CLINICAL STUDY PROTOCOL

Interventional Drug or Biologic

Efficacy, Safety, and Tolerability of MoviPrep® versus GoLYTELY® bowel preparation in hospitalized patients undergoing colonoscopy: a randomized control trial

Protocol Number

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Protocol Version

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REVISION HISTORY:

Revision #	Version Date

Synopsis

Primary Objective The primary objective of this study is whether the use of MoviPrep® in hospitalized patients undergoing colonoscopy is non-inferior to GoLYTELY® with respect to rates of adequate bowel prep.
Secondary Objective The secondary objectives of this study are to determine whether MoviPrep® improves tolerability of bowel preparation in hospitalized patients and whether it reduces delays in inpatient endoscopy and hospital length of stay compared to GoLYTELY®. In addition, we will understand whether MoviPrep increases cecal intubation rates and how it may effect intubation and withdrawal times in colonoscopy.
Study Duration Two years
Study Design Randomized, parallel assignment, non-inferiority clinical trial
Number of Study Sites Two study sites: • Yale-New Haven Hospital, York St. Campus (New Haven, CT) • Bridgeport Hospital (Bridgeport, CT)
Study Population Adult inpatients scheduled to undergo colonoscopy
Number of Participants 450 patients
Primary Outcome Variables • Bowel preparation quality
Secondary Outcome Variables • Tolerability of bowel preparation • Segmental colon cleansing quality • Rates of “excellent” bowel preparation • Cecal intubation rate • Cecal intubation time • Withdrawal time • Time to endoscopy • Hospital length of stay • Adverse events

Abbreviations

Abbreviation	Explanation
PEG	Polyethylene Glycol
BBPS	Boston Bowel Preparation Score
RR	Relative Risk
ECG	Electrocardiogram
FDA	Federal Drug Administration
IRB	Institutional Review Board
UP	Unanticipated Problem
DCF	Data Collection Form
UPIRSOs	Unanticipated Problems Involving Risks to Subjects or Others

Glossary of Terms

Glossary	Explanation

Table of Contents

1 Introduction

1.1 Introductory Statement

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP guidelines, and according to CFR 21 Part 312, other applicable government regulations and Institutional research policies and procedures.

2 Background

2.1.1 Preclinical Experience

MoviPrep [1] is a polyethylene glycol (PEG)-based bowel cleansing preparation that is approved for the use in adults preparing for colonoscopy. It uses several osmotic agents – PEG-3350 (200 g), sodium sulfate (15 g), ascorbic acid (9.4 g) and sodium ascorbate (11.8 g) administered in a 2 liter (approximately ½ gallon) electrolyte solution to retain fluid within the bowel lumen and cause an osmotic diarrhea. PEG-3350 is a nonabsorbable polymer that holds co-administered fluid within the colonic lumen. Ascorbic acid in quantities exceeding the intestine's absorptive capacity draws extracellular fluid across the bowel wall and keeps ingested fluids in the lumen. Sodium sulfate has a similar effect; because most oral sulfate is not absorbed, an electrochemical gradient is established that limits sodium absorption and promotes fluid efflux into the gut lumen. GoLYTELY [2] is a combination of PEG-3350 and electrolytes supplied in a 4-liter (approximately one gallon) disposable jug containing PEG-3350 (236 g), sodium sulfate (22.74 g), sodium bicarbonate (6.74 g), sodium chloride (5.86 g), and potassium chloride (2.97 g). GoLYTELY functions in similar manner to promote an osmotic diarrhea but requires a large volume of liquid which must be ingested. Given the significant clinical experience with GoLYTELY, it has been considered the standard bowel preparation to be used prior to colonoscopy for many years. For both bowel preparations, onset of effects occurs within 1 to 2 hours of ingestion. They both do not undergo hepatic or renal metabolism as the primary agent (PEG-3350) is not absorbed.

2.1.2 Clinical Experience

Multiple clinical trials have compared MoviPrep's efficacy and tolerability to existing bowel preparations. One randomized study of 308 patients compared 2L of MoviPrep with 4L of GoLYTELY and found that cleansing was considered effective in 88.9% and 94.8% of patients, respectively [3]. Moreover, patients rated MoviPrep as more tolerable, better tasting and easier to consume the entire dose. In another study, MoviPrep was compared to a low volume bowel preparation comprised of 238g Miralax in 64 oz of Gatorade along with bisacodyl in a randomized study of 150 patients [4]. In this study, MoviPrep was associated with significantly higher rates of high quality bowel cleansing of the right (84.6% vs. 61.6%) and transverse colon (86.4% vs. 72.1%) compared to the Miralax/Gatorade/Biscodyl preparation. Finally, MoviPrep has been compared to another low volume bowel prep, Suprep (oral sulfate solution), in a randomized study of 187 patients and was found to have similar rates of successful bowel cleansing (88.3% vs. 86%) without significant difference in patient-reported palatability, tolerability, or adverse events [5]. With regard to administration schedule, a meta-analysis assessing split versus single dosing of MoviPrep found both regimens demonstrated high rates of bowel cleansing efficacy, with success rates of 87.4% in the split-dose group and 73.4% in the single-dose group, suggesting that split-dosing of MoviPrep (1L the evening prior to colonoscopy, 1L the morning of colonoscopy) [6]. Moreover, a recent systematic review and meta-analysis of the tolerability and efficacy of low- and high-volume split dose regimens for bowel cleansing prior to colonoscopy demonstrated that low-volume split-dose regimens had higher odds for compliance or completion and tolerability without significant differences in adequacy of bowel cleansing [7]. Together, these findings strongly suggest that split-dosing of MoviPrep and GoLYTELY should be the preferred administration schedule for maximum efficacy and tolerability prior to colonoscopy.

