CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-881

MEDICAL REVIEW(S)

CLINICAL MOVIPREP® NDA REVIEW

Application Type	NDA
Submission Number	21-881
Submission Code	000
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Reviewer Name	Eric Brodsky, MD
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Established Name	PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid for oral solution
Trade Name	MOVIPREP®
Therapeutic Class	Purgative
Applicant	Norgine B.V.
Priority Designation	Standard
Formulation	Oral solution
Proposed Dosing Regimen	Take a total of 2 liters of MOVIPREP (240 mL every 15-30 minutes with concomitant clear fluids). Three administration options: 1) take the entire 2 liters the evening prior to the procedure, 2) [redacted] or 3) take one liter in the evening prior to the procedure and one liter in the early morning on the day of the procedure.
Proposed Indication	Bowel cleansing prior to colonoscopy. [redacted]
Intended Population	Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, this medical officer recommends **approval** of the MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) oral solution for **cleansing of the colon as a preparation for colonoscopy in adults** if the sponsor agrees to important labeling changes. If the sponsor does not agree to the important labeling changes, then this medical officer recommends an **approvable** action.

This medical officer does not recommend approval of two additional indications ("[redacted]"), proposed by the sponsor, because there is no clinical data to support these indications.

Two well-controlled, randomized, investigator-blinded, parallel-group, multi-center, European trials of MOVIPREP demonstrated substantial evidence of effectiveness and safety for the intended use of MOVIPREP as a colon preparation prior to a colonoscopy.

This medical officer recommends adding **WARNINGS** to the MOVIPREP label about the risk of generalized tonic-clonic seizures and electrolyte changes associated with use of polyethylene glycol (PEG) colon preparation products in patients with no prior history of seizures. In the controlled MOVIPREP trials, the most common drug-related adverse events associated with MOVIPREP use were abdominal distension, anal discomfort, nausea, and abdominal pain.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Risk management activities are not required.

1.2.2 Required Phase 4 Commitments

This medical officer does not recommend any phase 4 commitments.

1.2.3 Other Phase 4 Requests

This medical officer does not recommend additional phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Norgine B.V. (Norgine) submitted this new drug application [under 505(b)(1) of the Federal Food, Drug, and Cosmetic Act] on June 10, 2005 to support the approval of MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) oral solution, a purgative, "for bowel cleansing prior to colonoscopy, [redacted]." The proposed MOVIPREP dosage regimen consists of two liters of MOVIPREP, containing 200 grams of polyethylene glycol (PEG) 3350 and Vitamin C (sodium ascorbate and ascorbic acid), with one additional liter of clear fluid. For comparison, the approved GoLYTELY® oral solution (NDA 19-011), a PEG-based colon preparation product, contains 236 grams of PEG 3350 in four liters of fluid and the approved NuLYTELY® oral solution (NDA 19-797), another PEG-based colon preparation product, contains 420 grams of PEG 3350 in four liters of fluid. All of the approved PEG-based colon preparations including GoLYTELY and NuLYTELY do not contain Vitamin C.

Norgine submitted a total of six completed clinical studies to support the approval of their application. In the six trials, the entire safety database had a total population of 800 subjects/patients. Of the 800 subjects/patients, 413 (51.6%), 179 (22.4%), and 171 (21.4%) patients received MOVIPREP, GoLYTELY, and oral sodium phosphate solution (OSPS), respectively and 37 (4.6%) subjects received a two-liter PEG-based investigational product with 200 to 250 grams of PEG 3350. OSPS, under the monograph system, is approved for the over-the-counter treatment of occasional constipation and is professionally labeled over-the-counter for "bowel cleansing prior to medical procedures".

The most important clinical trials — to support the efficacy and safety of MOVIPREP in colon cleansing before colonoscopy — included two trials of patients scheduled to receive an elective colonoscopy in Europe (the German and French studies). The two trials had a safety subpopulation of 699 patients [of which 349 (49.9%), 179 (25.6%), and 171 (24.5%) patients received MOVIPREP, GoLYTELY, and OSPS, respectively]. The overwhelming majority of patients in the two trials were exposed to their colon preparation for less than 24 hours.

1.3.2 Efficacy

The two most important efficacy trials (the German and French studies) submitted in this NDA were randomized, investigator-blinded, active-controlled, parallel-group, European, multi-center (12 and 17 sites in the German and French studies, respectively), colon preparation trials of MOVIPREP in patients scheduled to have an elective colonoscopy.

In the German study, patients were randomized 1:1 to one of the two following regimens: two liters of MOVIPREP solution with one liter of clear fluid (a total of three liters of fluid) or four liters of GoLYTELY solution. In the French study, patients were randomized 1:1 to one of the two following regimens: two liters of MOVIPREP solution with one liter of clear fluid (a total of three

liters of fluid) or 90 mL of OSPS containing about 60 grams of sodium phosphate with two liters of concomitant clear liquids. In the German study, the study treatments were split between the evening prior to the colonoscopy and the morning of the colonoscopy (split-dosing). In contrast, in the French study, the study treatments were given entirely on the day prior to the colonoscopy.

In the German and French studies, the pre-specified **primary efficacy endpoint** was a responder analysis. Responders were defined as patients who had an overall effective colon preparation, allowing adequate visualization of the entire colonic mucosa — achievement of a grade A or B on a 4-level Overall Colon Cleansing Scale (see Table i). Non-responders were defined as patients who achieved a grade of C or D. The pre-specified statistical analysis in the German and French studies was a non-inferiority analysis with a pre-specified 15% margin between MOVIPREP and the active comparator (GoLYTELY in the German study and OSPS in the French study).

Table i: The 4-level Overall Colon Cleansing Scale in the German and French studies

LEVEL	DEFINITION
A	All colon segments with a VRS score of 3 or 4.
B	At least one colon segment with a VRS score of 2.
C	At least one colon segment with a VRS score of 1.
D	At least one colon segment with a VRS score of 0.

VRS is the Verbal Rating Scale (see Table ii)
Reference: Adapted from Volume 43.1, Section 11.1.1, Pages 23-24 and Volume 62.1, Section 11.1, Pages 70-71

In the German and French studies, the 4-level Overall Quality Colon Cleansing Scale was based on a 5-point, numerical Verbal Rating Scale (VRS) score (see Table ii) of five colonic segments (the ascending, transverse, descending, and sigmoid colon and the rectum).

Table ii: The 5-point VRS to assess cleansing in five colonic segments in the German and French studies

SCORE	RATING	DEFINITION
4	Very Good	Empty and clean
3	Good	Presence of clear liquid in the gut, but easily to be removed by suction*
2	Moderate	Brown liquid or semisolid remaining amounts of stool, fully removable by suction**
1	Bad	Semisolid amounts of stool, only partially removable with a risk of incomplete visualization of gut mucosa
0	Very Bad	Semisolid or solid amounts of stool; consequently colonoscopy incomplete or needs to be terminated

* In the French study, the good (3) rating was defined as "clear liquid (transparent, yellow, or green)".
** In the French study, the moderate (2) rating was defined as "brown liquid or semisolid remaining small amounts of stool, fully removable by suction or displaceable."
Reference: Adapted from Volume 43.1, Section 11.1.1, Page 23; Volume 62.1, Section 11.1, Page 70; and Section 16.1.2, Page 188.

The German and French studies had different procedures in classifying colonic segment scores for the primary efficacy endpoint. In the German study, three experienced gastroenterologists on a blinded expert panel — on the basis of videotapes recorded during the colonoscopies — graded the cleanliness of each colonic segment during the introduction of the colonoscopes (proximal direction) and during the withdrawal of the colonoscopes (distal direction). In this German study, the poorer of the two grades was used for the primary efficacy analysis. In contrast, in the French study, the colonoscopist and one expert gastroenterologist on a four-member blinded expert panel — on the basis of videotapes recorded during the colonoscopies — rated each colonic segment without regard to the introduction or withdrawal of the colonoscopes. In this French study, a second blinded expert made the final determination of the colon segment score in case of a discrepancy between the colonoscopist and the first blinded expert.

The German and French studies had 22 and 44 pre-specified analyses, respectively, conducted on the **secondary efficacy endpoints**. This medical officer believes that the most important analyses of the secondary efficacy endpoints in the German and French studies were the following: the frequency of effective overall colon cleansing (achievement of grade A or B on the 4-level Overall Quality Colon Cleansing Scale) graded by the colonoscopist; the mean degree of cleansing in the entire colon rated by the colonoscopist; and the mean degree of cleansing in the entire colon judged by the expert-panel. The sponsor did not conduct multiplicity analyses for these numerous analyses of the secondary endpoints in the German and French studies.

Primary Efficacy Endpoint Results: Table iii displays the results of the primary efficacy endpoint — the percentage of patients who had an overall effective colon preparation allowing adequate visualization of the entire colonic mucosa — in the German and French studies. In the German study, GoLYTELY was numerically better than MOVIPREP and in the French study, MOVIPREP was numerically better than OSPS. From a clinical perspective, the data support the efficacy of MOVIPREP in colon cleansing prior to colonoscopy.

Table iii: The number (%) of patients[a] with effective colon cleansing in the German and French studies

	Treatment Group	Responder (A or B) n (%= n/N)	Non-Responder (C or D) n (%=n/N)
German study	**MOVIPREP (split doses)**, N=153	136 (88.9)	17 (11.1)
	GoLYTELY (split doses), N=155	147 (94.8)	8 (5.1)
	Rate difference, (%)	(-5.9)[b]	
French study	**MOVIPREP (evening only)**, N=137	100 (73.0)	37 (27.0)
	OSPS (day before the colonoscopy), N=143	92 (64.3)	51 (35.7)
	Rate difference, (%)	(8.7)[c]	

a Patients in the per protocol population (the primary population)
b The lower bound of the 97.5% confidence interval was -12.0%
c The lower bound of the one-sided 97.5% confidence interval was -2.2%
Reference: Adapted from Volume 37.1, Table 10, Page 60; and Volume 75.1, Table 3.1.2, Page 71

In summary, the clinical data from the two well-controlled MOVIPREP studies support the efficacy of two MOVIPREP regimens (split-dosing and evening-only dosing) for cleansing of the colon as a preparation for colonoscopy.

1.3.3 Safety

Of the 800 subjects/patients in the total safety population in this NDA (including the two phase 1, the two phase 2, and the two phase 3 studies), 413 (51.6%), 179 (22.4%), and 171 (21.4%) patients received MOVIPREP, GoLYTELY, and OSPS, respectively and 37 (4.6%) subjects received a two-liter PEG-based investigational product with 200 to 250 grams of PEG 3350. Of the 413 patients who received MOVIPREP, 214 (51.8%) and 199 (48.2%) received the split-dose and evening-only regimens, respectively. Of the 413 patients who received MOVIPREP, 349 (84.5%) patients were in controlled MOVIPREP trials and 64 (15.5%) patients were in uncontrolled MOVIPREP studies. The overwhelming majority of patients in the MOVIPREP studies were exposed to their colon preparation for less than 24 hours.

In the four MOVIPREP studies (the German and French studies and two phase 2, uncontrolled MOVIPREP studies), no patient died and three patients experienced drug-related serious adverse events (one patient who received MOVIPREP and two patients who received OSPS). The three patients who experienced drug-related serious adverse events were:

1) A 60 year old female patient with a history of inflammatory bowel disease, chronic diarrhea, and baseline hypokalemia developed vomiting, had persistent hypokalemia, and required hospitalization after MOVIPREP administration;
2) A 42 year old female patient developed hypokalemia and required hospitalization after OSPS administration; and
3) A 40 year old female patient developed hypokalemia, ECG changes, and required hospitalization after OSPS administration.

In the four MOVIPREP studies, six patients experienced drug-related study discontinuations (four patients who received MOVIPREP and two patients who received GoLYTELY). Of the four patients who had MOVIPREP-related study discontinuations, two patients experienced nausea, one patient had malaise, and one patient vomited. Of the two patients who had GoLYTELY-related study discontinuations, one patient had nausea and the other patient had nausea and vomiting. Most of these adverse events resolved without sequelae.

In the two controlled MOVIPREP studies (the German and French studies), the most common drug-related adverse events associated with MOVIPREP administration were abdominal distension, anal discomfort, thirst, nausea, abdominal pain, and malaise. In these two studies there were no appreciable differences in the frequencies of the most common drug-related adverse events in patients who received MOVIPREP compared to the patients who received the active comparator.

The following are minor deficiencies in the safety monitoring program in the MOVIPREP studies:

1) Lack of any post-colonoscopy blood tests;
2) Lack of any post-colonoscopy follow-up safety visits;
3) Lack of ECGs performed in the screening, treatment, and post-treatment periods; and
4) No thorough QT/QTc study performed.

However, there have been few post-marketing reports of arrhythmias or prolonged QT associated with administration of PEG-based colon preparations products (including GoLYTELY and NuLYTELY) and these PEG-based products have been marketed in the United States for over 20 years. Therefore, this medical officer does not believe that a thorough QT/QTc study is required for approval of this application.

This medical officer believes that the sponsor's safety database exposure was acceptable. In summary, this medical officer believes that the sponsor has demonstrated the safety of MOVIPREP for cleansing of the colon as a preparation for colonoscopy.

1.3.4 Dosing Regimen and Administration

This medical officer recommends the following two MOVIPREP dosing regimens that the sponsor proposed for approval:

1) Split MOVIPREP dose regimen: The evening before the colonoscopy, take the first liter of MOVIPREP solution over one hour and then drink 0.5 liters of clear fluid. Then, on the morning of the colonoscopy, take the second liter of MOVIPREP solution over one hour and then drink 0.5 liters of clear liquid at least one hour prior to the start of the colonoscopy; and
2) Evening-only MOVIPREP dose regimen: Around 6 PM in the evening before the colonoscopy, take the first liter of MOVIPREP solution over one hour and then about 1.5 hours later take the second liter of MOVIPREP solution over one hour. In addition, take 1 liter of additional clear liquid during the evening before the colonoscopy.

This medical officer does not recommend the sponsor's proposed ——— MOVIPREP dosing regimen because the sponsor never studied this regimen in clinical trials.

1.3.5 Drug-Drug Interactions

There were no important drug-drug interactions in the MOVIPREP trials.

1.3.6 Special Populations

There are no special MOVIPREP dosing considerations for gender, age, race, patients with hepatic insufficiency, and patients with renal insufficiency.

This medical officer recommends a full waiver for pediatric studies that are required under the 2003 Pediatric Research Equity Act. This medical officer believes that pediatric studies are not necessary under 21 CFR 314.55(c)(2)(i) because the "drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients."

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Proposed Trade Name (established name): MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) for oral solution.

Proposed Indication: "MOVIPREP® is indicated for bowel cleansing prior to colonoscopy, [redacted]."

Proposed Age Group: Adults

Pharmacologic Class: Purgative

Route of Administration, Description, and Formulation: MOVIPREP is an oral solution having a lemon taste.

Proposed Treatment Regimen: The sponsor's recommended dose is 2 liters of MOVIPREP solution (with concomitant intake of clear fluids) prior to gastrointestinal examination. The entire proposed 2 liter MOVIPREP dosage regimen contains the following: 200 grams of PEG, 5.38 grams of sodium chloride, 2.03 grams of potassium chloride, 15 grams of [redacted] sodium sulphate, 9.4 grams of ascorbic acid, and 11.8 grams of sodium ascorbate.

The sponsor has proposed the following three administration options:

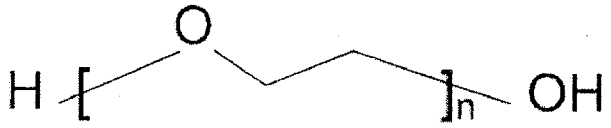
1) Evening only: Take 240 mL every 15 to 30 minutes until 2 liters of MOVIPREP solution are consumed in the evening before the gastrointestinal procedure;
2) Split doses: Take one liter of MOVIPREP solution (240 mL every 15 to 30 minutes) in the evening before the gastrointestinal procedure and then take the second liter of MOVIPREP solution (240 mL every 15 to 30 minutes) on the morning of the gastrointestinal procedure (consumption must be completed at least one hour before the procedure); or
3) [redacted]

For best results, no solid food should be taken after the initiation of MOVIPREP administration until after the gastrointestinal procedure.

Chemical Names of the six main ingredients in MOVIPREP: PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid.

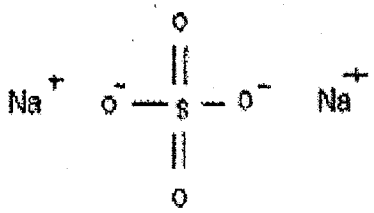
Molecular Formulas and Structural Formulas of the main MOVIPREP ingredients:

PEG 3350: The molecular formula is $H(C_2H_4O)_nOH$.



Where n represents the mean number of oxyethylene groups.

Sodium sulfate: The molecular formula is Na_2SO_4.



