL-101 were mostly willing to take it again ($P = 0.002$) (Figure 3).

An exploratory question assessing patients' taste experience revealed that the majority (76.7%) of patients taking DCL-101 found the solution to have no taste (see Figure, Supplementary Digital Content 2, http://links.lww.com/CTG/A432, taste cohorts 1 and 2), consistent with the taste responses on both the Lawrance and Mayo instruments.

Patients reported significantly less dread taking DCL-101 compared with patients taking PEG-ELS ($P = 0.047$ for 3L DCL-101 and $P = 0.019$ for 4L DCL-101 as compared to 4L PEG-ELS) (Figure 4).

Efficacy

Efficacy was demonstrated. There were no significant differences among the 3 treatments (3L DCL-101, 4L DCL-10, and 4L PEG-ELS) as defined by the centrally read BBPS, Aronchick, or OBPQS (Table 4; and see Table, Supplementary Digital Content 3, http://links.lww.com/CTG/A433, dichotomized BBPS). There were no examinations with inadequate cleanliness as judged by the performing endoscopist at the study site. There were no differences between DCL-101 and PEG-ELS regarding cecal intubation rate, insertion time, procedure time, or cleansing time.

During the planned quality control processes of cohorts 1 and 2, set forth in the Image Review Charter, it was discovered that intra-reader correlation and inter-reader correlation of the centrally read OBPQS were both low and did not meet predetermined standards set forth in the Image Review Charter of the study. Consultation with developers of the OBPQS was not successful in remedying this issue. A second set of expert readers then underwent training, were also blinded to treatment, and did meet the predetermined standards set forth in the Image Review Charter of the study. This second set of central readers observed no differences in OBPQS scores between DCL-101 and PEG-ELS. However, the absolute OBPQS scores measured by central readers (median OBPQS 8.5) and site endoscopists (median OBPQS 3.5) were quite different. Furthermore, the centrally read OBPQS scores are quite different from previously reported endoscopist-derived OBPQS scores for PEG-ELS (17–19). Although we report the OBPQS data for the sake of completeness, we caution interpretation of the OBPQS data. Nevertheless, the BBPS and Aronchick scores behaved in a reproducible fashion, correlated with the endoscopist impressions, and are consistent with previous studies.

The centrally read OBPQS was the planned primary endpoint of cohort 3 of the submitted protocol. As we had already gained useful data from cohorts 1 and 2, we believed it more appropriate to conclude the study after cohort 2 rather than proceed to cohort 3 of the protocol with an amended, alternative primary endpoint.