2.2 Background/prevalence of research topic

Adequate bowel cleansing is a critical component in the care of hospitalized patients undergoing diagnostic or therapeutic colonoscopy. Some factors that have been consistently associated with inadequate bowel preparation are inpatient status, older age, non-adherence to preparation instructions, constipation as a colonoscopy indication, and history of stroke/dementia [8, 9]. Inadequate bowel preparation is also associated with worse clinical outcomes, including increased rates of complications, missed pathologic lesions, repeated bowel preparation medication administration, and even aborted colonoscopy procedures [10-15]. This can result in increased hospital length of stay (LOS) and healthcare costs [10, 16]. An estimated 30-50% of inpatients undergoing colonoscopy suffer from inadequate colon cleansing [17, 18]. According to a survey of 545 colonoscopies performed at Yale-New Haven Hospital between July 2018 and June 2020, 29.9% were determined to be suboptimal (defined as physician rating of poor, inadequate, unsatisfactory or a Boston Bowel Preparation Score (BBPS) $\leq$5). Given the frequency of inadequate bowel preparation among hospitalized patients, significant healthcare resources are expended by delays stemming from poor preparation. However, few strategies have been rigorously shown to reduce the risk of inadequate bowel preparation and delays in inpatient colonoscopy [19-21].

One patient-centered reason for inadequate preparation is the inability to complete the bowel regimen as prescribed, secondary to patient discomfort or difficulty consuming the amount of fluid required. GoLYTELY (polyethylene glycol + electrolytes) requires the patient to consume 4 liters of fluids (approximately one gallon) in a single- or split-dosing regimen. However, a recent meta-analysis evaluating the efficacy and tolerability of low- vs. high-volume bowel cleansing regimens demonstrated no significant difference between the adequacy of the cleansing (RR 1.00, CI 0.98-1.02) or in adenoma detection rate (RR 0.96, CI 0.87-1.08). However, there was a higher odds ratio for compliance or completion (RR 1.06, CI 1.02-1.1), tolerability (RR 1.39, CI 1.12-1.74) and willingness to repeat the bowel preparation (RR 1.41, CI 1.12-1.74) associated with the low-volume preparations. There were no significant differences found when evaluating adverse effects [7].

MoviPrep (polyethylene glycol + ascorbic acid) is a low-volume bowel preparation, requiring 2.8 liters of fluid (approximately 0.7 gallons) in a split-dosing regimen. Most studies have found MoviPrep to be non-inferior to split-dose GoLYTELY, as split dosing is recommended in colonoscopy guidelines for increased safety and efficacy. As such, we are interested in assessing the use of MoviPrep in hospitalized patients and determine if it is non-inferior to GoLYTELY with respect to rates of adequate bowel prep but with improved tolerability and decreased delays in inpatient endoscopy.

3 Rationale/Significance

3.1 Problem Statement

Adequate bowel cleansing is a critical component in the care of hospitalized patients undergoing diagnostic or therapeutic colonoscopy. However, inpatient status is a well-established risk factor for inadequate bowel preparation. Inadequate bowel preparation is associated with worse clinical outcomes, including increased rates of complications, missed pathologic lesions, repeated bowel preparation medication administration, and even aborted colonoscopy procedures. However, few strategies have been rigorously shown to reduce the risk of inadequate bowel preparation and delays in inpatient colonoscopy.

3.2 Purpose of Study/Potential Impact

In this study, we plan to assess the use of a low volume bowel preparation, MoviPrep, in hospitalized patients and determine if it is non-inferior to standard high volume bowel preparation, GoLYTELY, with respect to rates of adequate bowel prep but with improved tolerability and decreased delays in inpatient endoscopy. This may lead to improved tolerability of bowel preparation among hospitalized patients as well as improved bowel preparation, which may lead to fewer patient complications as well as decreased hospital length of stay and expenditures.