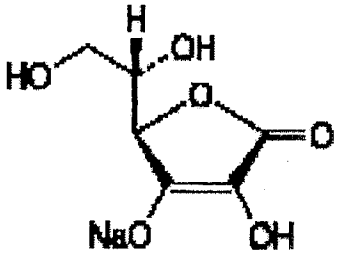
Sodium chloride: The molecular formula is NaCl.

$Na^+ Cl^-$

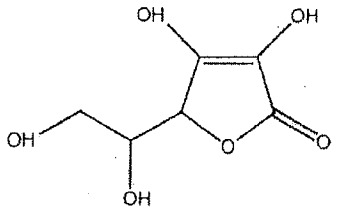
Potassium chloride: The molecular formula is KCl.

$K^+ Cl^-$

Sodium ascorbate: The molecular formula is $C_6H_7NaO_6$.



Ascorbic acid: The molecular formula is $C_6H_8O_6$.



For more information about the chemical structure of MOVIPREP, please see Dr. Sharon Kelly's review (Dr. Kelly is the chemistry reviewer).

2.2 Currently Available Treatment for Indications

There are two classes of colon preparation products approved in the United States: polyethylene glycol (PEG)-based products and sodium phosphate-based products (see Table 1).

Approved PEG-based products include GoLYTELY®, Colyte®, OCL Solution®, NuLYTELY®, and Tri Lyte™. HalfLytely® is a combination product containing two liters of a PEG-based oral solution and 20 mg of oral bisacodyl tablets (a stimulant laxative).

Approved sodium phosphate products include oral sodium phosphate solutions (OSPS) — which are marketed as professionally labeled products and sold over-the-counter (OTC) under the monograph system — and sodium phosphate oral tablets (Visicol® and OsmoPrep™). OsmoPrep, an oral sodium phosphate tablet product approved in March 2006, is similar to Visicol, except that OsmoPrep does not contain microcrystalline cellulose (MCC) and contains a lower amount of sodium phosphate (OsmoPrep has 48 grams of sodium phosphate and Visicol has 60 grams of sodium phosphate). The currently approved Visicol formulation contains 13% MCC. OsmoPrep uses PEG 8000 as a binder, instead of MCC. The sponsor claims that MCC occasionally obscures the appearance of the colon during colonoscopy and PEG 8000 does not obscure the colonic lumen.

Table 1: Approved prescription and OTC colon preparation products in the United States

Drug	NDA#	Sponsor	Approval Date	Ingredients	Total Fluid[1]
GoLYTELY®	19-011	Braintree	7/84	PEG 3350 + Electrolytes	Up to 4 liters
Colyte®	18-983	Schwarz Pharma	10/84	PEG 3350 + Electrolytes	Up to 4 liters
Oral Sodium Phosphate Solution	N/A[1]	Multiple	N/A[2]	Sodium Phosphate (30 grams)	Varies[3]
OCL Solution[4]®	19-284	Hospira	4/86	PEG 3350 + Electrolytes	Up to 4 liters
NuLYTELY®	19-797	Braintree	4/91	PEG 3350 + Electrolytes	Up to 4 liters
Visicol®	21-097	Inkine	9/00	Sodium Phosphate (60 grams)	At least 3.4 liters
HalfLytely® Bisacodyl Kit	21-551	Braintree	5/04	PEG 3350, Electrolytes, + Bisacodyl	At least 2 liters
Tri Lyte™	N/A[5]	Schwarz Pharma	2/04	PEG 3350 + Electrolytes	Up to 4 liters
OsmoPrep™	21-892	Inkine	3/06	Sodium Phosphate (48 grams) + PEG 8000	2 liters
MOVIPREP®	**21-881**	**Norgine BV**	**Not Approved, Under Review**	**PEG 3350, Electrolytes, + Vitamin C**	**3 liters**

1 Oral Sodium Phosphate Solutions (OSPS) are not under NDA regulations; rather, they are approved under OTC monograph regulations. The tentative final monograph was proposed in 1985. The Final Rule has not been completed. OSPS are professionally labeled and marketed OTC.
2 Total fluid includes the amount of fluid in the colon preparation and additional recommended fluid.
3 Manufacturers recommend different amounts of concomitant fluid intake for their colon preparation products.
4 OCL Solution has been discontinued and is not marketed in the United States.
5 Tri Lyte is a generic product (identical to NuLYTELY) approved under ANDA 76-491.
Reference: Adapted from current product labels and http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

In addition to the FDA-approved sodium phosphate-based and PEG-based colon preparations, many laxatives are prescribed off-label for colon cleansing in preparation for colonoscopy, surgery, and radiology examinations (such as barium enemas). Additionally, physicians prescribe several unapproved dose regimens of PEG-based and sodium phosphate-based colon preparation products. Additionally, physicians recommend various amounts of concomitant fluid intake during administration of colon preparations.

2.3 Availability of Proposed Active Ingredient in the United States

The main active ingredient in MOVIPREP is PEG 3350. PEG 3350 is a main component of several colon preparations prior to colonoscopy including GoLYTELY, NuLYTELY, Tri Lyte, HalfLytely, and Colyte. In addition, Miralax is a PEG-based drug product approved in February 1999 for the treatment of occasional constipation under NDA 20-698. Glycolax is a generic Miralax (PEG 3350) approved in July 2004 under ANDA 76-652.

Please see Table in Section 2.2 for the approval dates of the PEG-based colon preparation products. There have not been major labeling changes for the PEG-based colon preparation products since these products were approved.

2.4 Important Issues With Pharmacologically Related Products

In May 2005, Dr. Glen S. Markowitz, a renal pathologist at the Columbia College of Physicians and Surgeons medical center, gave a lecture entitled "Acute Phosphate Nephropathy Following Oral Sodium Phosphate Bowel Purgative: An Under-recognized Cause of Chronic Renal Failure" at the FDA. Subsequently, an internal working group was formed to evaluate serious complications of electrolyte abnormalities (such as renal failure, seizures, and arrhythmias) associated with colon preparations included the sodium phosphate-based and PEG-based products.

The colon preparation internal working group included this medical officer from the DGP, Ann Corken Mackey, RPh, MPH, from the Division of Drug Risk Evaluation (DDRE) in the Office of Drug Safety (ODS), and Dr. Karen Feibus from the Office of Nonprescription Products (ONP). The working group evaluated randomized, well-controlled colon preparation studies submitted to the FDA; and post-marketing adverse event (AE) reports and literature reports of serious complications of electrolyte abnormalities associated with sodium phosphate-based and PEG-based colon preparation products. On November 15, 2005, the working group presented the following post-marketing information to the Deputy Director of DGP, the office director of ONP, the division director of DDRE, a nephrology medical officer from the Division of Cardio-Renal Drug Products, and other members:

- According to the Adverse Event Reporting System (AERS), 5 fatalities, 5 seizures, one renal failure, and 1 ventricular fibrillation case (not mutually exclusive) were reported in patients using **PEG-based colon preparation products** between 1996 and 2003.

    - All four patients who developed nonfatal seizures developed hyponatremia (ranging from 110 to 116 mmoles/L) were hospitalized, and subsequently recovered. Three of these four patients had documented normal pre-dosing sodium levels and the fourth patient did not have a documented sodium level. Another patient (a 51 year old male with a history of diabetes hypertension, and end stage renal disease developed seizures and subsequently died after receiving a PEG-based colon preparation product. This patient, who had a normal baseline sodium level, developed hyponatremia (sodium level was 122 mmoles/L). All five patients did not have a known history of seizures.

- In four of the five fatalities, the patients had underlying medical conditions including chronic renal insufficiency, megacolon, history of bowel perforation, and ascites.
- The patient who developed renal failure had underlying end stage liver failure and was taken a concomitant diuretic.
- The patient who developed a ventricular arrhythmia developed hypokalemia. This patient was successfully cardioverted.

➢ According to the AERS, 11 fatalities and 33 renal failure, 2 seizure, and 12 serious cardiac event cases (not mutually exclusive) were reported in patients using **OSPS** as a colon preparation between 1969 and 2005. Since OSPS are under the monograph system and manufacturers of OSPS products are not required to report AEs, the AERS cases are most likely not the complete list of SAEs associated with OSPS. Most of these patients experienced clinically significant changes in electrolytes.

- Of the 11 fatalities, 2 were cardiac arrests with higher doses of OSPS, 2 were cardiac arrests with recommended OSPS doses, 2 were patients with baseline renal insufficiency and the patients were given higher OSPS doses, and 1 patient developed a seizure and aspiration pneumonia who took a higher OSPS dose.
- Of the 33 patients who developed renal failure associated with OSPS administration, 21 were over 65 years old. Of the 33 patients, 10 were male and 23 were female. Of the 33 patients, 22 had hypertension, 7 had type II diabetes, 4 had baseline renal insufficiency, 15 took an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), 4 took a non-steroidal anti-inflammatory drug (NSAID), and 7 took a diuretic. Also of the 33 patients, 5 patients received high OSPS doses. Acute renal failure onset was two days to about two months after OSPS administration. Of the 33 patients, 4 developed end stage renal failure, at least 22 developed permanent chronic renal failure, at least 9 were hospitalized, and 7 required dialysis (outcomes were not mutually exclusive).
- Of the 12 cases of serious cardiac events, 7 patients had cardiac arrest (5 of the 7 were fatal) and 5 patients had QT prolongation. Most of the patients with cardiac events had electrolyte abnormalities.

➢ According to the AERS, 1 fatality, 11 renal failure, 10 seizures, and 1 QT prolongation cases were reported in patients using **Visicol** as colon preparations between 2001 and 2005. Most of these patients experienced significant changes in their electrolytes.

- Of the 11 renal failure cases, 7 patients had hyperphosphatemia, 6 patients had hypocalcemia, 5 patients were over 65 years old, 7 patients were female and 5 patients were male, 10 had a history of hypertension, 4 had a history of diabetes type II, 2 had a history of chronic renal insufficiency, 9 were taking an ACE inhibitor or ARB, 6 were taking a NSAID, and 3 were taking a diuretic (not mutually exclusive). Of the 11 cases, 10 were hospitalized for renal failure and 2 required dialysis (not mutually exclusive).
- Of the 10 patients who experienced a seizure, 10 patients developed hyponatremia, 8 had hypokalemia, and 7 had hypocalcemia. In these cases, the seizure onset was between 2 to

16 hours after Visicol administration. Of the 10 patients, 1 had a history of a seizure disorder and 9 had no history of seizures.

- Dr. Glen Markowitz identified 21 cases of renal biopsy-proven acute phosphate nephropathy and renal failure associated with the administration of **sodium phosphate products** prior to colonoscopy.

Medical Reviewer's Comments: **This medical officer believes that the most significant post-marketing SAEs associated with PEG-based colon preparation administration were seizures. All of the seizures were associated with the development of acute hyponatremia from normal baseline (pre-dosing) sodium levels (one baseline sodium level was not reported).**

Many factors (including decreased oral intake, with diarrhea, and with various amounts and types of concomitant fluid intake) may have contributed to hyponatremia and subsequent seizures in these cases. Unfortunately, the safety of various fluid regimens have not been specifically studied in clinical colon preparation trials. Therefore, the optimum amount of concomitant fluid to decrease the risk of seizures and other SAEs associated with electrolyte changes is not known.

This medical officer recommends the addition of a paragraph in the WARNINGS section of the label regarding the association of PEG-based products with the rare development of seizures.

2.5 Presubmission Regulatory Activity

The highlights of the regulatory activity of MOVIPREP in the United States include the following:

- [redacted]
- In a July 2004 pre-IND. pre-NDA meeting between Norgine and the DGP. the following occurred:
  - The DGP stated, "There is no requirement for initial submission of videotapes of colonoscopies."
  - The DGP stated that the following two non-clinical studies are needed for NDA submission: 2 week repeated dose toxicity studies in rodents and non-rodents. Also, since the sponsor has performed genotoxicity and reproductive toxicity studies with MOVICOL (a PEG-based product, similar to MOVIPREP, approved for constipation and fecal impaction in the European Union and an investigational product in the United States for opioid-induced constipation under IND 67,947), new genotoxicity and reproductive toxicity studies will not be required for the proposed MOVIPREP NDA. The DGP stated that the sponsor should submit the MOVICOL studies [genotoxicity studies including an Ames test, an *in vitro* chromosomal aberration test, and an *in vivo* chromosome

aberration test; and reproductive toxicity studies (Segment II teratology studies in rats and rabbits)] in the planned MOVIPREP NDA.

- The sponsor asked if the two European, phase 3 clinical studies are adequate to support the submission and review of the planned NDA. The DGP responded by stating that two trials are needed to show replication of efficacy results.

➢ In an October 2004 pre-IND, chemistry meeting between Norgine and the DGP:

- The DGP stated that the sponsor's European and US drug products were "pharmaceutically equivalent based upon formulation comparisons (quantitative/qualitative)." The DGP asked the sponsor to provide verification of formulations for GoLYTELY, OSPS, and the comparator. Also, the DGP asked the sponsor to provide CMC information or cross reference all active substances in the proposed NDA.
- The sponsor stated that ascorbic acid and sodium ascorbate are active ingredients. Furthermore, the sponsor stated that since ascorbic acid and sodium ascorbate are

2.6 Other Relevant Background Information

There is no other relevant background information. MOVIPREP is not approved in any country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Dr. Sharon Kelly, the CMC reviewer, stated that the following chemistry issue remains: the MOVIPREP sponsor changed their manufacturing plant and the FDA is currently inspected their new manufacturing plant. Dr. Kelly believes if the inspection has no significant deficiencies then she will recommend approval of this application from a CMC standpoint. Please see Dr. Kelly's review for more details.

There were no microbiology issues with MOVIPREP.

3.2 Animal Pharmacology/Toxicology

Dr. Ke Zhang, the pharmacology/toxicology reviewer in the DGP, recommended approval of MOVIPREP for colon cleansing from a non-clinical standpoint. The sponsor conducted one 2-week oral toxicology rat study of MOVIPREP, one 2-week oral toxicology dog study of MOVIPREP, one 90-day oral toxicology rat study of MOVICOL, and one 90-day oral toxicology dog study of MOVICOL.

According to Dr. Zhang, the toxicology studies in rats demonstrated that the "kidney was the target organ of toxicity in rats based on the changes of the clinical chemistry and the kidney weight." Dr. Zhang added that the toxicology studies in dogs demonstrated that "the major treatment-related toxicity was decreased terminal body weight gain, emesis, diarrhea, and salvation." Therefore, Dr. Zhang stated that these "results suggested that the gastrointestinal tract was the target organ of toxicity in dogs." The toxicity profiles of MOVIPREP and MOVICOL were similar in the toxicology studies.

According to Dr. Zhang, MOVICOL "was not teratogenic in the Segment II teratology studies in rats and rabbits" and MOVICOL "was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y $TK^{+/-}$) forward mutation assay at tk locus, and the mouse micronucleus test."

For more pharmacology/toxicology details, please see Dr. Zhang's review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Six sponsor-conducted trials [Studies 98002, N00/01, 01/2000, 02/2000, 01/2001 (identified as the German Study), and 02/2001 (identified as the French Study)] were evaluated by this medical officer in this review (see Table 2). Of the six trials, two trials (the German and French studies) were the most important trials because they were randomized, actively-controlled, investigator-blinded, multi-center, parallel-group, phase 3 trials; they involved patients who had an elective colonoscopy (the proposed population); and they included a large safety exposure.

For this review, this medical officer evaluated clinical studies of approved PEG-based and sodium phosphate-based colon preparation products (including GoLYTELY, NuLYTELY, Visicol, oral sodium phosphate solutions, and OsmoPrep) that were submitted to the FDA and post-marketing safety reports of serious adverse events (SAEs) associated with PEG-based and sodium phosphate-based preparations. This medical officer also consulted with Ann Corken Mackey, (a safety reviewer from DDRE) regarding post-marketing reports of colon preparation products. In addition, for this review, this medical officer reviewed the sponsor/DGP meetings during the investigational phase of MOVIPREP.

Since this investigational product is not marketed anywhere in the world, foreign post-marketing reports are not part of the sources of information for this review.

4.2 Tables of Clinical Studies

Table 2 displays the six clinical trials submitted in the MOVIPREP NDA. The two most important trials for the efficacy and safety review of this NDA are the German and French studies. Table 2 also includes a listing of a phase 3, randomized, investigator-blinded, multi-center, parallel-group, German trial (Study 01/2004) in patients scheduled to have an elective colonoscopy for colon cancer

screening. This medical officer believes that this phase 3 study is also very important; however, a final study report was not submitted in this NDA.

Study 98002 used MOVICOL, a PEG-based product approved in the European Union for constipation and fecal impaction (MOVICOL is an investigational product in the United States under IND 67,947). Two liters of MOVICOL contains 210 grams of PEG, 2.96 grams of sodium bicarbonate, 5.6 grams of sodium chloride, 0.746 grams of potassium chloride, and lime and lemon flavor.