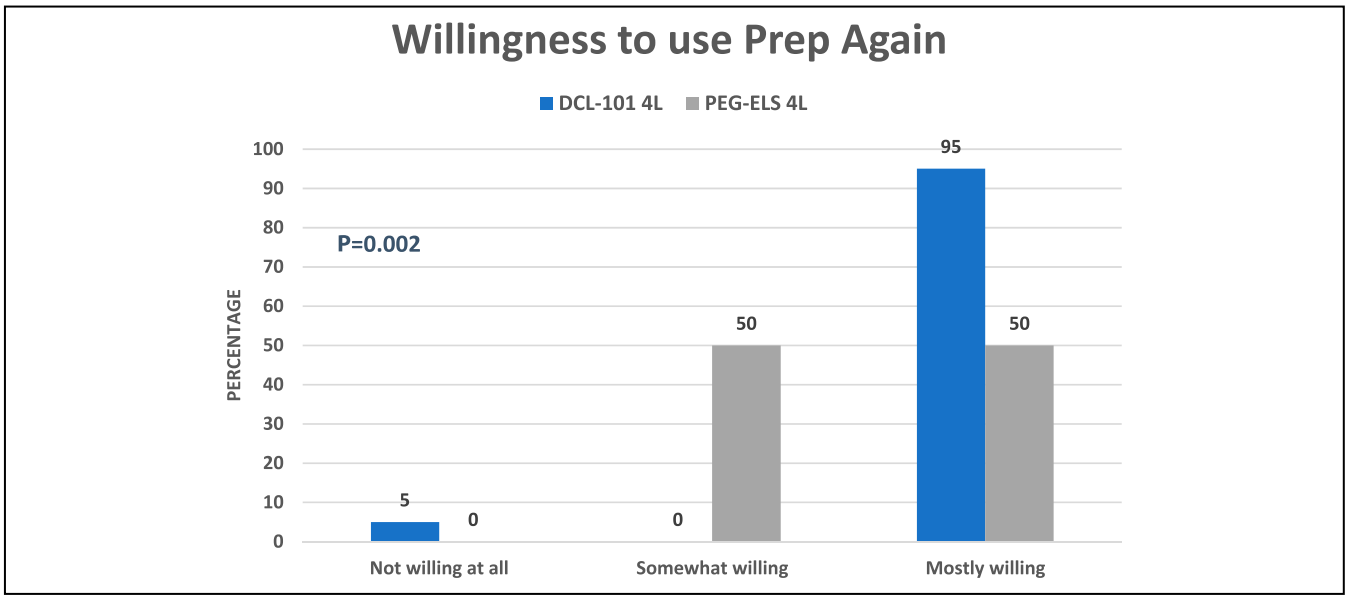

Figure 3. Mayo Questionnaire Tolerability Scores. More patients were mostly willing to use DCL-101 4L again compared with PEG-ELS 4L. PEG-ELS, polyethylene glycol-electrolyte solution.

DISCUSSION

In this phase 2a study of a novel formulated colonoscopy preparation, we found that DCL-101 at both 3L and 4L doses had superior tolerability and preliminary evidence for comparable safety and cleanliness compared with split-dose 4L PEG-ELS. A novel aspect of this study was the finding of the large impact of palatability on overall colon prep tolerability. 4L DCL-101 is compositionally identical to 4L PEG-ELS. Yet, the tolerability of a 4L prep was far superior when administered in a taste-free delivery system. So, if the taste problem is fixed, patients tolerate volume much better.

In a recent study, a novel sulfate tablet for colon cleansing, PBK-1701TC, had better tolerability compared with oral sulfate solution, further reinforcing the concept that delivering a purgative in a pill will improve tolerability compared with a salt solution (20). Improved tolerability also seems to remediate an associated common problem with colon preparation, the feeling of dread. Patients in both cohorts reported significantly less dread with DCL-101 compared with PEG-ELS.

Previous efforts to improve prep tolerability have focused on reduction of the volume of salt solution required for ingestion as well as the addition of flavoring in an attempt to mask the salty taste of these solutions. Most low-volume preps are hypertonic and require additional water intake such that the total fluid intake is 3 L or more (21,22). The hypertonic design of these low-volume preps makes dose escalation risky in difficult-to-prep patients and is not FDA-approved. The package insert for a new low-volume prep composed of PEG-ELS with ascorbic acid (Plenvu; Norgine), marketed as a 1L prep, directs patients to ingest an additional liter of water with the solution (23). Whether 1 L is an adequate amount of additional water to consume with this new prep is now a point of controversy as hypernatremia has been reported (24). It seems that colonoscopy preps have reached the safety limit of volume reduction as a strategy to improve tolerability.

There are multiple clinical scenarios where the safe administration of higher prep volume is essential and low-volume preps are inadequate. Several of the current published protocols for colonoscopy preparation of the difficult-to-prep patient all instruct the use of split-dose PEG-ELS at 4L dose or higher, not a low-volume prep (7). Indiana University published their experience with a similar protocol and reported that they prescribed 4L PEG-ELS to 40% of their patients (19). For all these patients, DCL-101 could be a much better option than what is currently advocated, i.e., 4–8 L of PEG-ELS.

In summary, DCL-101 Pill Prep is a novel strategy that vastly improves the taste and tolerability of PEG-ELS solutions. DCL-101 preserves the iso-osmotic quality of original PEG-ELS and thus allows doses of 4L and potentially greater total volumes without concerning dehydration or electrolyte imbalances. In this phase 2a study, DCL-101 seemed safe with only grade 1 adverse events and no serious adverse events. Efficacy seemed similar to split-dose 4L PEG-ELS, the benchmark for colonoscopy preparation, although the study was not formally powered to test efficacy (3).

Future development of DCL-101 will require phase 3 trials, sufficiently powered to confirm the superior characteristics demonstrated in this study. A highly tolerable, iso-osmotic colonoscopy prep such as DCL-101, which may be safe over a large range of doses, and could be dose-titrated as needed, would be a very useful tool in endoscopy.