3.2.1 Potential Risks

The potential risks incurred with the study include those associated with the clinically warranted procedure (i.e. colonoscopy), including bleeding, infection, missed lesion, and bowel perforation requiring surgical intervention. With the bowel preparations, there may some additional risk which are summarized as follows. With both MoviPrep and GoLYTELY, there is the risk of adverse reactions including malaise, nausea, abdominal pain (>10% of patients reported), as well as dyspepsia, upper abdominal pain and vomiting (1-10% of patients reported). Fluid and serum electrolyte abnormalities may occur which may also be associated with cardiac arrhythmias, seizures, renal impairment, ischemic colitis, and aspiration. To minimize risk, baseline and post-procedure electrolytes, BUN and creatinine will be monitored in patients at risk for renal impairment, seizure, or who have a history of electrolyte abnormality. In addition, a baseline and post-procedure electrocardiogram (ECG) for patients with risks for prolonged QT or arrhythmias will be performed. As the patients will be in the hospitalized setting, routine care and monitoring for physicians and nurses will also continue.

3.2.2 Potential Benefits

Anticipated direct benefits to participants include potentially decreased symptoms of nausea, bloating and abdominal cramping if randomized to the MoviPrep arm of the trial. Aside from this, potential direct benefits to society at large include decreased hospital length of stay and expenditures because of increased tolerability of a lower volume bowel preparation in hospitalized patients.

4 Study Objectives

4.1 Hypothesis

We hypothesize that among hospitalized adult patients who are scheduled for colonoscopy, the use of MoviPrep will be non-inferior to GoLYTELY in the rates of adequate of bowel preparation. We also hypothesize that MoviPrep will be better tolerated than GoLYTELY and will be associated with decreased time to endoscopy.

4.2 Primary Objective

The primary objective of this study is to determine whether MoviPrep (polyethylene glycol, electrolytes, ascorbic acid) is non-inferior to GoLYTELY (polyethylene glycol, electrolytes) for bowel cleansing in hospitalized adult patients who are scheduled for colonoscopy. An adequate bowel preparation will be defined as a BBPS ≥6 with no segment scoring less than 2. The BBPS is a validated scoring tool that assesses the three segments of the colon and rates them from 1-3 based on the ability to visualize the mucosa [22].

4.3 Secondary Objectives

The secondary objectives of this study are to compare the tolerability of MoviPrep compared to GoLYTELY, to determine the impact of MoviPrep on segmental cleansing (right, transverse, and left colon), cecal intubation rates, intubation/withdrawal time compared to GoLYTELY, and to determine if use of MoviPrep influences hospital length of stay or time to colonoscopy in hospitalized adult patients who are scheduled for colonoscopy. Tolerability will be assessed using the validated Mayo Clinic Bowel Prep Questionnaire [23].

4.4 Exploratory Objectives

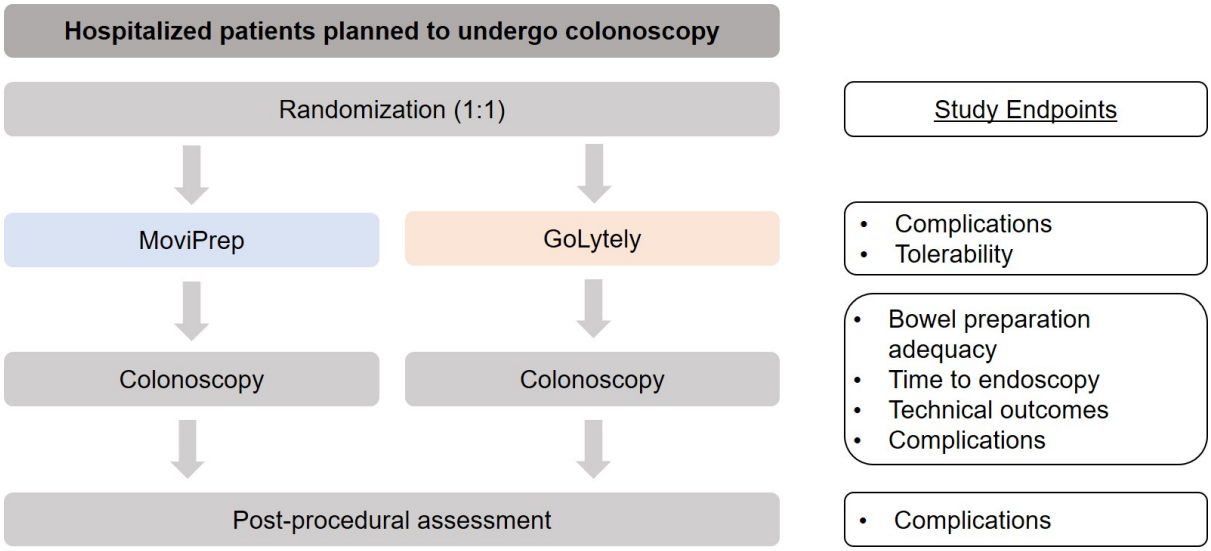
N/A.