Table 2: A Summary of all the studies submitted in the MOVIPREP NDA

Study	Design	Treatment Group(s)	N[a]
98002	**Part 1: Phase 1, French,** DB, SC, 2-period crossover, pharmacodynamic study in healthy subjects between 18 and 45 years old **Part 2: Phase 1, French,** open-labeled, uncontrolled, SC, pharmacodynamic study in healthy subjects between 18 and 45 years old	**Part 1:** 1) Solution A then Solution B 2) Solution B then Solution A Solution A was 2 liters of MOVICOL and 20 grams of ascorbic acid Solution B was 2 liters of MOVICOL and 20 grams of saccharose (placebo) **Part 2:** 2 liters of MOVICOL, 20 grams of ascorbic acid, and 11.2 grams of sodium sulphate	7
N00/01	**Phase 1, French,** R, DB, crossover, dose-finding, pharmacodynamic study in healthy subjects between 18 and 45 years old in two centers (subjects received one colon preparation and then after a washout period received another colon preparation)	1) PEG 200 grams; sodium sulfate 15 grams; ascorbic acid 0 grams; sodium ascorbate 0 grams, sodium chloride 5.38 grams; potassium chloride 2.12 grams 2) PEG 200 grams; sodium sulfate 15 grams; ascorbic acid 10 grams; sodium ascorbate 0 grams, sodium chloride 5.38 grams; potassium chloride 2.12 grams 3) PEG 200 grams; sodium sulfate 15 grams; ascorbic acid 10 grams; sodium ascorbate 10 grams, sodium chloride 5.38 grams; potassium chloride 2.12 grams 4) PEG 200 grams; sodium sulfate 15 grams; ascorbic acid 20 grams; sodium ascorbate 0 grams, sodium chloride 5.38 grams; potassium chloride 2.12 grams 5) PEG 200 grams; sodium sulfate 15 grams; ascorbic acid 10 grams; sodium ascorbate 10 grams; sodium chloride 5.38 grams, potassium chloride 1.64 grams 6) PEG 250 grams; sodium sulfate 15 grams;	30

		ascorbic acid 10 grams; sodium ascorbate 10 grams, sodium chloride 6.43 grams; potassium chloride 2.12 grams	
01/2000	**Phase 2, German**, open-label, uncontrolled, SC study in patients scheduled to have an elective colonoscopy	**MOVIPREP (split doses):** 1 liter of MOVIPREP solution and 0.5 L of water in the evening before the colonoscopy and on the day of the colonoscopy	34
02/2000	**Phase 2, French**, open-label, uncontrolled, SC study in patients scheduled to have an elective colonoscopy	**MOVIPREP (evening-only)** and 1 liter of water in the evening before the colonoscopy	30
01/2001 (German Study)	**Phase 3, German**, R (1:1), single-blind (open-label to the patient and investigator-blinded), MC, parallel-group study in patients scheduled to have an elective colonoscopy	**1) MOVIPREP (split doses):** 1 liter of MOVIPREP solution and 0.5 L of water in the evening before the colonoscopy and on the day of the colonoscopy **2) GoLYTELY (split doses):** 2 liters of GoLYTELY solution in the evening before the colonoscopy and on the day of the colonoscopy	180 179
02/2001 (French Study)	**Phase 3, French,** R, (1:1), single-blind (open-label to the patient and investigator-blinded), MC, parallel-group study in patients scheduled to have an elective colonoscopy	**1) MOVIPREP (evening-only):** 2 liters of MOVIPREP solution and 1 liter of water in the evening before the colonoscopy **2) Sodium Phosphate (day before the colonoscopy):** 90 mL of OSPS (60 grams of sodium phosphate) and 2 liters of water on the day before the colonoscopy	169 171
01/2004[b]	**Phase 3, German**, R (2:1), single-blind (open-label to the patient and investigator-blinded), MC, parallel-group study in patients scheduled to have an elective colonoscopy for colon cancer screening.	**1) Total MOVIPREP dose:** 2 liters of MOVIPREP solution with an additional 1 liter of water **2) OSPS**	242 114

OSPS – oral sodium phosphate solution; R = randomized; DB = double-blind, SC = single center; MC = multi-center
a ITT population
b This study was not submitted to the NDA. After an information request from the DGP, the sponsor submitted a summary report of this study on March 14, 2006. This summary report did not detail the amount of OSPS used as the comparator. In addition, this study did not detail the dosing regimens of the study drugs.
Reference: Adapted from Final Study Reports

4.3 Review Strategy

This medical officer is responsible for the entire safety and efficacy reviews of MOVIPREP. The German and French Studies were emphasized in the efficacy review because they were the only controlled trials of MOVIPREP. In addition, they were randomized, actively-controlled, investigator-blinded, multi-center, parallel-group, phase 3 trials; they involved patients who had an elective colonoscopy (the proposed population); and they included a large safety exposure.

The third phase 3 study (Study 01/2004) is an important study and it appears that it had a similar design to the German and French Studies. However, the sponsor did not submit a final study report for this study. The sponsor submitted a summary report of Study 01/2004 on March 14, 2006, 4 weeks prior to the PDUFA goal date of April 10, 2006. Therefore, the efficacy and safety results of Study 01/2004 are not included in this review.

Studies 98002 and N00/01 were not used in the efficacy review because MOVIPREP was not one of the study treatments and no colonoscopies were performed (pharmacodynamic endpoints including stool volume and stool weight were used). Studies 01/2000 and 02/2000 were not used in the efficacy review because they were small, open-labeled, uncontrolled, single-arm studies.

All six trials were used in the safety analysis; however, the German and French trials were emphasized in the safety review for the cited reasons.

4.4 Data Quality and Integrity

One site in the [redacted] and one site in the [redacted] were selected for Division of Scientific Investigation (DSI) to conduct audits (see Table 3). [redacted] in [redacted] was selected because MOVIPREP appeared to demonstrate robust colon cleansing efficacy (compared to GoLYTELY) amongst all of the sites in the [redacted]. In addition, [redacted], had a large number of patients who discontinued study drug compared to the other centers. [redacted] in [redacted] was selected because it contained the largest number of patients per site in the [redacted] Study. [redacted] included 31 and 43 patients in the safety population, respectively.

Table 3: DSI-selected sites in the [redacted]

Proposed Indication	Phase 3 Study	Site (Investigator Name and Center Address)	Number of Subjects*
Colon cleansing prior to colonoscopy [redacted]	[redacted]	[redacted]	[redacted]
Colon cleansing prior to colonoscopy [redacted]	[redacted]	[redacted]	[redacted]

* The safety population
Reference: Volume 43.1 amendment #2 of the protocol, Page 9; Volume 41.1, Tables 14.2.4.2.1 to 14.2.4.2.4, Pages 719-766; Volume 61.1, Section 11.4.2.4, Summary Table 18, Page 73; Volume 37.1, Section 11.4.2.2, Figure 4, Page 62.

At the time of this NDA review, the DSI inspections of [redacted] in the [redacted] study and [redacted] in the [redacted] study were not complete.

4.5 Compliance with Good Clinical Practices

According to the sponsor, the six trials (performed in France and Germany) submitted in this NDA were conducted in agreement with the following directives and guidelines:

- The revised Declaration of Helsinki (Somerset West Amendment in 1996);
- The German Drug Law and the German Directives regarding the conduct of clinical studies or current French regulations;
- The Guidelines of the European Community: Good Clinical Practice for Trials on Medicinal Products in the European Community; and
- The ICH Guidance: E6 Good Clinical Practice: Consolidated Guideline.

According to the sponsor, each subject/patient, in all six submitted studies, was provided with oral and written information describing the nature and duration of the study. Written informed consent form was signed voluntarily by each subject/patient prior to study entry in all the studies.

4.6 Financial Disclosures

According to the sponsor (Norgine), all of the clinical investigators — involved in the submitted studies to NDA 21-881 — have not entered into any financial arrangement with Norgine whereby the value of compensation could be affected by the outcome of the studies as defined in 21 CFR 54.2(a). Furthermore, according to the sponsor, all of the investigators did not disclose any proprietary interest in MOVIPREP or any significant equity interest in Norgine as defined in 21 CFR 54.2(b). Finally, no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

There were no pharmacokinetic studies of MOVIPREP.

5.2 Pharmacodynamics

There were no MOVIPREP pharmacodynamic studies in this NDA.

5.3 Exposure-Response Relationships

There were no dose ranging MOVIPREP studies in this NDA; thus, exposure-response relationships were not assessed.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Methods

The German and French Studies were used for the efficacy review because they were the only controlled trials of MOVIPREP. In addition, they were randomized, actively-controlled, investigator-blinded, multi-center, parallel-group, phase 3 trials; they involved patients who had an elective colonoscopy (the proposed population); and they included a large safety exposure.

The third phase 3 study (Study 01/2004) is an important study and it appears that it had a similar design to the German and French Studies. However, the sponsor did not submit a final study report for this study. The sponsor submitted a summary report of this study on March 14, 2006, 4 weeks prior to the PDUFA goal date of April 10, 2006. Therefore, the efficacy results of Study 01/2004 are not included in this review.

6.2 General Discussion of Endpoints

German Study

The German Study had 23 pre-specified, efficacy endpoints including 1 primary endpoint, 7 expert-based secondary endpoints, 12 investigator-based secondary endpoints, and 3 patient-based secondary endpoints.

Primary Efficacy Endpoint: In the German Study, the primary efficacy endpoint was the frequency of effective colon cleansing as judged by a blinded expert panel on the basis of videotapes recorded during the colonoscopy. Patients who had an overall effective colon preparation allowing adequate visualization of the entire colonic mucosa — achievement of a grade A or B on a 4-level "Overall Quality of Gut Cleansing Scale" (see Table 4) — were considered to be responders. Patients who achieved a grade of C or D on the 4-level, alphabetical scale were considered non-responders. Since the "Overall Quality of Gut Cleansing Scale" was classified by the expert panel twice — initially during introduction of the colonoscope (proximal direction) and secondly during its withdrawal (distal direction) — the poorer of the two assessments was used in the primary analysis.

Table 4: The 4-level Overall Quality of Gut Cleansing Scale in the German Study

LEVEL	DEFINITION
A	All colon segments with a VRS score of 3 or 4.
B	At least one colon segment with a VRS score of 2.
C	At least one colon segment with a VRS score of 1.
D	At least one colon segment with a VRS score of 0.

VRS is the Verbal Rating Scale (see Table 5)
Reference: Adapted from Volume 43.1, Section 11.1.1, Pages 23-4.

The 4-level "Overall Quality of Gut Cleansing Scale" was based on the 5-point, numerical Verbal Rating Scale (VRS). The VRS was determined by the consensus of three experienced gastroenterologists in a blinded expert panel on the basis of videotapes recorded during the colonoscopy. For the VRS rating (see Table 5), the experts graded each of five colonic segments (the rectum, sigmoid colon, descending colon, transverse colon, and the ascending colon) from 0 (very bad) to 4 (very good).

Table 5: The 5-point Verbal Rating Scale (VRS) to assess the degree of cleansing in five colonic segments* in the German Study

SCORE	RATING	DEFINITION
4	Very Good	Colon empty and clean.
3	Good	Presence of clear liquid in the gut, but easily to be removed by suction.
2	Moderate	Brown liquid or semisolid remaining amounts of stool, fully removable by suction.
1	Bad	Semisolid amounts of stool, only partially removable with a risk of incomplete visualization of gut mucosa.
0	Very Bad	Semisolid or solid amounts of stool; consequently colonoscopy incomplete or needs to be terminated.

* The five colonic segments were the rectum, sigmoid colon, descending colon, transverse colon, and the ascending colon.
Reference: Adapted from Volume 43.1, Section 11.1.1, Page 23.

Medical Reviewer's Comments: **This medical officer believes that the 5-point Likert VRS has responses that offer a clear distinction between choices.**

The VRS is different than the primary efficacy assessment scales used in prior colon cleansing product trials.

The original protocol and the protocol amendments did not detail the composition of the expert panel. The final study report clarified that the blinded expert panel had three gastroenterologists. Additionally, the original protocol and the protocol amendments did not state how discrepancies of the three members of the expert panel would be decided. The sponsor responded to us by stating that the "consensus view of the (expert) panel" made the primary assessments of colonic cleansing.

Expert-Panel-Based Secondary Efficacy Endpoints: In the German Study, the 7 pre-specified analyses of secondary efficacy endpoints — based on the assessment of the three-member, blinded, gastrointestinal expert panel — were the following:

1) Five endpoints: The degree of gut cleansing in **each** of the **five** predefined **colon segments** (rectum, sigmoid colon, descending colon, transverse colon, and ascending colon) as rated by the expert panel (on the basis of videotapes recorded during the colonoscopy) according to the 5-point VRS (see Table 5);
2) One endpoint: The mean degree of cleansing in the **entire colon** as rated by the expert panel. The mean degree of gut cleansing score was calculated by averaging the mean expert-panel VRS score in all five colonic segments; and
3) One endpoint: The "Global Quality of Colonic Cleansing" as rated by the expert panel on a 0 mm (dirty) to 100 mm (perfectly clean) visual analog scale (VAS).

Investigator-Based Secondary Efficacy Endpoints: In the German Study, the 12 pre-specified colonoscopist-based (investigator-based) analyses of secondary efficacy endpoints were the following:

1) One responder analysis: The frequency of effective overall colon cleansing as judged by the colonoscopist. Effective colon cleansing was defined as achievement of grade A or B on the 4-level "Overall Quality of Gut Cleansing Scale" (see Table 4). Non-responders were patients who achieved a Grade C or D on this 4-level alphabetical scale;
2) Five endpoints: The degree of gut cleansing in **each** of the **five** predefined **colon segments** (rectum, sigmoid colon, descending colon, transverse colon, and ascending colon) as rated by the colonoscopist according to the 5-point VRS;
3) One endpoint: The mean degree of cleansing in the **entire colon** as rated by the colonoscopist. The mean degree of gut cleansing score was calculated by averaging the mean colonoscopist VRS score in all five colonic segments;
4) One endpoint: The "Global Quality of Colonic Cleansing" as rated by the colonoscopist on a 0 mm (dirty) to 100 mm (perfectly clean) visual analog scale (VAS).
5) One endpoint: The "Overall Judgment of the Colon Preparation" as rated by the colonoscopist on a 5-point scale [1 (very good), 2 (good), 3 (moderate), 4 (bad), and 5 (unacceptable)];
6) One endpoint: The "Overall Easiness" to perform the colonoscopy as rated by the colonoscopist on a 3-point scale [1 (easy to perform), 2 (some difficulties to perform), and 3 (difficult to perform)];
7) One endpoint: Amount of water injected into the colon during the colonoscopy; and
8) One endpoint: Amount of liquids aspirated out of the colon during the colonoscopy.

Medical Reviewer's Comments: The first investigator-based secondary endpoint (the responder analysis of the frequency of effective overall colon cleansing) was similar to the primary efficacy endpoint (responder analysis assessed by the expert panel). However, the procedures for the assessment of the VRS score were different. The expert panel rated each of the five colonic segments on introduction of the colonoscope (proximal movement) and the removal of the colonoscope (distal movement). The final score was based on the worse of the two "Overall Quality of Gut Cleansing" scores (proximal and distal movements). In contrast, the investigators were instructed to assess one "Overall Quality of Gut Cleansing" score, determined by the entire colonoscopy procedure, which included the introduction and the removal of the colonoscope.

Since the primary efficacy endpoint and the first investigator-based secondary endpoint had different procedures, different results may occur. Most likely the investigator scores will be higher than the expert scores because the experts will take the worst of two scores.

Patient-Based Secondary Efficacy Endpoints: In the German Study, the 3 pre-specified patient-based analyses of secondary efficacy endpoints were the following:

1) The taste of the solution according to the patient on a 3-level scale (acceptable, satisfactory, and not acceptable).
2) The degree of satisfaction according the patient on a 0 (excellent) to 100 (very bad) VAS scale.
3) The acceptability of gut preparation according to the patient on a 0 (excellent) to 100 (very bad) VAS scale.

Medical Reviewer's Comments: The protocol did not clarify the difference between the acceptability and the satisfaction of the gut preparations. Additionally, the case report forms had vastly different VAS scales than the protocol.

This medical officer believes that the three most important secondary endpoints include the investigator-based frequency of effective overall colon cleansing (achievement of grade A or B on the 4-level "Overall Quality of Gut Cleansing Scale"); the investigator-based mean degree of cleansing in the entire colon, and the expert-based mean degree of cleansing in the entire colon.

French Study

The French Study had 45 pre-specified, efficacy endpoints including 1 primary endpoint, 19 expert-based secondary endpoints, 24 investigator-based endpoints, and 1 patient-based secondary endpoint.