CONFLICTS OF INTEREST

Guarantor of article: Dale R. Bachwich, MD.
Specific author contributions: Dale R. Bachwich, MD, and James D. Lewis, MD, MSCE, contributed equally to this article and are cofirst authors. D.R.B., J.D.L., and V.O.K.: conception and design; analysis and interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; and final approval of the article. B.C.J.: conception and design; analysis and interpretation of the data; critical revision of the article for important intellectual content;

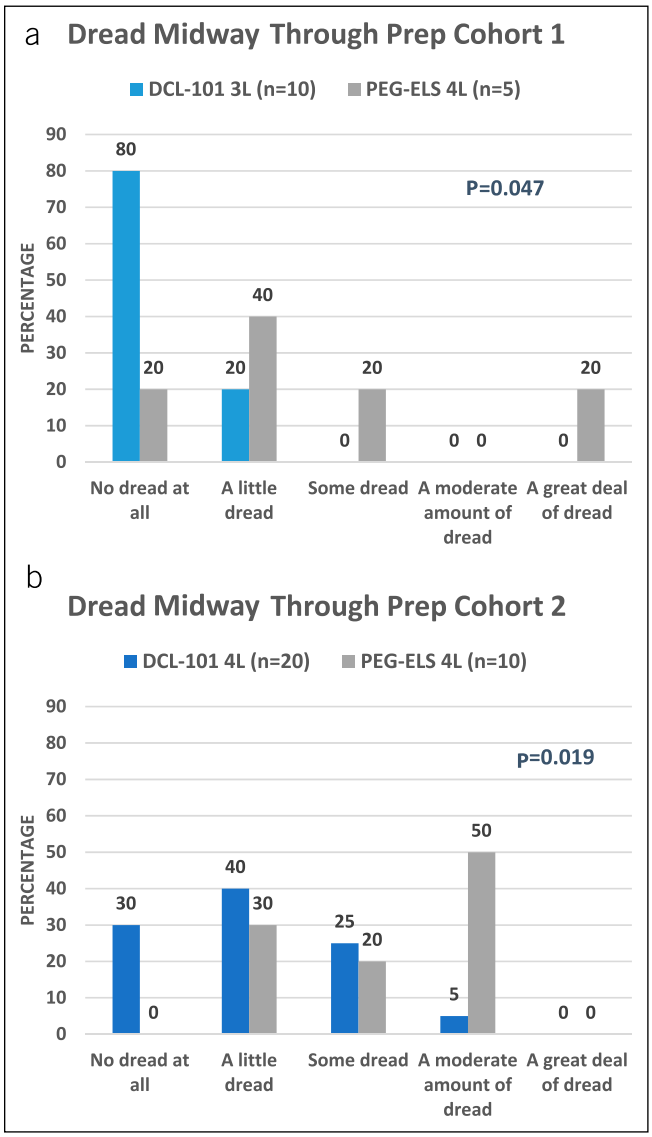

Figure 4. Exploratory question regarding dread once prep was one-half completed for (**a**) cohort 1 and (**b**) cohort 2. Patients taking DCL-101 reported less dread than those taking PEG-ELS. PEG-ELS, polyethylene glycol-electrolyte solution.

and final approval of the article. A.H.C.: analysis and interpretation of the data; critical revision of the article for important intellectual content; and final approval of the article. M.L.K.: conception and design; analysis and interpretation of the data; critical revision of the article for important intellectual content; and final approval of the article. All the authors had full access to the data during the creation of this manuscript, and all authors approved the final version of this article, including the authorship list.

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Potential competing interests: D. R. Bachwich: Shareholder, Board Member, and Executive of Dark Canyon Laboratories, LLC. J. D. Lewis: Shareholder and Advisory Board Member of Dark Canyon Laboratories, LLC. V. O. Kowal: Shareholder, Board Member, and Executive of Dark Canyon Laboratories, LLC. B. C. Jacobson: Consultant to Dark Canyon Laboratories, LLC, and Motus GI Holdings. A. H. Calderwood: Consultant to Dark Canyon Laboratories, LLC. M. L. Kochman: Shareholder and Advisory Board Member of Dark Canyon Laboratories, LLC; Consultant to Olympus, Boston Scientific, and Pentax; Shareholder and Consultant to Virgo Surgical Video Solutions.