5 Study Design

5.1 General Design Description

This study will be a single-blind (to the outcomes assessor), parallel assignment, randomized, non-inferiority trial comparing the rates of adequate bowel preparation in hospitalized adult patients undergoing bowel preparation for colonoscopy with either a low-volume bowel preparation (MoviPrep) or a traditional high-volume bowel preparation (GoLYTELY). While the endoscopist and the patient will not be blinded to the nature of the randomization, a central outcomes assessor that will be scoring the adequacy of the colonoscopy preparation via the BBPS will be blinded to the bowel preparation used.

Figure 1. Trial design



5.1.1 Study Date Range and Duration

Two and a half years (approximately January 2022 to July 2024)

5.1.2 Number of Study Sites

Two study sites:

1. Yale-New Haven Hospital, York St. Campus (New Haven, CT)
2. Bridgeport Hospital (Bridgeport, CT)

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

The primary outcome of this study is the rate of adequate bowel preparation prior to colonoscopy. An adequate bowel preparation will be defined as a BBPS ≥6 with no segment scoring less than 2. The BBPS is a validated scoring tool that assesses the three segments of the colon and rates them from 1-3 based on the ability to visualize the mucosa [22]. This has been a standard primary outcome for many bowel preparation studies since the development of the BBPS.

5.2.2 Secondary Outcome Variables

Several secondary outcomes will be evaluated as part of this study. These include:

- Tolerability of bowel preparation, assessed using the Mayo Bowel Preparation Questionnaire [23].
- Segmental colon cleansing, defined as BBPS component score given to the right colon, transverse colon, and left colon on withdrawal.
- Rates of "excellent" bowel preparation, defined by a BBPS of 8 or 9.
- Rates of cecal intubation, defined by percentages of colonoscopies that reach the cecum.
- Cecal intubation time, defined by time in minutes from insertion of the colonoscope into the rectum to reaching the cecum.
- Withdrawal time, defined by time from reaching the cecum to completion of examination.
- Time to endoscopy, defined as time from initial consultation to start of colonoscopy.
- Hospital length of stay

5.2.3 Exploratory Outcome Variables

N/A.

5.3 Study Population

Hospitalized adult patients (≥18 years of age) scheduled to undergo colonoscopy.

5.3.1 Number of Participants

Number of participants anticipated to be screened and/or enrolled by site:

Site	*# Screened*	*# Enrolled*
Yale New Haven Hospital, York St. Campus	400	320
Bridgeport Hospital	160	128
Total	560	458

5.3.2 Eligibility Criteria/Vulnerable Populations

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 18 or greater
4. Hospitalized patient scheduled to undergo colonoscopy with bowel preparation (not including preparation with enemas alone)
5. Ability to take bowel preparation and be willing to adhere to the regimen

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients presenting to the hospital with ileus, toxic megacolon, evidence of gastrointestinal obstruction
2. Receipt of bowel preparation for other reasons during their hospitalization prior to their colonoscopy

3. Patients with prior significant gastrointestinal surgeries including colonic resection, subtotal colectomy, abdomino-perineal resection, Hartmann's procedure or other similar surgeries involving structure/function of small intestine or colon
4. Unable to give informed consent to the procedure
5. Known glucose-6-phosphate dehydrogenase deficiency
6. Known phenylketonuria
7. Known hypersensitivity to polyethylene glycols or ascorbic acid
8. Patients undergoing colonoscopy for foreign body removal and/or decompression
9. Pregnancy or lactating women

6 Methods

6.1 Treatment

6.1.1 Identity of Investigational Product

The test product is MoviPrep (polyethylene glycol 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, ascorbic acid). This is a Federal Drug Administration (FDA)-approved oral bowel preparation for the purposes of cleansing of the colon in preparation for colonoscopy in adults.

The active control is GoLYTELY (polyethylene glycol 3350 + electrolytes). This is also an FDA-approved oral bowel preparation for the purposes of cleansing of the colon in preparation for colonoscopy in adults.

6.1.2 Dosage, Administration, Schedule

For MoviPrep, the dose, schedule, and route of administration are as follows:

- On the evening prior to the colonoscopy, mix the powder with lukewarm water to a total volume of 32 oz. Drink 8 oz. every 15 minutes until the solution is finished. Drink 16 oz. of clear liquids before bed.
- On the morning of the procedure, repeat the above steps and make sure all fluids are consumed at least 2 hours prior to colonoscopy.
- Limit food intake to a regular breakfast, light lunch and clear soup or plain yogurt for dinner on the day prior to the colonoscopy (completed at least 1 hour prior to the first MoviPrep dose.
- Consume only clear liquids from the start of MoviPrep until after the colonoscopy.