Primary Efficacy Endpoint: In the French Study, the primary efficacy endpoint was a responder analysis of the PP population: the frequency of effective colon cleansing allowing adequate visualization of the entire colonic mucosa — achievement of grade A or B on the 4-level "Overall Quality of Colonoscopy Cleansing Scale" (see Table 6) — judged by the colonoscopist and one expert gastroenterologist on the four-member blinded panel. The gastroenterology expert graded the colonoscopy cleansing on the basis of videotapes recorded during the colonoscopy. Patients who were given a final grade of A or B were considered responders and patients who were given a final grade of C or D were considered to be non-responders. In case of a discrepancy between the colonoscopist and the blinded expert, a second blinded expert on the four member panel would make the final determination if the patient had effective colon cleansing (if the patient was a responder). Four gastroenterologists had dual roles in this study: they served on the expert panel and also they performed colonoscopies.

Table 6: The 4-level Overall Quality of Gut Cleansing Scale in the French Study

LEVEL	DEFINITION
A	All colon segments with a VRS score of 3 or 4.
B	At least one colon segment with a VRS score of 2.
C	At least one colon segment with a VRS score of 1.
D	At least one colon segment with a VRS score of 0.

Reference: Adapted from Volume 62.1, Section 11.1, Pages 70-71.

The "Overall Quality of Colonoscopy Cleansing" Scale was based on the 5-point VRS degree of colon cleansing scale (see Table 7). The grading of the Overall Quality of Gut Cleansing Scale was calculated automatically based on the 5-point VRS scale.

Table 7: The 5-point Verbal Rating Scale (VRS) to assess the degree of cleansing in five colonic segments* in the French Study

SCORE	RATING	DEFINITION
4	Very Good	Empty and clean.
3	Good	Clear liquid (transparent, yellow, or green).
2	Moderate	Brown liquid or semisolid remaining small amounts of stool, fully removable by suction or displaceable.
1	Bad	Semisolid, only partially removable stools.
0	Very Bad	Semisolid or solid amounts of stool; consequently colonoscopy incomplete or needs to be terminated.**

* The five colonic segments were the rectum, sigmoid colon, descending colon, transverse colon, and the ascending colon.
** The case report forms stated "heavy, hard stools"; they did not state "Semisolid or solid amounts of stool; consequently colonoscopy incomplete or needs to be terminated."
Reference: Adapted from Volume 62.1, Section11.1, Page 70 and Section 16.1.2, Page 188

Medical Reviewer's Comments: **The procedures for the experts in the German and French Studies were different for the primary efficacy endpoint. In the French Study, experts were required to make one comprehensive judgment (including the cleanliness of the colon during both the introduction (proximal movement) and the withdrawal (distal movement) of the colonoscope. In contrast, experts were required to make two distinct assessments of segment cleanliness during the introduction (proximal movement) and the withdrawal (distal movement) of the colonoscopes in the German Study. In this German Study, the poorer of the two assessments was used for the primary analysis.**

In the French Study, the primary efficacy endpoint was determined by the assessment of one of the blinded experts and the colonoscopist. If there was a discrepancy, a second blinded expert would determine the final outcome. Thus, the primary efficacy endpoint was determined by the judgment of two experts and the colonoscopist who performed the procedure. Therefore,

experts had sole input into the primary efficacy endpoint and the colonoscopist (who performed the procedure) did not factor into the final determination of the primary efficacy endpoint.

For the primary efficacy endpoints in the German and French Studies, the experts solely determined the primary efficacy endpoint and the colonoscopist essentially did not have a final determination in the primary efficacy.

These disparate procedures may produce vastly different results between these two phase 3 studies.

Expert-Panel-Based Secondary Efficacy Endpoints: In the French Study, the 19 pre-specified analyses of the secondary efficacy endpoints — based on one of four members of a blinded, gastroenterology (expert) panel (using videotapes taken during the colonoscopies) — were the following:

1) One endpoint: The frequency of effective colon cleansing in the MITT population allowing adequate visualization of the entire colonic mucosa — achievement of grade A or B on the 4-level "Overall Quality of Colonoscopy Cleansing Scale" (see Table 6);
2) Fifteen endpoints: The mean VRS score (see Table 7) in each of five colonic segments (rectum, sigmoid colon, descending colon, transverse colon, and the ascending colon) in the ITT, MITT, and PP populations; and
3) Three endpoints: The mean overall VRS score of the five colonic segment scores in the ITT, MITT, and PP populations.

Medical Reviewer's Comments: The procedure for assessing the expert-based responder analysis was equivocal in the protocol. There are many possible procedures of evaluating this expert-based secondary endpoint including using the identical procedure defined for the primary efficacy endpoint, having one gastroenterologist on the panel evaluate the VRS score, or having a consensus of the four gastroenterologists on the panel.

Investigator-Based Secondary Efficacy Endpoints: In the French Study, the 24 analyses of the secondary efficacy endpoints — based on the judgment of the colonoscopist — were the following:

1) Three endpoints: A responder analysis of the MITT, ITT, and PP populations: The frequency of effective colon cleansing allowing adequate visualization of the entire colonic mucosa — achievement of grade A or B on the 4-level "Overall Quality of Colonoscopy Cleansing Scale";
2) Three endpoints: Global quality of the colonoscopy preparation assessed by a 0 (excellent) to 100 (very bad) mm VAS in the MITT, ITT, and PP populations;
3) Fifteen endpoints: The mean VRS score (see Table 7) in each of five colonic segments (rectum, sigmoid colon, descending colon, transverse colon, and the ascending colon) in the ITT, MITT, and PP populations; and

4) Three endpoints: The mean overall VRS score of the five colonic segment scores in the ITT, MITT, and PP populations.

Medical Reviewer's Comments: The global quality of the colonoscopy preparation VAS was dramatically modified during the protocol. The original protocol defined the VAS from 0 (very bad) to 100 (perfectly clean). However, the second amendment (on June 13, 2002) dramatically altered this VAS scale — while the study was ongoing — to 0 (excellent) to 100 (very bad).

In an information request, this medical officer queried the sponsor regarding this discrepancy during the review of the NDA. According to the sponsor, the case report forms — used throughout the conduct of the study — labeled the colonoscopy preparation VAS from to 0 (excellent) to 100 (very bad). Thus, the sponsor states the original protocol was incorrect and amendment #2 (June 13, 2002) corrected the mistake. The sponsor also acknowledges that one of the corrections in amendment #2 was incorrect when it stated that the VAS score was 0 to 100 (excellent).

It is possible, that the investigators used the protocol's scale to grade the colonoscopy preparation VAS. According to this medical officer, the results of this VAS secondary endpoint are suspect and this medical officer will not evaluate the results of this secondary endpoint.

Patient-Based Secondary Efficacy Endpoints: In the French Study, the one patient-based analysis of a secondary efficacy endpoint was the following: the acceptability of the colonoscopy preparation using a VAS scale from 0 mm (totally acceptable) to 100 mm (totally unacceptable) in the ITT population.

6.3 Study Design

Study 01/2001 (German Study)

Title: Study NRL994-01/2001 (identified in this NDA as the German Study) entitled "A randomized, multicentric, single-blinded, pivotal phase III trial to assess the efficacy, acceptability and safety of a new 2 litre gut cleansing solution NRL994 versus a standard colon preparation with PEG+E (Klean Prep®)."

Klean Prep contains identical quantities of the active ingredients in GoLYTELY.

Study Objective: To demonstrate that MOVIPREP® (NRL994) is not considerably less effective than GoLYTELY® (PEG+E; Klean Prep®), the current standard treatment, in overall colon preparation quality in patients scheduled to receive a colonoscopy.

Study Design: This was a randomized (1:1), single-blinded (to the colonoscopist), active-controlled, parallel-group, multi-center (12 sites in Germany), phase 3 trial comparing the efficacy, safety, and

acceptability of MOVIPREP versus GoLYTELY in the colon preparation of hospitalized patients scheduled to receive an elective colonoscopy.

Eligibility Criteria: Table 8 displays the eligibility criteria of the German Study.

Table 8: Eligibility criteria of the German Study

Inclusion Criteria: To be eligible to participate in the study, patients had to have met all of the following criteria: ➢ Male or female in-patients, aged 18 to 85 years, with indication for a complete colonoscopy; ➢ Willing and able to complete the entire procedure and to comply with study instructions; ➢ Written informed consent prior to inclusion; and ➢ Females of childbearing potential employing an adequate method of contraception.	**Exclusion Criteria:** If patients had the following conditions, they were not eligible to participate in the study in case of the following: ➢ Ileus; ➢ Intestinal obstruction or perforation; ➢ Toxic megacolon; ➢ Congestive Heart Failure (NYHA class III and IV); ➢ Acute life-threatening cardiovascular disease; ➢ Untreated or uncontrolled arterial hypertension: SBP ≥ 170 mmHg and/or DBP ≥ 100 mmHg; ➢ Severe renal or liver failure; ➢ Known glucose-6-phosphatase dehydrogenase deficiency; ➢ Known phenylketonuria; ➢ Known hypersensitivity to PEGs and/or vitamin C; ➢ Concurrent participation or previous participation in a study involving an investigational drug within the last 30 days before inclusion; ➢ Females who were pregnant, nursing or planning a pregnancy or females of childbearing potential, not using reliable methods of contraception; or ➢ Patients who had a condition or were in a situation which would have put them at significant risk or would confound study results.

Reference: Adapted from Volume 43.1, Section 6.1 and 6.2, Page 17.

Medical Reviewer's Comments: **The eligibility criteria were reasonable. Patients with severe renal failure, severe hepatic failure, and congestive heart failure are at higher risk of complications from electrolyte abnormalities than healthy subjects; therefore, it was reasonable to exclude these populations. Additionally, the use of high doses of Vitamin C in patients with glucose-6-phosophatase dehydrogenase deficiency has been associated with hemolytic anemia. Since MOVIPREP contains high doses of Vitamin C, it was reasonable to exclude patients with known glucose-6-phosophatase dehydrogenase deficiency.**

Drugs: Patients were randomized (1:1) to 2 liters of MOVIPREP with one liter of clear fluid (a total of 3 liters of fluid) or 4 liters of GoLYTELY. All patients received half of each study drug on the evening prior to the colonoscopy and the other half on the morning of the colonoscopy.

Patients who received MOVIPREP had to drink the first liter of MOVIPREP over one hour and then drink 0.5 liters of clear fluid before 10:00 PM on the evening prior to the colonoscopy. Then they

had to drink the second liter of MOVIPREP from 6:00 to 7:00 AM on the morning of the colonoscopy and then drink 0.5 liters of clear fluid before noon.

Patients who received GoLYTELY had to drink the first 2 liters of GoLYTELY between 8:00 PM and 10:00 PM on the evening prior to the colonoscopy. Then they had to drink the second two liters of GoLYTELY starting at 5:00 AM to 7:00 AM on the morning of the colonoscopy.

All patients had to be finished with their morning colon preparation at least one hour before the start of the colonoscopy.

Schedule of Procedures and Evaluations: See Table 9 for the schedule of procedures and evaluations in the German Study.

Table 9: Schedule of procedures and evaluations in the German Study

Schedule of assessments	Day -2	Day -1	Day 0	
		before start of bowel preparation	upon completion of bowel preparation	upon completion of colonoscopy
Informed consent	X	(X)[1]		
Demographic data	X	(X)[1]		
Check of inclusion / exclusion criteria	X	(X)[1]		
medical history / concomitant medication	X	(X)[1]		
medical examination	X	(X)[1]		
Vital signs, body weight	X	(X)[1]	X	X[3]
Blood sampling (safety lab.)	X	(X)[1]	X[4]	
Instructions for use / diary card		hand-out	return	
Standard diet		X	X	
Administration of test or reference solution [2]		X X		
Registration of procedural data			X	
Degree of gut cleansing (investigator rating)				X
Recording of AEs		⟷	⟷	⟷
End of study participation				X

1 Alternative schedule in case the patient was enrolled on the day prior to colonoscopy
2 First dose in the evening of Day -1 (up to 10:00 PM), second dose in the morning of day 0 (from 5:00 AM onwards)
3 Vital signs were to be assessed prior to and after the colonoscopy, a second measurement of the body weight was to be performed exclusively in case of premature withdrawal (e.g. because of a SAE)
4 Blood sampling for determination of safety laboratory parameters was to be performed either directly before or within 2 hours after colonoscopy.
Reference: Volume 37, Section 9.5.1, Page 35.

Screening Period: All study patients were screened 48 hours prior to the colonoscopy. An information leaflet detailing the dietary and concomitant fluid procedures was given to patients. Data from the history and physical exam (including body weight, blood pressure, and heart rate) was recorded as well as concomitant medications. Baseline blood tests (including creatinine, BUN, protein, sodium, potassium, chloride, bicarbonate, SGOT, SGPT, and CBC) were taken 1-2 days prior to the colonoscopy.

Treatment Period: On the day before the colonoscopy, patients were allowed to have a normal morning breakfast, a light lunch containing solid food, and clear soup and yogurt for supper. Supper had to be completed one hour before initiation of study treatment. Body weight, blood pressure, and heart rate were measured before the colonoscopy.

No food intake was allowed on the day of the colonoscopy. Concomitant medications were given as usual. Laxatives, colon preparations, or other medications known to cause colon cleansing were not allowed. All patients were to be finished with their morning colon preparation at least one hour before the start of the colonoscopy. The patient was to undergo a complete colonoscopy before 1 PM on the day of colonoscopy. All colonoscopies were to be videotaped to allow an assessment of the gut cleansing by an independent expert panel of gastroenterologists. Blood tests (including creatinine, BUN, protein, sodium, potassium, chloride, bicarbonate, SGOT, SGPT, and CBC) were taken prior to the colonoscopy or within two hours after the colonoscopy.

Once the colonoscopy was finished the amount of fluid injected during the procedure and removed from the colon was documented. After the colonoscopy and after the patient was fully awake, blood pressure and heart rate were performed.

Medical Reviewer's Comments: **This medical officer believes that the sponsor should have conducted follow safety-visits (including complete histories, physical exams, and laboratory testing) several days after the colonoscopy. The lack of a safety follow-up visit reduces the trial's ability to record all of the adverse events.**

No screening and post-treatment ECGs were performed. This medical officer believes that these ECGs should have been performed because ECG testing is a standard part of phase 3 trials. Furthermore, PEG-based colon preparations have been associated with electrolyte disorders that are associated with arrhythmias. According to Ann Corken Mackey, two post-marketing cases of clinically significant electrolyte changes associated with serious arrhythmias (after PEG-based colon preparation use) were reported. The post-marketing cases came from AERS and the medical literature. However, the number of post-marketing cases of arrhythmias reported with PEG use was less than the number of post-marketing arrhythmias associated with sodium phosphate colon preparation use. In addition, the PEG-based colon preparations have been marketed in the United States for over 20 years.

Statistical Methods in the German Study: The following were the three defined statistical populations in the German Study:

1) Intention to treat (ITT) population: All randomized patients who received at least one dose of the study drug.
2) Safety population: Identical to the ITT population.
3) Per protocol (PP) population: Patients who fulfilled all of the eligibility criteria; took 100% of the total daily dose of the study drug; did not receive any unauthorized concomitant medication: and had a colonoscopy on day 0 starting before 1:00 PM. The primary statistical analysis will be performed on the PP population.

The primary hypothesis is that the frequency rate of effective colon cleansing [A or B in the 4-level "Overall Quality of Gut Cleansing Scale" (see Table 4] in patients prepared with MOVIPREP will not be inferior to that of patients prepared with GoLYTELY (the active-control group) by more than 15%. The primary comparison of the two treatment groups will be performed with a one-sided confidence interval. The non-inferiority of MOVIPREP versus GoLYTELY will be accepted if the lower limit of the one-sided 97.5% confidence interval is more than -0.15.

According to the sponsor, the PP and the ITT populations will be used for the 22 secondary efficacy endpoints (7 expert-based, 12 investigator-based, and 3 patient-based). The treatment differences will be presented with one-sided 97.5% confidence intervals.

According to the statistical analysis plan, patients with missing data for the primary and secondary efficacy endpoints will be counted as treatment failures.

Medical Reviewer's Comments: The sponsor failed to justify the choice of the 15% non-inferiority margin in the German study.

The sponsor selected the identical 15% non-inferiority margin in the two phase 3 studies even though the French study used a different active comparator (OSPS) than the German study (GoLYTELY). The sponsor also failed to justify the choice of the 15% non-inferiority margin in the French study. The sponsor failed to justify why the pre-specified margins in the German and French studies were identical even though the two comparators were different products with different mechanisms of action. Furthermore, the sponsor did not meet with the DGP before the studies were initiated to discuss the appropriateness of the non-inferiority margins. The first meeting between the sponsor and the DGP took placed after both the German and the French studies were completed.

Additionally, it is difficult to construct a margin based upon historical trials when the French and German studies used novel primary efficacy endpoints. Non-inferiority margins are supposed to be selected on a comparison of historical studies with similar primary efficacy endpoints.