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Table 4. Boston Bowel Preparation Scale (BBPS), Aronchick, and Ottawa Bowel Preparation Quality Scale (OBPQS) scores

	Cohort 1			Cohort 2		
Item	DCL 3L (n = 10)[a]	PEG-ELS 4L (n = 5)[a]	*P* value[b]	DCL 4L (n = 20)[a]	PEG-ELS 4L (n = 10)[a]	*P* value[b]
Aronchick scale	2.0 (1.5–2.0)	2.0 (2.0–2.0)	0.95	1.5 (1.5–2.0)	2.0 (1.5–2.0)	0.99
BBPS						
Right colon segment	2.0 (2.0–2.0)	2.0 (2.0–2.5)	0.59	2.25 (2.0–2.5)	2.25 (2.0–2.5)	0.77
Transverse colon segment	2.0 (2.0–2.5)	2.0 (2.0–2.0)	0.60	2.5 (2.0–2.5)	2.0 (2.0–2.5)	0.45
Left colon segment	2.25 (2.0–2.5)	3.0 (2.5–3.0)	0.07	2.5 (2.0–2.75)	2.5 (2.0–3.0)	0.81
Total score	6.25 (6.0–7.0)	7.0 (7.0–7.0)	0.30	7.0 (6.0–8.0)	6.75 (6.0–8.0)	0.93

Table 4. (*continued*)

Item	Cohort 1			Cohort 2		
	DCL 3L (n = 10)[a]	PEG-ELS 4L (n = 5)[a]	*P* value[b]	DCL 4L (n = 20)[a]	PEG-ELS 4L (n = 10)[a]	*P* value[b]
OBPS						
Right colon segment	2.5 (2.0–2.5)	2.5 (2.0–2.5)	0.94	3.0 (2.5–3.0)	3.0 (2.0–3.0)	1.00
Midcolon segment	2.5 (2.0–3.0)	2.0 (2.0–3.0)	0.90	2.75 (2.25–3.0)	2.25 (2.0–3.0)	0.25
Rectosigmoid colon segment	2.0 (2.0–2.5)	2.0 (0.5–2.0)	0.44	2.0 (1.5–2.5)	2.0 (1.5–2.5)	0.87
Fluid	1.75 (1.0–2.0)	1.0 (0.5–1.0)	0.24	1.5 (1.0–1.75)	2.0 (1.5–2.0)	0.17
Total score	8.75 (7.0–9.0)	7.0 (6.5–8.0)	0.15	8.5 (7.5–10.0)	8.75 (8.0–9.5)	0.99

Aronchick scale: 1 = excellent; 2 = good; 3 = fair; 4 = poor; and 5 = inadequate.
BBPS segment: 0 = unprepared colon segment with mucosa not seen; 1 = portion of mucosa of segment seen, but other areas not well seen; 2 = mucosa of segment well seen, but minor amounts of residual staining, small fragments of stool, and/or opaque liquid; 3 = entire mucosa of segment well seen, with no residual staining, small fragments of stool, or opaque liquid.
OBPQS segment: 0 = excellent, 1 = good, 2 = fair, 3 = poor, and 4 = inadequate; OBPQS fluid: 0 = small amount, 1 = moderate amount, and 2 = large amount; OBPQS total = sum of segment and fluid scores.
PEG-ELS, polyethylene glycol-electrolyte solution.
[a]Data are presented as the sample median (interquartile range; 25th percentile–75th percentile).
[b]Data were analyzed using the Wilcoxon rank-sum test.

Study Highlights

WHAT IS KNOWN

- ✓ The gold standard for colonoscopy prep safety and efficacy is 4L polyethylene glycol-electrolyte solution (PEG-ELS).
- ✓ Forty percent of patients have known risk factors for a suboptimal prep, and 4L PEG-ELS is recommended for this population.
- ✓ The tolerability of 4L PEG-ELS is limited by its taste and volume.

WHAT IS NEW HERE

- ✓ DCL-101 is a novel pill-based colonoscopy prep that is taste-free and compositionally identical to 4L PEG-ELS.
- ✓ DCL-101 is significantly better tolerated than 4L PEG-ELS.
- ✓ Palatability has a large impact on overall colon prep tolerability.

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