For GoLYTELY, the dose, schedule, and route of administrate are as follows:

- On the evening prior to the colonoscopy, mix powder with lukewarm water to a total volume of 4 liters (approximately one gallon). Drink 2 liters (approximately ½ gallon) of the solution and store the rest in the refrigerator.
- Drink the remaining 2 liters (approximately ½ gallon) on the morning of the procedure.
- Limit food intake to a light breakfast on the day prior to the colonoscopy, followed by only clear liquids until the procedure is complete.
- Avoid red and purple liquids.

6.1.3 Method of Assignment/Randomization

Randomization will occur at the time when the bowel preparation for upcoming colonoscopy. A computer-generated randomization list stratified by center will be used. Patients will be centrally randomized in a 1:1 manner with the randomized list being created and held by the hospital pharmacy. When the bowel preparation is ordered, the hospital pharmacy will be contacted and will assign and provide the correct treatment for the enrolled patient so the investigator or the coordinator will not be involved in allocation.

6.1.4 Blinding and Procedures for Unblinding

The outcomes assessor (see Section 6.2.1 for details) will be formally blinded as they will receive a de-identified video recording of the colonoscopy itself and will judge the adequacy of the bowel preparation. The patient will not be blinded in this case as the differences in the

volume of bowel preparation will make blinding impossible. The endoscopist will be encouraged to avoid looking at the medication administration records or asking the patient regarding the bowel preparation but will not be formally blinded.

6.1.5 Packaging/Labelling

MoviPrep is supplied as a single-use carton containing a disposable container for reconstitution and 4 pouches of powdered drug labelled Pouch A (2) and Pouch B (2).

GoLYTELY is supplied in powdered form in a disposable jug or packet.

6.1.6 Storage Conditions

MoviPrep should be stored at 68-77°F with excursions permitted at 59 to 86°F. When reconstituted, keep solution refrigerated and use within 24 hours.

GoLYTELY should be stored in a sealed container at 5-86°F. When reconstituted, keep solution refrigerated and use within 48 hours.

6.1.7 Concomitant therapy

No restrictions.

6.1.8 Restrictions

No restrictions.

6.2 Assessments

6.2.1 Efficacy

The primary assessment of efficacy in this study is the frequency of adequate bowel preparation prior to colonoscopy associated with each arm. An adequate bowel preparation will be defined as a BBPS ≥6 with no segment scoring less than 2. The BBPS is a validated scoring tool that assesses the three segments of the colon and rates them from 1-3 based on the ability to visualize the mucosa [22] and has been a standard primary outcome for many bowel preparation studies since the development of the BBPS.

The assessment of bowel preparation quality will be determined through review of de-identified video recordings of the colonoscopy of enrolled patients. Recording the colonoscopy will not add any extra time to the procedure. All images and videos will be recorded without any patient identifier and uploaded onto a Yale Secure Box folder based on the patient, endoscopist, and center identification numbers. These recordings will be accessed by dedicated central reviewers who will score the quality of the bowel preparation on withdrawal via the BBPS. BBPS scoring will be recorded on a form that will be provided to the central reviewers (**Appendix 1**).

The secondary outcome of tolerability of the bowel preparation will be assessed using the Mayo Clinic Bowel Preparation Questionnaire [23] (**Appendix 2**). The answers to each of the nine questions will be tabulated and compared between the two arms of the trial.

Additional secondary outcomes of cecal intubation rate, cecal intubation time, withdrawal time will be determined during the procedure by recording whether or not the cecum was reached

during the colonoscopy (as identified by the visualization of the appendiceal orifice and the ileocecal valve), the time from insertion of the colonoscope to cecal intubation, and the time from cecal intubation to complete withdrawal of the colonoscopy, respectively.

The secondary outcome of time to endoscopy will be calculated as the time from bowel preparation order to the start of the colonoscopy.

The secondary outcome of hospital length of stay will be assessed at time of patient discharge.

6.2.2 Safety Monitoring

To monitor and evaluate the safety of the intervention, we will perform the following monitoring tests:

Prior to bowel preparation:
- Electrolytes, BUN, creatinine
- ECG

Post-procedure:
- Electrolytes, BUN, creatinine
- ECG

6.2.3 Adverse Events Definition and Reporting

Definitions
Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).
An AE or suspected adverse reaction is considered "serious" (SAE) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
- death,
- a life-threatening adverse event,
- prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Severity
Adverse events will be graded according to Common Terminology Criteria for Adverse Events v5.0. For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.
- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

Relationship to Investigational Product
All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expectedness
The Principal Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Reporting
Adverse event reports will be submitted to the IRB by the Principal Investigator in accordance with the respective IRB procedures. Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 5 business days following the primary investigator receipt of the respective information.

6.2.4 Pharmacokinetics

N/A.

6.2.5 Biomarkers

N/A.

6.3 Study Procedures

6.3.1 Study Schedule

There will be a total of 4 visits as part of the study. An initial visit while the individual is in the hospital for standard of care procedure, we will conduct screening and consent, a second visit after completion of the bowel preparation and before the colonoscopy during which the bowel preparation questionnaire is administered, a third visit during which the colonoscopy is performed as standard of care, and a follow-up visit post-procedure as per standard of care at each center to assess interim events.