The protocol did not adjust for the 22 pre-specified, secondary efficacy endpoints and it did not specify a primary statistical population for these secondary endpoints.

Study 02/2001 (French Study)

Title: Study NRL994-02/2001 (identified in this NDA as the French study) entitled "A prospective randomized single-blinded multi-centric and pivotal phase III study comparing the efficacy, safety, and acceptability of new 2 liters gut lavage solution NRL 994 (MOVIPREP) versus a sodium phosphate solution for colonoscopy preparation."

Study Objective: To assess efficacy and the safety of MOVIPREP versus a sodium phosphate solution for colon cleansing prior to colonoscopy.

Study Design: This was a randomized, single-blinded (to the colonoscopist), active-controlled, parallel-group, multi-center (17 sites in France), phase 3 trial comparing the efficacy, safety, and acceptability of MOVIPREP versus an oral sodium phosphate solution (OSPS) in the colon preparation of patients scheduled to receive an elective colonoscopy.

Eligibility Criteria: Table 10 displays the eligibility criteria of the French Study.

Table 10: Eligibility criteria of the French study

Inclusion Criteria: To be eligible to participate in the study, patients had to have met all of the following criteria:	**Exclusion Criteria:** If patients had the following conditions, they were not eligible to participate in the study in case of the following:
➢ Male or female outpatients or inpatients, aged 18 to 74 years, who were scheduled for a diagnostic or therapeutic colonoscopy; ➢ Willing and able to complete the entire procedure and to comply with study instructions; ➢ Written informed consent obtained prior to inclusion; and ➢ Females of childbearing potential employing an adequate method of contraception	➢ Ileus; ➢ Suspected intestinal occlusion or perforation; ➢ Toxic or congenital megacolon; ➢ History of colonic resection; ➢ Crohn's disease or ulcerative colitis; ➢ Congestive Heart Failure (NYHA class III and IV); ➢ Documented renal insufficiency (creatinine > 170 µM/L); ➢ Known glucose-6-phosphatase dehydrogenase deficiency; ➢ Known phenylketonuria; ➢ Known hypersensitivity to PEGs, NaP, or vitamin C; ➢ Concurrent participation or previous participation in a study involving an investigational drug within the last 90 days before study entry; ➢ Females who were pregnant or planning a pregnancy or females of childbearing potential, not using reliable methods of contraception; or ➢ Patients who had a condition or were in a situation which would have put them at significant risk or would confound study results.

Reference: Adapted from Volume 62, Sections 6.1 and 6.29.3.2, Page 16

Medical Reviewer's Comments: Both phase 3 studies had similar eligibility criteria. The French study differed from the German study in the following two ways:

1) **Outpatients and inpatients were included in the French study; in contrast, inpatients were only allowed to participate in the German study; and**
2) **Patients with a history of colonic resection, crohn's disease, or ulcerative colitis were excluded in the French study; in contrast, these patients were allowed to participate in the German study.**

This medical officer believes that the eligibility criteria in the German and French studies were reasonable.

Drugs: Patients scheduled for an elective colonoscopy were randomized 1:1 to MOVIPREP or OSPS.

Patients who received MOVIPREP had to drink the first liter of MOVIPREP within one hour at 6 PM on the evening before the colonoscopy and 1.5 hours later patients had to drink the second liter of MOVIPREP within one hour. Patients had to drink at least 1 liter of additional clear liquid before midnight. Patients were instructed to fast after midnight until the colonoscopy. Thus, patients received a total of 3 liters of fluid the night before the colonoscopy. Patients who received MOVIPREP were allowed to receive a normal breakfast, a normal lunch, and a light dinner (clear soup, yogurt, and compote). The light dinner was supposed to be completed before starting the MOVIPREP around 6 PM

Patients who received OSPS initially had to drink at least 250 mL of clear liquids (including water, light soup, black coffee, tea, sodas, or fruit juice diluted without pulp). Then patients had to drink the first dose of 45 ml of OSPS dissolved in 125 mL of water at 7 AM followed by at least 250 mL of clear liquids. Patients were instructed to drink at least 750 mL of clear liquids at 1 PM. Patients were instructed not to eat breakfast, lunch, or dinner on the day prior to the colonoscopy. Before the second OSPS dose patients were instructed to take at least 250 mL of clear liquids. The second dose of 45 mL of OSPS (dissolved in 125 mL of water) was ingested at 7 PM followed by at least 250 mL of clear liquids. Patients were instructed to fast after midnight until the colonoscopy. Thus, patients received a total of at least 2 liters of concomitant fluid.

Medical Reviewer's Comments: The two study treatments had different procedures regarding the type of meals and the timing of the meals allowed in this French study. Patients who received MOVIPREP were allowed to eat a full breakfast, a full lunch, and a light dinner; in contrast, patients who received OSPS were instructed not to eat any food on the day prior to the colonoscopy. The amount of food and the timing of eating solid food before the colonoscopy can influence the efficacy of colon cleansing. Since MOVIPREP patients received food closer to the colonoscopy, this medical officer believes that they were less likely to have a clean colonoscopy preparation compared to the OSPS patients.

Schedule of Procedures and Evaluations: See Table 11 for the schedule of procedures and evaluations in the French Study.

Table 11: Schedule of procedures and evaluations in the French Study

	Day-30 to -4	Day -1	Day 0
Informed consent	X		
Medical history	X		
Inclusion/exclusion criteria	X		
Clinical examination	X		
Blood sample (12 ml) *	◄	———	► X
Allocation of study treatment £	X		
Instruction leaflet handed to the patient	X		
Study Solution Intake		X	
Nurse filled with the patient the questionnaire prior to colonoscopy **			X
Investigator assess the efficacy of the solution **			X
Recording in CRF Adverse events			X

* Hematology and chemistry blood tests
** Investigator-blinded

Screening Phase: Patients were screened within 30 days of the colonoscopy. Patients received a leaflet containing dietary and fluid intake details. Blood tests (including hematocrit, sodium, potassium, chloride, bicarbonate, BUN, creatinine, protein, calcium, and phosphate) were performed within 30 days of the colonoscopy (Day -30 to Day -1).

Treatment Period: Concomitant medications were allowed in trial, except for laxatives on the day prior to the colonoscopy and the day of the colonoscopy. On the morning of the colonoscopy, patients completed a questionnaire to assess the tolerance of their study medication. Blood tests (including hematocrit, sodium, potassium, chloride, bicarbonate, BUN, creatinine, protein, calcium, and phosphate) were performed immediately before the colonoscopy. The colonoscopy was performed in the morning of the colonoscopy from 8 AM to 1 PM. All colonoscopies were videotaped to allow an assessment from an expert review panel of gastroenterologists. Each blinded gastroenterology expert reviewed the quality of the colonoscopy preparation. In case of a discrepancy between the colonoscopist and an expert, a second expert reviewed the videotape of the colonoscopy.

A final visit was performed after the colonoscopy on the day of the colonoscopy.

Medical Reviewer's Comments: This medical officer believes that a follow-up safety visit (including complete histories, physical exams, and laboratory testing) several days after the colonoscopy should have been conducted in this French Study. The lack of a safety follow-up visit reduces the trial's ability to record all of the adverse events.

No screening and post-treatment ECGs were performed. This medical officer believes that these ECGs should have been performed because ECG testing is a standard part of phase 3 trials. Furthermore, PEG-based colon preparations have been associated with electrolyte disorders that are associated with arrhythmias. According to Ann Corken Mackey, two post-marketing cases of clinically significant electrolyte changes associated with serious arrhythmias (after PEG-based colon preparation use) were reported. The post-marketing cases came from AERS and the medical literature. However, the number of post-marketing cases of arrhythmias reported with PEG use was less than the number of post-marketing arrhythmias associated with sodium phosphate colon preparation use. In addition, PEG-based products have been marketed in the United States over 20 years.

Statistical Populations in the French Study: The following three patient populations were pre-specified in the French Study:

1) Intention to treat (ITT): All randomized patients who took at least 25% of the study drug. Patients who did not have an assessment of the quantity of study drug taken were not included in this population. The safety population was the ITT population;
2) Modified ITT (MITT): All ITT patients who had no major protocol violations and for whom at least one assessment was performed; and
3) Per protocol (PP): All MITT patients who satisfied the eligibility criteria, took at least 75% of the study drug, and adhered to the protocol in the study. The PP population was the primary statistical population for the primary efficacy endpoint.

Statistical Analysis in the French Study: The sponsor pre-specified a non-inferiority margin of 15%.

Medical Reviewer's Comments: The sponsor failed to justify the choice of the 15% non-inferiority margin in the French Study.

The sponsor selected the identical 15% non-inferiority margin in the two important, phase 2 studies even though the French Study used a different active comparator (OSPS) than the German Study (GoLYTELY). The sponsor also failed to justify the choice of the 15% non-inferiority margin in the French Study. The sponsor failed to justify why the pre-specified margins in the German and French Studies were identical even though the two comparators were different products with different mechanisms of action. Furthermore, the sponsor did not meet with the DGP before the studies were initiated to discuss the appropriateness of the non-inferiority margins. The first meeting between the sponsor and the DGP took placed after both the German and the French studies were completed.

Additionally, it is difficult to construct a margin based upon historical trials when the French and German Studies used novel primary efficacy endpoints. Non-inferiority margins are supposed to be selected on a comparison of historical studies with similar primary efficacy endpoints.

The protocol did not adjust for the 44 pre-specified, secondary efficacy endpoints and it did not specify a primary statistical population for these secondary endpoints.

6.4 Efficacy Findings

Disposition of Patients: In the German and French phase 3 studies, there were four main populations: randomized, ITT, MITT, and PP populations. Table 12 displays the number and frequency of patients in these populations. The safety population was identical to the ITT population.

Table 12: Patient disposition in the MOVIPREP German and French studies

Study	Treatment Group	Randomized N (%)*	ITT** N (%)*	MITT N (%)*	Per Protocol Population N (%)*
German Study	MOVIPREP (split doses)	180 (100)	180 (100)	175 (97)	153 (85)
	GoLYTELY	180 (100)	179 (99)	172 (96)	155 (86)
	Total	**360 (100)**	**359 (100)**	**347 (96)**	**308 (86)**
French Study	MOVIPREP (evening-only)	175 (100)	169 (97)	168 (96)	137 (78)
	OSPS	177 (100)	171 (97)	170 (96)	143 (81)
	Total	**352 (100)**	**340 (97)**	**338 (96)**	**280 (80)**
Total in the phase 3 studies		**712 (100)**	**699 (98)**	**685 (96)**	**588 (83)**

* % is the percentage of the randomized population
** The ITT population was identical to the safety population
Reference: Adapted from many volumes from the final study reports in the German and French studies

Table 13 displays the frequencies of rationales in which patients had colonoscopies in the German and French studies.

Table 13: Reasons* why the colonoscopies were performed in the safety population in the German and French studies

	German Study		French Study	
	MOVIPREP Split doses (N=180)	**GoLYTELY** (N=179)	**MOVIPREP** Evening-only (N=169)	**OSPS** (N=171)
Cancer screening	24%	29%	56%	63%
Abdominal Pain	31%	39%	36%	30%
Blood in the Stools	26%	20%	18%	22%
Constipation	8%	10%	15%	11%
Diarrhea	16%	16%	15%	12%
Anemia	8%	10%	2%	6%
Other	33%	26%	15%	11%

* Reasons are not mutually exclusive
Reference: Volume 75.1, Table 1.2.1.3, Pages 27-28; Volume 75.1, Table 1.2.2.3, Pages 33-34

Medical Reviewer's Comments: The reasons for colonoscopy procedures were similar in the study treatments in the German and French studies.

German Study:

Primary Efficacy Endpoint: In the German Study, the primary efficacy endpoint was the frequency of effective colon cleansing as judged by a blinded expert panel on the basis of videotapes recorded during the colonoscopy. Patients who had an overall effective colon preparation allowing adequate visualization of the entire colonic mucosa — achievement of a grade A or B on a 4-level "Overall Quality of Gut Cleansing Scale" (see Table 4) — were considered to be responders. Patients who achieved a grade of C or D on the 4-level, alphabetical scale were considered non-responders.

The percentage of patients in the MOVIPREP and GoLYTELY treatment groups who responded to the effective colon cleansing scale (the primary efficacy endpoint) was 88.9% and 94.8%, respectively (see Table 14). The rate difference between the MOVIPREP and GoLYTELY treatment groups for the primary efficacy assessment was -5.9% and the lower bound of the 97.5% confidence interval was -12.0%. Since the pre-specified non-inferiority margin was 15%, the two treatment groups were non-inferior to one another.

Table 14: The number (%) of PP* patients with effective colon cleansing rated by the expert panel (primary efficacy endpoint in the German study)

Treatment Group	Responder (A or B) n (%)	A n (%)	B n (%)	Non-Responder (C or D) n (%)	C n (%)	D n (%)
MOVIPREP N=153	**136 (88.9)**	22 (14.4)	114 (74.5)	17 (11.1)	15 (9.8)	2 (1.3)
GoLYTELY N=155	**147 (94.8)**	18 (11.6)	129 (83.2)	8 (5.1)	7 (4.5)	1 (0.6)
Rate difference, (%)	**(-5.9)****	(2.6)	(-8.7)	(6.0)	(5.3)	(0.7)

* PP (per protocol) was the primary population
** The lower bound of the 97.5% confidence interval was -12.0%
Reference: Adapted from the final German study report, Volume 37.1, Table 10, Page 60

Medical Reviewer's Comments: **This medical officer stated that the sponsor failed to justify the 15% margin in this German study. If the pre-specified non-inferiority margin was 10% (instead of 15%) then the treatment groups would not be inferior to one another.**

However, if the results of the MOVIPREP treatment group were compared to a historical placebo group, then this medical officer believes that the MOVIPREP treatment group would demonstrate colon cleansing efficacy compared to the historical placebo group.

Important secondary endpoint in the German study: The percent of per protocol patients with effective colon cleansing rated by the blinded colonoscopist (see Table 15).

Table 15: Number (%) of PP* patients with effective colon cleansing as judged by the colonoscopist (secondary endpoint) in the German study

Treatment Group	Responder (A or B)	A	B	Non-Responder (C or D)	C	D
MOVIPREP n=153	**137 (89.5)**	83 (54.2)	54 (35.3)	16 (10.5)	16 (10.5)	0 (0)
GoLYTELY N=155	**143 (92.3)**	86 (55.5)	57 (36.8)	12 (7.7)	12 (7.7)	0 (0)

* PP (per protocol) was the primary population
Reference: Adapted from the final German study report, Volume 37.1, Table 15, Page 69

Important secondary endpoint in the German study: The mean score of the 5-point (0-4) Verbal Rating Scale (VRS) scores of the five colonic segments (see Table 16).

Table 16: The mean score 5-point Verbal Rating Scale score to assess the cleansing effectiveness in the five colonic segments* in the German study in the PP population

	COLONOSCOPIST	EXPERT (upwards)	EXPERT (downwards)
MOVIPREP	3.0 (0.6) n=153	2.5 (0.5) n=152	2.5 (0.5) n=151
GoLYTELY	3.0 (0.6) n=155	2.5 (0.4) n=153	2.5 (0.4) n=151

The VRS scale is a 5-point colon cleansing scale: 4 (very good), 3 (good), 2 (moderate), 1 (bad), and 0 (very bad). For more details see Table 5.

* The five colonic segments were the rectum, sigmoid colon, descending colon, transverse colon, and the ascending colon.

Reference: Adapted from Volume 41.1, Table 14.2.5.2.1, Page 798

Medical Reviewer's Comments: **The above secondary endpoints results support the efficacy of MOVIPREP in colon cleansing. MOVIPREP had similar results compared to GoLYTELY in these three important secondary efficacy endpoints.**

French Study:

Primary Efficacy Endpoint: Percent of per protocol patients with effective colon cleansing — achievement of grade A or B on the 4-level "Overall Quality of Colonoscopy Cleansing Scale" (see Table 6) — judged by the colonoscopist and one expert gastroenterologist on the four-member blinded panel. Patients who were given a final grade of A or B were considered responders and patients who were given a final grade of C or D were considered to be non-responders. The primary efficacy endpoint results in the French study are displayed in Table 17. MOVIPREP was numerical better than OSPS and MOVIPREP demonstrated non-inferiority compared to OSPS in colon cleansing.