Table 1. Study Schedule

	Screening	**Treatment**		**Follow-up**
Time	Before bowel preparation	After bowel preparation	During colonoscopy	1-3 days
Procedures & Activities	- Assess patient eligibility from medical records - Informed consent - Randomize patient	- Administer bowel preparation questionnaire	- Assess bowel preparation quality	- Follow-up visit per standard of care at each center - Assessment of interim events
Data Collection	- Patient characteristics	- Tolerability - Complications	- Recording and assessment of bowel preparation quality - Procedure characteristics	- Complications

6.3.2 Informed Consent

Informed consent will be obtained for the purposes of recruitment of patients to this study. Non-English-speaking subjects will be invited with the use of a translator. If the patient is cognitively impaired, their legally authorized representative will be approached for consent. The study will be explained to the prospective subject and they will be allowed ample time to determine if they want to participate in the study. At that time, they will be asked to sign the consent form. If subjects initially enrolled via a legally authorized representative regains decisional capacity before the completion of their participation in their study, informed consent will be obtained from the subject.

6.3.3 Screening

Screening for potential subjects will be performed by a member of the study team (which includes the Principal Investigator, co-investigators, and research coordinators). Patients being evaluated by the General GI and Advanced Endoscopy consultation team who are planned to undergo colonoscopy will be screened by review of medical records.

6.3.4 Enrollment

Enrollment in the study will take place after they have been screened and meet eligibility criteria and have been consented. Subjects will be consented during an in-person visit in the patient's hospital room by a member of the study team. Subjects will be given at minimum 30 minutes to decide upon their participation in the study and will more than likely have several hours to do so.

6.3.5 On Study Visits

Study Visit 1 (prior to bowel preparation):
- Informed consent
- Randomization

Study Visit 2 (after bowel preparation, before colonoscopy)
- Administration of the Mayo Clinic Bowel Preparation Questionnaire (for research purposes)
- Assessment for adverse events and complications from bowel preparation (standard of care)

Study Visit 3 (colonoscopy)
- Colonoscopy (standard of care)
- Video recording of colonoscopy and assessment of bowel preparation quality by central reviewer (for research purposes)
- Procedure characteristics (standard of care)

Study Visit 4 (1-3 days post-procedure)
- Assessment for adverse events and complications from procedure (standard of care)

6.3.6 End of Study and Follow-up

The study will be completed for the patient once Study Visit 4 (1-3 days post-procedure) has occurred. Results of the colonoscopy will be shared with the inpatient primary team as per standard of care. Data regarding length of hospital stay for each subject will be collected but will be done so retrospectively without the need for an additional follow-up visit.

6.3.7 Removal of subjects

Subjects may withdraw their consent for the use of their data at any time, if the material or data is identifiable, by calling the Principal Investigator or a member of the research team. In this event, the Principal Investigator will indicate in the database that consent from the subject is no longer active.

Data that was collected before the subject withdrew their consent may still be used to complete the research that has already commenced. The researchers will anonymize the data by removing and destroying all identifiers and links to identifiers so that it can never be associated with the subject, but the researchers will not destroy the data.

6.4 Statistical Methods

6.4.1 Statistical Design

Continuous variables will be described as mean and standard deviation while categorical variables will be described as percentages. A 2-sided student's t test will be used to compare the means of continuous variables and a chi-squared test was used to compare categorical variables. Results from the patient tolerability questionnaire were pooled and compared between treatment arms using the chi-square test. Univariate and multivariate logistic regression will be performed to determine factors that are associated with adequate bowel preparation. A p-value of <0.05 will be considered statistically significant.

6.4.2 Sample Size Considerations

A sample size estimation of **219** patients per arm was determined based on expected overall cleansing rates of 85% for both arms, a noninferiority margin of 10%, power of 90%, and a 5% significance level. Thus, with an anticipated 80% rate of enrollment and minimal anticipated dropout rate, we would anticipate needing to screen a total of 550 patients. Because the primary outcome measure will be assessed based on video recording of the standard of care colonoscopy, we do not anticipate any dropouts.

6.5 Planned Analyses

6.5.1 Primary Objective Analysis

The primary assessment of efficacy in this study is the frequency of adequate bowel preparation prior to colonoscopy associated with each arm. An adequate bowel preparation will be defined as a Boston Bowel Preparation Score (BBPS) ≥6 with no segment scoring less than 2. The BBPS is a validated scoring tool that assesses the three segments of the colon and rates them from 1-3 based on the ability to visualize the mucosa [22] and has been a standard primary outcome for many bowel preparation studies since the development of the BBPS.

The assessment of bowel preparation quality will be determined through review of de-identified video recordings of the colonoscopy of enrolled patients. These video recordings will be uploaded onto a Yale Secure Box folder and will be accessed by dedicated central reviewers who will score the quality of the bowel preparation on withdrawal via the BBPS. BBPS scoring will be recorded on a form that will be provided to the central reviewers (**Appendix 1**).

6.5.2 Secondary Objectives Analyses

The secondary outcome of tolerability of the bowel preparation will be assessed using the Mayo Clinic Bowel Preparation Questionnaire [23] (**Appendix 2**). The answers to each of the nine questions will be tabulated and compared between the two arms of the trial.

Additional secondary outcomes of cecal intubation rate, cecal intubation time, withdrawal time will be determined during the procedure by recording whether the cecum was reached during the colonoscopy (as identified by the visualization of the appendiceal orifice and the ileocecal valve), the time from insertion of the colonoscope to cecal intubation, and the time from cecal intubation to complete withdrawal of the colonoscopy, respectively.

The secondary outcome of time to endoscopy will be calculated as the time from bowel preparation order to the start of the colonoscopy.

The secondary outcome of hospital length of stay will be assessed at time of patient discharge.

Adverse events and complications will be summarized descriptively and be analyzed as described in Section 6.4.1.

6.5.3 Exploratory Objectives Analyses

N/A.

6.5.4 Safety

Safety analysis will be performed as described in Sections 6.4.1 and 6.5.2.

6.5.5 Analysis of Subject Characteristics

For baseline characteristics, continuous variables will be described as mean and standard deviation while categorical variables will be described as percentages. The following characteristics will be collected:

- Demographics
  - Age
  - Sex
  - Race
  - Ethnicity
- Clinical Characteristics
  - Body Mass Index
  - Indication for colonoscopy
  - ASA class
  - Charlson comorbidity scale
- Medical Comorbidities
  - Hypertension
  - Diabetes Mellitus
  - Malignancy
  - Chronic Kidney Disease
  - Cirrhosis
  - Dementia
- Medications
  - Opioids
  - Tricyclic antidepressants
  - Antithrombotics
  - Anti-hypertensives
- Laboratory Tests at baseline
  - Sodium
  - Potassium
  - BUN
  - Creatinine
  - Glucose
  - Hemoglobin
  - Platelets
  - PT
  - INR

6.5.6 Interim Analysis

N/A.

6.5.7 Health economic evaluation

We will also plan a cost-effectiveness analysis comparing the overall hospital expenditures in patients receiving MoviPrep and GOLYTELY.

6.5.8 Other

No other additional analyses will be performed.

6.5.9 Subsets and Covariates

Safety and efficacy outcomes will be assessed in the following subgroups:

- Patients on prescribed narcotics
- Patients with chronic kidney disease
- Age >65
- Age >75
- Patients with admission primarily for assessment of gastrointestinal disease (i.e. gastrointestinal bleeding, inflammatory bowel disease, diarrhea, iron deficiency anemia)

6.5.10 Handling of Missing Data

Missing outcome data will not be included in the final analysis.

7 Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

Informed consent and HIPAA authorization will be obtained for the purposes of recruitment of patients to this study. Non-English-speaking subjects will be invited with the use of a translator. If the patient is cognitively impaired, their legal representative will be approached for consent. No payment will be provided for participation. It is possible that a previously unknown condition will be discovered as the result of the study procedure but no data will be collected on this as part of the study.

7.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required.

The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year. A study closure report will be submitted to the IRB after all research activities have been completed. Other study events (e.g. data breaches, protocol deviations) will be submitted per the Yale IRB's policies.

7.3 Subject Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval. All research activities will be conducted in as private a setting as possible.

Representatives of the IRB, regulatory agencies or study sponsor/funding agency may inspect all documents and records required to be maintained by the investigator for the participants in this study. The study site will permit access to such records.

The study participant's contact information will be securely stored at each study site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, regulatory, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on a REDCap (Research Electronic Capture) database or a Yale Secure Box folder. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. Subject medical record review will be limited to just the elements needed to complete the study. A master list linking the unique study number to the human subject will be maintained in a locked drawer in LMP 1080 at the Yale School of Medicine.

The study data entry and study management systems used will be secured and password protected. Only authorized HIPAA trained study team members will be allowed to extract research data from medical records and enter it into the REDCap database. At the end of the study, all study databases will be de-identified and archived in a locked cabinet in the Principal Investigator's office. All data will be transferred and stored on encrypted devices.

7.4 Deviations/Unanticipated Problems

A protocol deviation is any noncompliance with the protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to identify and report deviations within 5 calendar days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the study sponsor, and the reviewing IRB per their policies.

Unanticipated problems (UPs) involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If the study team becomes aware of an unanticipated problem (e.g. data breach, protocol deviation), the event will be reported to the IRB.

The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs will be reported to the IRB within 5 calendar days of the investigator becoming aware of the event.