Table 17: The number (%) of PP* patients with effective colon cleansing rated by the colonoscopist and one expert gastroenterologist (primary efficacy endpoint in the French study)

Treatment Group	Responder (A or B) n (%)	A n (%)	B n (%)	Non-Responder (C or D) n (%)	C n (%)	D n (%)
MOVIPREP (evening-only) N=137	100 (73.0)	66 (48.2)	34 (24.8)	37 (27.0)	32 (23.4)	5 (3.6)
OSPS N=143	92 (64.3)	35 (24.5)	57 (39.9)	51 (35.7)	42 (29.4)	9 (6.3)
Rate difference, (%)	(8.7)[c]					

* The rate difference was +8.6% and the lower bound of the one-sided 97.5% confidence interval was -2.3%
Reference: Adapted from Volume 75.1, Table 3.1.2, Page 71

Medical Reviewer's Comments: **Thus, in the French study, MOVIPREP was not considerably worse than the OSPS comparator.**

The demonstration of non-inferiority of MOVIPREP compared to GoLYTELY in the German study and OSPS in the French study supports the efficacy of MOVIPREP in colon cleansing. Both GoLYTELY and OSPS are approved medications for colon cleansing. Since GoLYTELY and OSPS have different ingredients (PEG-based versus sodium phosphate-based) the demonstration of non-inferiority compared to these two different products, supports the efficacy of MOVIPREP in colon cleansing.

Secondary Efficacy Endpoint: Percent of patients with effective colon cleansing rated by the colonoscopist (achievement of grade A or B on the 4-level Overall Quality of Colonoscopy Cleansing Scale).

Table 18: The number (%) of PP* patients with effective colon cleansing rated by the colonoscopist (a secondary efficacy endpoint in the French study)

Treatment Group	Responder (A or B) n (%)	A n (%)	B n (%)	Non-Responder (C or D) n (%)	C n (%)	D n (%)
MOVIPREP (evening-only) N=137	91 (**66.4**)	39 (28.5)	52 (38.0)	46 (**33.6**)	38 (27.7)	8 (5.8)
OSPS N=143	99 (**69.2**)	41 (28.7)	58 (40.6)	44 (**30.8**)	39 (27.3)	5 (3.5)

Reference: Adapted from Volume 75.1, Table 4.1.1.2, Page 77

Two Secondary Efficacy Endpoints: The mean score of the 5-point (0-4) Verbal Rating Scale (VRS) scores of the five colonic segments as judged by expert gastroenterologists and colonoscopists (see Table 19).

Table 19: The mean score 5-point Verbal Rating Scale score to assess the cleansing effectiveness in the five colonic segments* in the French study in the PP population

	Expert-based	Colonoscopist-based
MOVIPREP (evening-only)	2.82 (0.56) n=137	2.75 (0.71) n=164
OSPS	2.80 (0.62) n=144	3.0 (0.63) n=164

Reference: Adapted from Volume 61.1, Table 15, Page 67

Medical Reviewer's Comments: **The similar scores of MOVIPREP compared to OSPS in the three important secondary efficacy endpoints supports the efficacy of MOVIPREP in colon cleansing.**

6.5 Clinical Microbiology

This section is not applicable.

6.6 Efficacy Conclusions

In the German, phase 3 study, GoLYTELY was numerically better than MOVIPREP in colon cleansing. In the French phase 3 study, MOVIPREP was numerically better than oral sodium phosphate solution (OSPS) in colon cleansing. In summary, this medical officer believes that the German and French efficacy results support the efficacy of MOVIPREP in colon cleansing in preparation for a colonoscopy in adult patients.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths in any of the patients in the four MOVIPREP studies (the German Study, the French Study, Study 01/2000, and Study 02/2000). In addition, there were no deaths in any of the healthy subjects in the two pharmacodynamic studies that did not include MOVIPREP treatment groups (Studies 98002 and N00/01).

7.1.2 Other Serious Adverse Events

In all four of the MOVIPREP studies (the German study, the French study, Study 01/2000, and Study 02/2000), five patients developed SAEs (see Table 20 for the narratives). Of the five SAEs, two occurred in patients who received MOVIPREP and three occurred in the patients who received OSPS. In the two pharmacodynamic studies that did not include MOVIPREP dosing (Studies 98002 and N00/01), there were no SAEs in any of the healthy subjects.

Table 20: Patient narratives of SAEs in the MOVIPREP trials (the German and French studies and Studies 01/2000 and 02/2000)

	Study/ Patient ID#	Study Drug	Medical History and SAEs
1	**French Study/ Patient 255 in Center 6**	**OSPS**	47 year old female received OSPS before an elective colonoscopy. During the colonoscopy, the patient developed **acute hypoxia** that required supplemental oxygen and the colonoscopy needed to be stopped. The patient recovered without sequelae and the colonoscopy was completed. The investigator did not believe that this SAE was secondary to the study treatment.
2	**French Study/ Patient 268 in Center 10**	**OSPS**	42 year old female received OSPS before an elective colonoscopy. Post-treatment the patient developed **asymptomatic hypokalemia** (potassium level equal to 2.87 mmol/L). She was treated in a hospital with potassium supplementation and discharged on the same day. The patient recovered without sequelae.
3	**French Study/ Patient 267 in Center 10**	**OSPS**	40 year old female received OSPS before an elective colonoscopy. She developed **hypokalemia** (potassium level was 2.74 mmol/L) right before the colonoscopy on the colonoscopy day. She had no clinical symptoms; however, she had **flattening of her T waves** on her ECG. She required hospitalization with intravenous potassium supplementation. The patient recovered without sequelae.
4	**Study 01/2000 Patient 17**	**MOVIPREP**	29 year old male who developed bloody diarrhea was admitted to the hospital for evaluation. He was treated with volume replacement and he recovered. The patient received MOVIPREP. On the next day, colonoscopy showed **colonic ulcers** (which were treated with argon plasma coagulation). The investigator did not feel the ulcers were drug-related.
5	**Study 02/2000 Patient 29**	**MOVIPREP**	60 year old female with a history of inflammatory colon disease with chronic diarrhea and baseline hypokalemia (potassium equal to 2.4 mmol/L) on the day prior to the colonoscopy was scheduled for an elective colonoscopy to evaluate her diarrhea. She received the first liter of MOVIPREP on the evening before the colonoscopy. Subsequently, after beginning the second liter of MOVIPREP, she **vomited** and could not complete the colon preparation. Her blood tests, showed **hypokalemia** (potassium equal to 2.7 mmol/L) before the colonoscopy on the day of the colonoscopy. Her hypokalemia was treated with intravenous potassium supplementation which prolonged her hospitalization. On the following day, the colonoscopy displayed a polyp. The patient had no lasting sequelae from her SAEs.

Reference: Adapted from Volume 61.1, Section 12.3.2, Page 87; Volume 13.1 Section 12.2, Pages 54-55; Volume 19.1, Section 12.3.1.2, Page 37.

Medical Reviewer's Comments: This medical officer believes that one of the two MOVIPREP-associated SAEs was drug-related and the other SAE was not drug-related. This medical officer believes that MOVIPREP contributed to Patient 29's SAE. MOVIPREP most likely contributed to Patient 29's vomiting which worsened her hypokalemia. However, this medical officer believes that MOVIPREP was not the only contributing factor to her hypokalemia. Most likely Patient 29's baseline hypokalemia, possibly from her chronic diarrhea, contributed to her persistent hypokalemia. This medical officer believes that this SAE was not specific to MOVIPREP and it is likely that this SAE would have occurred with another approved colonoscopy preparation.

This medical officer believes that MOVIPREP did not contribute to Patient 17's SAE.

Out of 413 patients exposed to MOVIPREP in the four clinical MOIVPREP studies, 1 (0.24%) patient had a drug-related SAE.

This medical officer believes that two of the three OSPS-associated SAEs were drug-related because sodium phosphate colon preparations have been associated with hypokalemia and arrhythmias. Out of 171 patients exposed to OSPS in the one French Study, 2 (1.17%) patients had drug-related SAEs.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In the MOVIPREP studies submitted in this NDA (the German Study, the French Study, Study 01/2000, and Study 02/2000), 6 patients developed AEs and discontinued from the study and did not receive a colonoscopy (see Table 21 for the narratives). Of these 6 patients, 4 received MOVIPREP and 2 received GoLYTELY. The AEs included nausea, vomiting, and malaise.

Table 21: Narratives of patients who experienced AEs and who discontinued from participation from the MOVIPREP studies (the German Study, French Study, and the two phase 2 studies)

	Patient ID#	Study (Center)	Study Drug	Narratives
1	Patient 39	Study 01/2000	MOVIPREP	37 year old female, with no significant past medical history, received 1 liter of MOVIPREP and then had **nausea**. The patient discontinued study treatment and did not have a colonoscopy.
2	Patient 20	German Study (in Center 5)	GoLYTELY	35 year old female, with no significant past medical history, who was referred for a colonoscopy because of blood in her stool, diarrhea, and weight loss. After taking 250 mL of GoLYTELY, she developed **nausea and vomiting** which required

				discontinuation of study medication. She did not have a colonoscopy. She recovered from her AEs with no sequelae. The investigator believed that her AE was definitely related to her study drug.
3	**Patient 27**	**German Study** (in Center 9)	**MOVIPREP**	43 year old male, with a history of Crohn's disease, appendectomy, non-Hodgkin's lymphoma, Chlamydia, depression, arthralgia, and vitiligo, received about 500 mL of MOVIPREP and then had **nausea and mild malaise**. He did not have a colonoscopy. The investigator thought these AEs were probably related to the study medication. The AEs resolved without sequelae.
4	**Patient 2**	**German Study** (in Center 13)	**MOVIPREP**	77 year old female with a past medical history of constipation, cardiac failure, rheumatoid arthritis, osteoporosis, glaucoma, and abdominal pain received MOVIPREP. She experienced **malaise** during the evening before the colonoscopy and stopped the study drug and did not have a colonoscopy. The investigator considered the AE probably related to the study medication.
5	**Patient 29**	**German Study** (in Center 13)	**GoLYTELY**	66 year old female (with a history of GERD, abdominal pain, nausea, *H. pylori,* headache, myalgia, extrapyramidal disorder, depressed mood, and insomnia) who was taking omeprazole, tramadol, metoclopramide, clarithromycin, metronidazole, temazepam, and amitriptyline who was referred for a colonoscopy for colon cancer screening. She developed **mild nausea** after taking GoLYTELY and did not have the colonoscopy. The investigator believed that her AE was definitely related to her study drug. She recovered without sequelae.
6	**Patient 55**	**French Study** (in Center 5)	**MOVIPREP**	56 year old female with a past medical history of cholecystectomy, myocardial infarction, and coronary angioplasty was referred for a screening colonoscopy. After two glasses of MOVIPREP, she **vomited** and the study drug was discontinued. The AE resolved without sequelae and the investigator stated that the AE was probably related to the study medication. The patient did not have the colonoscopy.

Reference: Adapted from Volume 13.1, Section 12.2, Pages 54-55; Volume 61.1, Section 10.1.1, Table 7, Page 52; the case report forms in Volumes 85.1, 86.1, and 87.1; and the March 22, 2006 submission from the sponsor.

Medical Reviewer's Comments: The AEs that contributed to study discontinuation (nausea, vomiting, and malaise) were also some of the most common drug-related AEs.

Patients who received MOVIPREP were not more likely to discontinue the study compared to patients who received GoLYTELY. This supports the safety of MOVIPREP.

7.1.3.2 Adverse events associated with dropouts

Please see responses to Section 7.1.3.1.

7.1.3.3 Other significant adverse events

There are no other significant AEs.

7.1.4 Other Search Strategies

Please see Section 7.1.7 (Laboratory Findings) for a detailed review of the electrolyte changes associated with MOVIPREP administration.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

AEs were recorded in the four MOVIPREP studies after the patients received their colon preparation. In these four studies, patients were allowed to record AEs throughout the treatment period and in these four studies patients had visits on the colonoscopy day. The patients were encouraged to report AEs spontaneously in their diary cards or in more serious cases by contacting the investigator.

In the German study, patients were asked in their diary cards to state if the following five symptoms occurred after dosing with study medication: indisposition, nausea, vomiting, stomach-ache, and abdominal pain.

In the French study, patients were given a questionnaire including the following 11 AEs: shiver, anal irritations, bloating or abdominal fullness, sleep loss, nausea, vomiting, weakness, hunger sensation, abdominal cramps or pain, thirsty sensation, and dizziness.

Medical Reviewer's Comments: The procedures for AE collection in the four MOVIPREP studies were similar. All four studies only had one treatment period visit.

This medical officer believes that the safety follow-up monitoring was suboptimal in the four MOVIPREP studies. All four studies did not have any follow-up safety monitoring visits. Since PEG-based products have been associated with electrolyte disorders that have lasted for

several days after the colonoscopy and rare clinical events (including seizures) have occurred, optimal safety follow-up visits should have been conducted in the MOVIPREP studies.

This medical officer would expect higher frequencies of AEs that were highlighted in the patient's diaries in the German and French studies.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor used Medical Dictionary for Regulatory Activities (MEDRA) version 5.1 to classify preferred AE terms.

7.1.5.3 Incidence of common adverse events

Table 22 displays the frequencies of the most common AEs (≥ 1% in at least one of the treatment groups) in order of frequency in the German study.

Table 22: The number (%) of the most common AEs (≥ 1%) in the safety population in the German study

Preferred Terms*	MOVIPREP Split doses (N=180)	GoLYTELY (N=179)
Malaise, n (%)	38 (21.1)	39 (21.8)
Nausea, n (%)	27 (15.0)	42 (23.5)
Abdominal pain, n (%)	26 (14.4)	31 (17.3)
Vomiting, n (%)	14 (7.8)	23 (12.8)
Upper abdominal pain, n (%)	10 (5.6)	11 (6.1)
Dyspepsia, n (%)	5 (2.8)	5 (2.8)
Headache n (%)	2 (1.1)	1 (0.6)
Post-procedural hemorrhage n (%)	2 (1.1)	0 (0)

* MedDRA 5.1 preferred terms
Reference: Volume 37.1, Table 21, Page 80; and Volume 2.1, Section 2.7.4.2.1.1.3, Table 2.7.4.2-5, Pages 17-18

Table 23 displays the frequencies of the most common AEs (≥ 1% in at least one of the treatment groups) in order of frequency in the French study.

Table 23: The number (%) of the most common AEs (≥ 1% in one of the treatment groups) in the safety population in the French study

Preferred Terms*	MOVIPREP Evening-only (N=169)	OSPS (N=171)
Abdominal distension, n (%)	101 (59.8)	70 (40.9)
Anal discomfort, n (%)	87 (51.5)	89 (52.0)
Thirst, n (%)	80 (47.3)	112 (65.5)
Nausea, n (%)	80 (47.3)	80 (46.8)
Abdominal pain, n (%)	66 (39.1)	55 (32.2)
Sleep disorder, n (%)	59 (34.9)	49 (28.7)
Rigors, n (%)	57 (33.7)	51 (29.8)
Hunger, n (%)	51 (30.2)	121 (70.8)
Malaise, n (%)	45 (26.6)	90 (52.6)
Vomiting, n (%)	12 (7.1)	14 (8.2)
Dizziness, n (%)	11 (6.5)	31 (18.1)
Headache n (%)	3 (1.8)	9 (5.3)
Dysphagia, n (%)	2 (1.2)	0 (0)
Upper abdominal pain, n (%)	1 (0.6)	2 (1.2)
Hypokalemia, n (%)	0 (0)	12 (7.0)
Hyperphosphatemia, n (%)	0 (0)	10 (5.8)
Migraine, n (%)	0 (0)	2 (1.2)
Dyspepsia, n (%)	0 (0)	0 (0)

* MedDRA 5.1 preferred terms
Reference: Volume 66.1, Complementary Table 8, Page 106; and Volume 2.1, Section 2.7.4.2.1.1.3, Table 2.7.4.2-8, Pages 19-21

Medical Reviewer's Comments: **This medical officer selected only the two controlled MOVIPREP studies to display the common AEs.**

The most frequent AEs in the German and French studies are common AEs associated with colon preparations. In the German study, the patients in the MOVIPREP treatment group had lower (or similar) frequencies of common AEs compared to the patients in the GoLYTELY treatment group. In the French study, the patients in the MOVIPREP treatment group had lower (or similar) frequencies of the overwhelming majority of common AEs compared to the patients in the OSPS treatment group.

Patients in the MOVIPREP treatment group had numerically higher frequencies of abdominal pain, abdominal distension, sleep disorders, and rigors compared to the patients in the OSPS treatment group. These discrepancies may be due to the higher required total volume of the

MOVIPREP treatment (3 liters which includes 2 liters of MOVIPREP and 1 liter of fluid) compared to the OSPS treatment (2 liters of fluid which is mostly concomitant fluid).

In general the patients in the French study experienced more GI AEs compared to the patients in the German study. One possibly explanation is that the French study had patients taking the colon preparation in a shorter time (only on the day prior to the colonoscopy). In contrast, the German study had patients split the colon preparation doses into two days (the evening prior to and the day of the colonoscopy). Additionally, the two phase 3 studies had different procedures and they were conducted in two different countries.

7.1.5.4 Common adverse event tables

Please see Section 7.1.5.3.

7.1.5.5 Identifying common and drug-related adverse events

Table 24 displays the frequencies of the most common drug-related AEs (≥ 1% in at least one of the treatment groups) in order of frequency in the German study.

Table 24: The number (%) of the most common drug-related AEs* (≥ 1%) in the safety population in the German study

Preferred Terms**	MOVIPREP Split doses (N=180)	GoLYTELY (N=179)
Malaise, n (%)	35 (19.4)	32 (17.9)
Nausea, n (%)	26 (14.4)	36 (20.1)
Abdominal pain, n (%)	24 (13.3)	27 (15.1)
Vomiting, n (%)	14 (7.8)	23 (12.8)
Upper abdominal pain, n (%)	10 (5.6)	11 (6.1)
Dyspepsia, n (%)	5 (2.8)	2 (1.1)

* Drug-related AEs were AEs that were possibly, probably, or definitely related to the study drug;
** MedDRA 5.1 preferred terms
Reference: Volume 75.1, Table 6.2.3.1, Page 136; and Volume 2.1, Section 2.7.4.2.1.1.3, Table 2.7.4.2-6, Pages 18-19

Table 25 displays the frequencies of the most common drug-related AEs (≥ 1% in at least one of the treatment groups) in order of frequency in the French study.

Table 25: The number (%) of the most common drug-related AEs* (≥ 1%) in the safety population in the French study

Preferred Terms**	MOVIPREP Evening-only (N=169)	OSPS (N=171)
Abdominal distension, n (%)	101 (59.8)	70 (40.9)
Anal discomfort, n (%)	87 (51.5)	89 (52.0)
Thirst, n (%)	80 (47.3)	112 (65.5)
Nausea, n (%)	80 (47.3)	80 (46.8)
Abdominal pain, n (%)	66 (39.1)	55 (32.2)
Sleep disorder, n (%)	59 (34.9)	49 (28.7)
Rigors, n (%)	57 (33.7)	51 (29.8)
Hunger, n (%)	51 (30.2)	121 (70.8)
Malaise, n (%)	45 (26.6)	90 (52.6)
Vomiting, n (%)	12 (7.1)	14 (8.2)
Dizziness, n (%)	11 (6.5)	31 (18.1)
Headache n (%)	3 (1.8)	9 (5.3)
Dysphagia, n (%)	2 (1.2)	0 (0)
Upper abdominal pain, n (%)	1 (0.6)	2 (1.2)
Hypokalemia, n (%)	0 (0)	10 (5.8)
Hyperphosphatemia, n (%)	0 (0)	10 (5.8)
Migraine, n (%)	0 (0)	2 (1.2)
Dyspepsia, n (%)	0 (0)	0 (0)

* Drug-related AEs were AEs that were possibly, probably, or definitely related to the study drug

** MedDRA 5.1 preferred terms

Reference: Volume 66.1, Complementary Table10, Page 109; and Volume 2.1, Section 2.7.4.2.1.1.3, Table 2.7.4.2-9, Pages 21-22

Medical Reviewer's Comments: **The frequencies of the most common AEs and the most common drug-related AEs in the German and French studies are almost identical. Please see the medical officer comments in Section 7.1.5.5.**

The frequency of hyperphosphatemia in the OSPS patients (5.8%) in the French study was much lower than the frequency of hyperphosphatemia in other sodium phosphate trials. In four Visicol studies (one phase 1, one phase 2, and two phase 3 studies), two OsmoPrep studies, and one OSPS study, the frequency of hyperphosphatemia was about 95% in patients who received 60 grams of sodium phosphate.

The difference in the frequencies of hyperphosphatemia between the French Study and the other sodium phosphate studies can be explained by the different timing of the phosphate measurements relative to the last dose of sodium phosphate administration. In the four Visicol studies, two OsmoPrep studies, and one OSPS study, the dose of sodium phosphate was split into the evenings before the colonoscopy and the days of the colonoscopy. In contrast, in the French study, the sodium phosphate dose was split between the mornings (starting at 7 AM) on the day prior to the colonoscopy and the evenings (starting at 7 PM) before the colonoscopy. In the Visicol, OsmoPrep, and prior OSPS studies, the duration between the last sodium phosphate administration and the phosphate blood test was usually performed about three hours later; in contrast, the duration between the last sodium phosphate administration and the phosphate blood test was over 12 hours in the French study. In the French study, most likely the phosphate level rose above normal in the overwhelming majority of patients within several hours after the last sodium phosphate dose (in the evening before the colonoscopy) and the phosphate level normalized 12 hours later on the morning of the colonoscopy when the phosphate blood tests were taken.

In the French study, each of the 15 centers had their own normal ranges of blood tests. The lower bound of normal phosphate level for the 15 centers was 0.70 mmoles/liter (2.1 mg/dL) and the upper bound of normal phosphate level for the 15 centers was 1.5 mmoles/liter (4.5 mg/dL).

7.1.5.6 Additional analyses and explorations

Medical Reviewer's Comments: **Patients in the MOVIPREP evening-only dose (in the French study) had more drug-related AEs compared to patients in the MOVIPREP split dose (in the German study). It is possible that the former group experienced more drug-related AEs because they received the 3 liters of MOVIPREP preparation (the 2 liters of MOVIPREP and the concomitant 1 liter of fluid) over a shorter period time compared to the later group. However, it is difficult to extrapolate the safety information because these phase 3 studies were conducted in two different countries.**

Adaptation, dose dependency, and delayed AEs can not be explored with the design of the colon preparation studies.

7.1.6 Less Common Adverse Events

Since this NDA has a relatively small safety database, this medical officer will not analyze less common AEs.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In all four MOVIPREP trials, laboratory tests were performed prior to study treatment dosing) and on the day of the colonoscopy. Thus, laboratory testing was performed twice: at baseline and once after study treatment administration. No MOVIPREP study included safety follow-up laboratory testing several days after the colonoscopy. All four studies differed in the types of laboratory tests and in the timing of the two blood draws. The following list describes the specific blood tests and the timing of those blood tests in the four MOVIPREP studies:

- In the German study, laboratory testing [including creatinine, BUN, protein, sodium, potassium, chloride, bicarbonate, SGOT (AST), SGPT (ALT), and CBC tests] were performed at baseline (1 to 2 days prior to the colonoscopy) and on the day of the colonoscopy (prior to the colonoscopy or within two hours after the colonoscopy).
- In the French study, laboratory testing (including hematocrit, sodium, potassium, chloride, bicarbonate, BUN, creatinine, protein, calcium, and phosphate tests) were performed at baseline (within 30 days prior to the colonoscopy) and on the day of the colonoscopy (immediately before the colonoscopy).
- In Study 01/2000, laboratory testing (including SGOT, SGPT, alkaline phosphatase, gamma-GT, CBC, sodium, potassium, creatinine, and BUN tests) were performed at baseline (1 to 2 days prior to the colonoscopy) and on the morning of the colonoscopy.
- In Study 02/2000, laboratory testing (including SGOT, SGPT, alkaline phosphatase, gamma-GT, CBC, sodium, potassium, chloride, bicarbonate, total protein, creatinine, and BUN tests) were performed at baseline (on the day prior to the colonoscopy) and on the morning of the colonoscopy.

Medical Reviewer's Comments: **The laboratory tests included a larger variety of tests compared to other colon preparation studies.**

This medical officer believes that the safety laboratory monitoring was suboptimal. None of the four MOVIPREP studies included a safety follow-up laboratory visit several days after the colonoscopy. In the two Visicol phase 3 trials (which compared the safety and efficacy of Visicol and NuLYTELY in patients referred for an elective colonoscopy), NuLYTELY, a PEG-based colon preparation, was associated with hyponatremia in 31% to 36% of the patients 2-3 days after the colonoscopy. Additionally, in these trials, NuLYTELY was associated with hypocalcemia in 8% to 10% of the patients 2-3 days after the colonoscopy. Since PEG-based colon preparations are associated with electrolyte changes (several days after the colonoscopy), optimal safety testing of PEG-based colon preparations include post-colonoscopy laboratory testing.

Additionally, this medical officer believes that optimum laboratory testing would include more frequent post-dosing laboratory tests. All four MOVIPREP studies only conducted laboratory tests one time after study drug administration.

In addition, coagulation blood tests (including INR and PTT) were not performed in the MOVIPREP studies.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This medical officer selected the German study and the French study to compare laboratory values between the treatment groups because these were the only two controlled MOVIPREP trials submitted in this NDA, they contained the proposed patient population (patients who will undergo elective colonoscopy), and included the two proposed MOVIPREP dosing regimens. Furthermore, both studies had active control treatment groups (GoLYTELY in the German study and OSPS in the French study), approved in the cleansing of the colon before colonoscopy.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Table 26 displays the mean baseline and post-dosing levels of the main laboratory parameters in the German and French studies.

Table 26: Central tendencies of laboratory measurements in the safety population in the German and French studies

		German Study		French Study	
Laboratory Test	**Measurement Day**	**MOVIPREP**	**GoLYTELY**	**MOVIPREP**	**OSPS**
Mean Phosphate level (mmole/L)	Screening	N/A	N/A	1.33	1.03
	Colonoscopy Day	N/A	N/A	1.32	1.55
	Mean Change	N/A	N/A	-0.01	0.52
Mean Sodium level (mmole/L)	Screening	139.56 (n=172)	139.31 (n=171)	140.0	140.2
	Colonoscopy Day	139.88 (n=172)	139.69 (n=171)	140.7	141.35
	Mean Change	0.33	0.38	0.70	1.15
Mean Potassium level (mmole/L)	Screening	4.25 (n=173)	4.31 (n=172)	4.18	4.15
	Colonoscopy Day	4.21 (n=173)	4.10 (n=172)	4.02	3.67
	Mean Change	-0.04	-0.21	-0.16	-0.48
Mean Calcium level (mmole/L)	Screening	N/A	N/A	2.38	2.38
	Colonoscopy Day	N/A	N/A	2.33	2.29
	Mean Change	N/A	N/A	-0.05	-0.09
Mean Creatinine	Screening	87.09 (n=172)	82.70 (n=171)	80.91	79.73

level (µmol/L)	Colonoscopy Day	84.35 (n=172)	77.23 (n=171)	79.9	79.42
	Mean Change	-2.73	-5.48	-1.01	0.31
Mean BUN level (µmol/L)	Screening	4.95 (n=160)	5.12 (n=156)	5.59	5.48
	Colonoscopy Day	4.33 (n=160)	4.26 (n=156)	4.89	4.76
	Mean Change	-0.62	-0.87	-0.70	-0.72
Mean Hematocrit level (U/L or %)* in German Study and % in French Study)	Screening	0.39 (n=175)	0.39 (n=173)	41.7	41.1
	Colonoscopy Day	0.39 (n=175)	0.38 (n=173)	41.47	40.62
	Mean Change	0	-0.01	-0.23	0.48
AST (U/L)	Screening	14.27 (n=171)	13.38 (n=166)	N/A	N/A
	Colonoscopy Day	15.95 (n=171)	13.76 (n=166)	N/A	N/A
	Mean Change	1.67	0.38	N/A	N/A
ALT (U/L)	Screening	16.44 (n=172)	15.52 (n=166)	N/A	N/A
	Colonoscopy Day	18.05 (n=172)	15.94 (n=166)	N/A	N/A
	Mean Change	1.61	0.43	N/A	N/A
Serum Osmolality (mosm/kg)	Screening	297.49 (n=136)	294.04 (n=130)	N/A	N/A
	Colonoscopy Day	291.90 (n=136)	292.91 (n=130)	N/A	N/A
	Mean Change	-5.58	-1.13	N/A	N/A

The French study did not perform AST, ALT, or serum osmolality tests; thus these tests are not available (N/A)
The German study did not perform calcium and phosphate tests, thus these tests are not available (N/A)
* The German study used U/L and the French study used % for the Hematocrit parameters
Reference: Adapted from Volume 61.1, Section 12.4.2, Summary Table 29, Page 95 and Volume 41.1, Tables 14.3.3.1.1 and 14.3.3.1.2, Pages 856-861

Medical Reviewer's Comments: **In the German study, there was no clinically significant change in the following blood tests for the MOVIPREP treatment group: sodium, potassium, creatinine, BUN, and hematocrit. In the German study, there was a slight mean increase in the hepatic enzyme tests compared to GoLYTELY; however, the change was not clinically meaningful. In addition, there was a slight drop in the serum osmolality in the MOVIPREP group compared to GoLYTELY in the German study. However, this is not clinically meaningful.**

In the French study, there was no clinically significant change in the following blood tests for the MOVIPREP treatment group: phosphate, sodium, potassium, calcium, creatinine, BUN, and hematocrit. In this study, the OSPS treatment group had a greater increase in the phosphate level and a greater decline in the potassium level compared to MOVIPREP. This is consistent with other sodium phosphate colon preparation studies.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 27 displays electrolyte abnormalities that occurred after patients received study treatment in the German and French studies. These tables exclude patients who had baseline abnormal electrolyte levels. For example, patients who had baseline hypernatremia were excluded in the frequencies of hypernatremia. However, patients with baseline hyponatremia and patients with normal sodium levels were included in the hypernatremia analyses in Table 27.

Table 27: Electrolyte shifts in the safety population in the German and French studies

	German Study		French Study	
Laboratory Abnormality	**MOVIPREP n (%)**	**GoLYTELY n (%)**	**MOVIPREP n (%)**	**OSPS n (%)**
Hypernatremia[a]	2 (1.1)	2 (1.1)	4 (2.4)	9 (5.3)
Hyponatremia[b]	4 (2.2)	4 (2.2)	0 (0)	3 (1.8)
Hypokalemia[a]	9 (5.0)	15 (8.4)	14 (8.3)	53 (31.0)
Hyperkalemia[b]	0 (0)	0 (0)	2 (1.2)	2 (1.2)
Increased creatinine[b]	4 (2.2)	2 (1.1)	1 (0.6)	4 (2.3)
Increased BUN[b]	0 (0)	0 (0)	2 (1.2)	3 (1.8)
Decreased Hematocrit[a]	13 (7.2)	16 (8.9)	17 (10.1)	10 (5.8)
Increased AST[b]	13 (7.3)	9 (5.1)	N/A	N/A
Increased ALT[b]	6 (3.4)	5 (2.8)	N/A	N/A

Not all of the patients had laboratory blood tests

a Patients with baseline hyponatremia, hypokalemia, and decreased hematocrit were excluded from hyponatremia, hypokalemia, and decreased hematocrit analyses, respectively.

b Patients with baseline hypernatremia, hyperkalemia, increased creatinine, increased BUN, increased AST, and increased ALT were excluded from hypernatremia, hyperkalemia, increased creatinine, increased BUN, increased AST, and increased ALT analyses, respectively.

AST and ALT levels were not performed in the French study.

Reference: Adapted from Volume 75.1, Tables 6.4.1.1.1 to 6.4.8.2.2, Pages 163-209 and Volume 41.1, Table 14.3.3.3, Pages 885-889

Medical Reviewer's Comments: **The MOVIPREP treatment groups had equal or lower frequencies of hypernatremia, hyperkalemia, hyponatremia, hypokalemia, and increased BUN compared to the comparator groups in the German and French studies. MOVIPREP had a**

higher percentage of decreased hematocrit compared to OSPS in the French study, but had a lower percentage of decreased hematocrit compared to GoLYTELY in the German study.

The most common electrolyte abnormality associated with MOVIPREP administration in the German and French trials was hypokalemia. MOVIPREP was not associated with a significant frequency of hyponatremia in the two trials. However, there have been several post-marketing seizures (with a mean sodium level of 120) after PEG-based colon preparation administration.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Please see Section 7.1.7.3.2.

7.1.7.4 Additional analyses and explorations

Please see Section 7.1.7.3.2.

7.1.7.5 Special assessments

Please see Table 26 for central tendencies of AST and ALT lab tests in the German study and Table 27 for the frequencies of increased AST and ALT levels in the German study. AST and ALT tests were not performed in the French study. The sponsor did not perform albumin, alkaline phosphatase, and total bilirubin levels in controlled MOVIPREP trials. Although alkaline phosphatase levels were drawn in Studies 01/2000 and 02/2000, these phase 2 studies had no control group so this medical officer will not comment on these alkaline phosphatase results.

Medical Reviewer's Comments: The frequencies of increased ALT and increased AST levels in the German study were similar in the MOVIPREP and GoLYTELY treatment groups. In addition the mean changes in ALT and AST levels, compared to baseline, were not clinically significant in the German study.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The German and the French studies performed heart rate and blood pressure measurements at screening and right before the colonoscopy on the day of the colonoscopy. In addition, the German study conducted weight measurements at screening and right before the colonoscopy.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

This medical officer selected the German study and the French study to compare vital signs results between the treatment groups because these were the only two controlled MOVIPREP trials submitted in this NDA, they contained the proposed patient population (patients who will undergo

elective colonoscopy), and they included the two proposed MOVIPREP dosing regimens. Furthermore, both studies had active control treatment groups (GoLYTELY in the German study and OSPS in the French study), approved in the cleansing of the colon before colonoscopy.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Tables 28 and 29 display the central tendencies of systolic blood pressure, diastolic blood pressure, and heart rate in the German and French studies, respectively.