7.5 Data Collection

Yale-New Haven Hospital (York St. Campus) will act as the coordinating center through the study. At each site, data will be entered on Data Collection Forms (DCFs) (**Appendix 3**) and transferred into an electronic database (REDCap) after the procedure. Each site investigator is responsible for complete data ascertainment at their site and entry into the electronic database. Each site will maintain a hard copy of completed DCFs and a key to participant code. All data that is collected will be de-identified. Only members of the study staff (Principal Investigator, co-investigators, research coordinators) will have access to the electronic database.

REDCap will be used as a central location for data processing and management. Vanderbilt University, with funding from the National Institutes of Health (NIH) and collaboration from a consortium of institutional partners, developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process. REDCap was developed specifically around HIPAA security guidelines. REDCap has been disseminated for use locally at other institutions and currently supports 240+ academic/non-profit consortium partners on six continents and over 26,000 research end-users (https://www.project-redcap.org). REDCap includes safeguards to ensure complete data entry and minimizing erroneous entries. If needed, missing or additional information will be obtained from local site investigators.

Video recordings and scanned documents will be uploaded onto a Yale Secure Box folder that is only accessible to members of the study team.

7.6 Data Quality Assurance

The primary investigator will maintain records in accordance with Good Clinical Practice guidelines; to include:

- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports.
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s).
- Signed Investigator's Agreements and Certifications of Financial Interests
- Master randomization list.
- Copies of correspondence between primary and site investigators.

7.7 Study Records

- IRB protocols (current and past versions)
- IRB correspondence related to the clinical protocol
- Consent forms
- Data Collection Forms
- Boston Bowel Preparation Score Form
- Mayo Clinic Bowel Preparation Questionnaire
- Adverse Event Reports
- Master Randomization List
- Copies of correspondence between primary and site investigators

7.8 Access to Source Documents

Source documents will be kept in a locked cabinet that resides in a locked office at each site. Clinical data will be warehoused in a secure, online REDCap database or in a Yale Secure Box folder. The Principal investigator and site investigators will be responsible for maintaining the records. Members of the research team will be authorized to access source documents.

7.9 Data or Specimen Storage/Security

Clinical data will be warehoused in a secure, online REDCap database or Yale Secure Box folder as previously described. The Principal investigator will be responsible for maintaining the records. Members of the research team will be authorized to access source documents. No specimens will be collected as part of this study.

7.10 Retention of Records

Study documents will be retained for the duration of the study and for a minimum of 2 years after completion of the study. If permission is needed to move or destroy the records, the Principal Investigator should be contacted.

7.11 Study Monitoring

Study monitoring, including appropriate consent documentation and clinical study documentation, progress of the trial, assessments of data quality and timeliness, participant recruitment, and participant risk versus benefit will be monitored quarterly by the Principal Investigator. There is no increased risk to subjects due to their participation in research versus normal clinical practice since both treatments are already used in clinical practice.

7.12 Data Safety Monitoring Plan

Appropriate consent documentation and clinical study documentation, progress of the trial, including assessments of data quality and timeliness, participant recruitment, and participant risk versus benefit will be monitored quarterly by the Principal Investigator.

The Principal Investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator or the IRB have the authority to stop or suspend the study or require modifications. REDCap will be used as the centralized data collection system, which has integrated quality control checks for collected data. These will include checks on completion of required data at the time of data entry. Site-specific data query will be available to identify missing follow-up data. A Yale Secure Box folder will be used for storage of video recordings and scanned documents.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design and graded by the Principal Investigator, Darrick Li MD, PhD, as described in Sections 6.2.3. All serious adverse events (as defined in Section 6.2.3) will be reviewed by the Principal and co-investigators to assess whether a complication was related to study participation.

The Principal Investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND

3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented*.* These reviews will assure additional independent assessment and evaluation of possible adverse events.

The principal investigator, Darrick Li MD, PhD, will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

7.13 Study Modification

The Principal Investigator and the IRB have the authority to stop or suspend the study or require modifications. Any modifications to the study will first be submitted to the IRB for approval.

7.14 Study Discontinuation

If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

7.15 Study Completion

Study completion will occur when the number of enrolled patients meets the pre-calculated sample size calculation. A study closure report will be submitted to the IRB after all research activities have been completed.

7.16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who

have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

All investigators will follow the applicable conflict of interest policies.

7.17 Funding Source

This study is not funded.

7.18 Publication Plan

The results from this study may be used by the Principal Investigator and research team for future publication and presentation and/or secondary parties who are conducting IRB-approved research that request the use of de-identified data from this trial. The Principal Investigator holds the primary responsibility for publishing the study results.

8 Appendices

Appendix #	Title	Section	Topic
1	Boston Bowel Preparation Score Form	6.2.1	Assessments (Efficacy)
2	Mayo Clinic Bowel Preparation Questionnaire	6.2.1	Assessments (Efficacy)
3	Data Collection Form	7.5	Data Collection

9 List of Tables

10 References

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