Table 28: Central tendencies of vital signs in the safety population in the German study

		MOVIPREP		GoLYTELY	
Laboratory Test	**Measurement Day**	Actual	Change	Actual	Change
Mean (SD) systolic blood pressure (mm of Hg)	Screening	129.5 (17.4) (n=180)		128.1 (17.2) (n=179)	
	Evening before Colonoscopy	135.7 (20.1) (n=177)	6.0 (21.2) (n=177)	140.3 (22.1) (n=175)	12.1 (21.5) (n=175)
	After Colonoscopy	127.4 (20.4) (n=176)	-2.3 (20.0) (n=176)	126.4 (20.6) (n=174)	-1.9 (22.0) (n=174)
Mean (SD) diastolic blood pressure (mm of Hg)	Screening	77.3 (10.3) (n=180)		76.5 (11.1) (n=179)	
	Evening before Colonoscopy	78.9 (10.6) (n=177)	1.5 (12.2) (n=177)	81.2 (11.6) (n=175)	-4.7 (13.5) (n=175)
	After Colonoscopy	76.9 (12.5) (n=176)	-0.6 (13.1) (n=176)	77.1 (12.4) (n=174)	0.6 (13.8) (n=174)
Mean (SD) pulse rate (beats per minute)	Screening	74.6 (10.7) (n=180)		73.6 (9.0) (n=178)	
	Evening before Colonoscopy	78.7 (13.3) (n=177)	4.0 (14.4) (n=177)	79.1 (14.5) (n=175)	5.7 (15.2) (n=174)
	After Colonoscopy	82.6 (16.2) (n=177)	7.9 (16.5) (n=177)	81.6 (16.0) (n=173)	8.2 (15.9) (n=172)

Reference: Adapted from Volume 41.1, Tables 14.3.4.1, 14.3.4.2, and 14.3.4.3, Pages 890-892

Table 29: Central tendencies of vital signs in the safety population in the French study

		MOVIPREP		OSPS	
Laboratory Test	**Measurement Day**	Actual	Change	Actual	Change
Mean (SD) systolic blood pressure (mm of Hg)	Screening	129.4 (14.2)		127.8 (16.0)	
	Colonoscopy Day	129.5 (15.0)	0.1	128.6 (16.1)	0.8
Mean (SD) diastolic blood pressure (mm of Hg)	Screening	76.3 (10.3)		76.3 (9.9)	
	Colonoscopy Day	76.5 (10.2)	0.2	76.6 (9.9)	0.3
Mean (SD) pulse rate (beats per minute)	Screening	71.2 (10.8)		71.7 (9.5)	
	Colonoscopy Day	71.0 (10.8)	-0.2	71.5 (9.0)	-0.2

Reference: Adapted from Volume 66.1, Table 13, Page 19; Table 14, Page 19; Complementary Table, Page 153; and Complementary Table, Page 153.

Medical Reviewer's Comments: **In the German and French studies, there were no clinically meaningful changes in the systolic and diastolic blood pressure measurements after study treatment dosing. In addition, in the German and French studies, there were no clinically meaningful differences in the systolic and diastolic blood pressure and heart rate measurements in the MOVIPREP groups and the comparators.**

In the German study, the heart rate increased after study treatment dosing (MOVIPREP and GoLYTELY). Patients who receive colon preparations prior to colonoscopy have decreased food intake and are likely to have slight intravascular depletion which leads to a secondary increase in heart rate. These changes are consistent with the safety results of other colon preparation trials. This medical officer does not believe that the increased heart rate is specific to MOVIPREP.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Given the results of the central tendency analyses of vital signs, this medical officer did not evaluate outliers or shifts in vital sign measurements.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Given the results of the central tendency analyses of vital signs, this medical officer did not evaluate marked outliers in vital sign measurements.

7.1.8.4 Additional analyses and explorations

There were no additional analyses of vital signs performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

All of the MOVIPREP studies did not have ECGs performed at baseline, during the treatment period, or after the treatment period.

Medical Reviewer's Comments: This medical officer believes that routine ECG testing should have been performed in the MOVIPREP trials because ECG testing is standard for phase 3 trials. Additionally, MOVIPREP and PEG-based products have been associated with hypokalemia and hypokalemia increases the risk of prolongation of the QT interval. However, in the AERS database from 1996 to 2003, only one post-marketing case of ventricular arrhythmia with hypokalemia occurred in a patient who received a PEG-based colon preparation. Also MOVIPREP was associated with a lower frequency of hypokalemia then the approved colon preparation comparators in the German and French studies.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

All of the MOVIPREP studies did not have ECGs performed at baseline, during the treatment period, or after the treatment period.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

All of the MOVIPREP studies did not have ECGs performed at baseline, during the treatment period, or after the treatment period.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

All of the MOVIPREP studies did not have ECGs performed at baseline, during the treatment period, or after the treatment period.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

All of the MOVIPREP studies did not have ECGs performed at baseline, during the treatment period, or after the treatment period

7.1.9.4 Additional analyses and explorations

All of the MOVIPREP studies did not have ECGs performed at baseline, during the treatment period, or after the treatment period.

7.1.10 Immunogenicity

MOVIPREP is not a protein and does not demonstrate evidence for immunogenicity.

7.1.11 Human Carcinogenicity

Since the proposed MOVIPREP dosage regimen is for short-term use — two days of treatment — human carcinogenicity studies were not required.

Non-clinical carcinogenicity studies were not required because of the proposed short duration of MOVIPREP use.

7.1.12 Special Safety Studies

The sponsor did not perform a thorough QT/QTc study for this NDA. There were no other studies to evaluate specific safety concerns.

Medical Reviewer's Comments: This medical officer believes that a thorough QT/QTc study would have been optimal for this NDA. However, there have not been a significant number of post-marketing reports of arrhythmias or prolonged QT associated with administration of PEG-based colon preparation products that have been marketed in the United States for over 20 years. Therefore, this medical officer does not believe that a thorough QT/QTc study is required for approval of this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

All laxatives and purgatives (including MOVIPREP) have the potential for abuse by bulimia nervosa patients who frequently have binge eating and vomiting.

The safety monitoring in the German and French studies was not adequate to detect withdrawal, abuse, or other post-dosing affects.

7.1.14 Human Reproduction and Pregnancy Data

There has been no MOVIPREP exposure in pregnant women.

7.1.15 Assessment of Effect on Growth

MOVIPREP was not studied in the pediatric population. Height measurements in the treatment period were not performed in the MOVIPREP development program.

7.1.16 Overdose Experience

According to the sponsor, no case of overdose was seen during the MOVIPREP clinical program. According to the sponsor, the expected clinical consequence of overdose of a PEG-based colon preparation is diarrhea and possibly dehydration.

Medical Reviewer's Comments: Purposeful or accidental ingestion of more than the recommended dose of MOVIPREP might be expected to lead to severe electrolyte disturbances, including hyponatremia and/or hypokalemia, as well as dehydration and hypovolemia, with signs and symptoms of these disturbances. Severe electrolyte disturbances resulting from overdose may lead to cardiac arrhythmias, seizure, renal failure, and/or death. The patient who has taken an overdose should be monitored carefully, and treated symptomatically for complications until stable.

7.1.17 Postmarketing Experience

MOVIPREP has never been approved in the United States or any foreign country; therefore, no post-marketing data is available.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Table 30 displays all of the subjects/patients in the MOVIPREP development program. The most important patients in the MOVIPREP development program were the patients who were referred for an elective colonoscopy in the three phase 3 trials (German study, French study, and Study 01/2004). However, the sponsor only submitted a summary of Study 01/2004 on March 14, 2006 (four weeks prior to the PDUFA goal date of April 10, 2006) and did not submit the final study report. Therefore, the most relevant studies in this NDA from a safety and efficacy standpoint are the German and French, phase 3 studies.

Study 98002 used MOVICOL, a PEG-based product approved in the European Union for constipation and fecal impaction (MOVICOL is an investigational product in the United States under IND 67,947). Two liters of MOVICOL contains 210 grams of PEG, 2.96 grams of sodium

bicarbonate, 5.6 grams of sodium chloride, 0.746 grams of potassium chloride, and lime and lemon flavor.

Table 30: A Summary of all the studies submitted in the MOVIPREP NDA

Study	Design	Treatment Group(s)	N[a]
98002	**Part 1: Phase 1, French,** DB, SC, 2-period crossover, pharmacodynamic study in healthy subjects between 18 and 45 years old **Part 2: Phase 1, French,** open-labeled, uncontrolled, SC, pharmacodynamic study in healthy subjects between 18 and 45 years old	**Part 1:** 1) Solution A then Solution B 2) Solution B then Solution A Solution A was 2 liters of MOVICOL and 20 grams of ascorbic acid Solution B was 2 liters of MOVICOL and 20 grams of saccharose (placebo) **Part 2:** 2 liters of MOVICOL, 20 grams of ascorbic acid, and 11.2 grams of sodium sulphate	7
N00/01	**Phase 1, French,** R, DB, crossover, dose-finding, pharmacodynamic study in healthy subjects between 18 and 45 years old in two centers (subjects received one colon preparation then after one to two week washout received another colon preparation)	1) PEG 200 grams; sodium sulfate 15 grams; ascorbic acid 0 grams; sodium ascorbate 0 grams, sodium chloride 5.38 grams; potassium chloride 2.12 grams 2) PEG 200 grams; sodium sulfate 15 grams; ascorbic acid 10 grams; sodium ascorbate 0 grams, sodium chloride 5.38 grams; potassium chloride 2.12 grams 3) PEG 200 grams; sodium sulfate 15 grams; ascorbic acid 10 grams; sodium ascorbate 10 grams, sodium chloride 5.38 grams; potassium chloride 2.12 grams 4) PEG 200 grams; sodium sulfate 15 grams; ascorbic acid 20 grams; sodium ascorbate 0 grams, sodium chloride 5.38 grams; potassium chloride 2.12 grams 5) PEG 200 grams; sodium sulfate 15 grams; ascorbic acid 10 grams; sodium ascorbate 10 grams; sodium chloride 5.38 grams, potassium chloride 1.64 grams 6) PEG 250 grams; sodium sulfate 15 grams; ascorbic acid 10 grams; sodium ascorbate 10 grams, sodium chloride 6.43 grams; potassium chloride 2.12 grams	30
01/2000	**Phase 2, German**, open-	**MOVIPREP (split doses):** 1 liter of	34

	label, uncontrolled, SC study in patients scheduled to have an elective colonoscopy	MOVIPREP solution and 0.5 L of water in the evening before the colonoscopy and on the day of the colonoscopy	
02/2000	**Phase 2, French,** open-label, uncontrolled, SC study in patients scheduled to have an elective colonoscopy	**MOVIPREP (evening-only)** and 1 liter of water in the evening before the colonoscopy	30
01/2001 (German Study)	**Phase 3, German**, R (1:1), single-blind (open-label to the patient and investigator-blinded), MC, parallel-group study in patients scheduled to have an elective colonoscopy	**1) MOVIPREP (split doses):** 1 liter of MOVIPREP solution and 0.5 L of water in the evening before the colonoscopy and on the day of the colonoscopy **2) GoLYTELY (split doses):** 2 liters of GoLYTELY solution in the evening before the colonoscopy and on the day of the colonoscopy	180 179
02/2001 (French Study)	**Phase 3, French,** R, (1:1), single-blind (open-label to the patient and investigator-blinded), MC, parallel-group study in patients scheduled to have an elective colonoscopy	**1) MOVIPREP (evening-only):** 2 liters of MOVIPREP solution and 1 liter of water in the evening before the colonoscopy **2) Sodium Phosphate (day before the colonoscopy):** 90 mL of OSPS (60 grams of sodium phosphate) and 2 liters of water on the day before the colonoscopy	169 171
01/2004[b]	**Phase 3, German**, R (2:1), single-blind (open-label to the patient and investigator-blinded), MC, parallel-group study in patients scheduled to have an elective colonoscopy for colon cancer screening.	**1) Total MOVIPREP dose:** 2 liters of MOVIPREP solution with an additional 1 liter of water **2) OSPS**	242 114

a ITT population
b This study was not submitted to the NDA. After an information request from the DGP, the sponsor submitted a summary report of this study on March 14, 2006. This summary report did not detail the amount of OSPS used as the comparator. In addition, this study did not detail the administration of the study drugs.
R = randomized; DB = double-blind, SC = single center; MC = multi-center
OSPS – oral sodium phosphate solution
Reference: Adapted from Final Study Reports and the summary report of Study 01/2004.

7.2.1.2 Demographics

Table 31 displays the demographics in the controlled MOVIPREP trials (the German and French studies) that the sponsor submitted in this NDA. The sponsor did not prospectively collect information regarding race in the MOVIPREP trials.

Table 31: Demographic characteristics of the safety population in the phase 3 MOVIPREP studies

Parameter		German Study		French Study	
		MOVIPREP split dose	GoLYTELY	MOVIPREP evening-only	OSPS
Safety Population	N	180	179	169	171
Age	Mean age in years (SD)	58.2 (14.6)	59.5 (15.7)	52.5 (12.4)	52.5 (11.9)
	< 65 years old, n	118	101	144[a]	119[a]
	Between 65 and 75 years old,	36	51	23[b]	26[b]
	> 75 years old, n	26	27		
Gender	Male n (%)	92 (51.1)	81 (45.3)	92 (54.4)	87 (50.9)
	Female n (%)	88 (48.9)	98 (54.7)	77 (45.6)	84 (49.1)
Creatinine Clearance[c] (CC) in mL/minute	CC > 80, %	61%	55%	N/A	N/A
	50 < CC ≤ 80, %	28%	35%	N/A	N/A
	CC ≤ 50, %	10%	9%	N/A	N/A
Concomitant IBD[d]	%	9%	5%	N/A	N/A
Weight in Kilograms	Mean (SD)	75.2 (16.3)	74.6 (16.4)	N/A	N/A

a This number is from the PP population.
b This is the combined number of patients who are > 65 years old in the PP population.
c Creatinine clearance calculated by the Cockroft and Gault formula
d IBD is inflammatory colon disease
Safety population – randomized patients who received at least one dose of study drug
N/A is not available. The DGP sent an information request regarding the percentages of each race in the French study. At the time of this review, this information request is pending.
Reference: Volume 42.1, Table 1.1, Page 1; Volume 75.1, Table 1.2.1.1, Page 24; Volume 75.1, Table 1.2.2.1, Page 29; Volume 37.1, Table 4, Page 51; Volume 38.1, Table 14.2.2.1.4, Page 21.

In the sponsor's March 14, 2006 response to DGP's information request, the sponsor stated that it did not prospectively collect race and ethnicity data in the MOVIPREP development program including the German and French Studies. According to the sponsor, all of the MOVIPREP studies were conducted in Europe and predominantly enrolled Caucasian patients of European decent. According to the sponsor, MOVIPREP "exhibits several intrinsic properties that reduce the

probability that ethnicity may effect its use as a bowel-cleansing agent. The active ingredients in MOVIPREP are not absorbed, distributed, metabolized or excreted to any appreciable extent in the human body." The sponsor stated that "the pharmacodynamic and clinical behavior of MOVIPREP in the ethnically diverse region of the United States will be similar to that observed in the clinical trials conducted in Europe."

Medical Reviewer's Comments: Since MOVIPREP is similar to many PEG-based colon preparations approved in the United States since 1984, this medical officer does not believe that the lack of ethnicity data impairs the approvability of this application. This medical officer recommends that the sponsor prospectively collect ethnicity and race data in future MOVIPREP clinical trials.

The MOVIPREP and GoLYTELY treatment groups in the German study had similar demographics including gender, age, weight, baseline renal function, and concomitant IBD. In addition, the MOVIPREP and OSPS treatment groups in the French study had similar demographics including age and gender.

7.2.1.3 Extent of exposure (dose/duration)

Patients scheduled for a colonoscopy received their entire dose of study drug within 24 hours of the colonoscopy. Table 32 displays the exposure of MOVIPREP in the MOVIPREP studies.

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Table 32: Exposure to MOVIPREP in the safety population in the studies submitted to the MOVIPREP NDA

	MOVIPREP (all dose regimens)	MOVIPREP (evening-only) in German Study	MOVIPREP (split doses) in French Study	GoLYTELY in German Study	OSPS in French Study
Dosage and Administration	2 liters of MOVIPREP and 1 liter of water	2 liters of MOVIPREP and 1 liter of water taken the evening prior to the colonoscopy	1 liter of MOVIPREP and 0.5 liters of water taken the evening prior to the colonoscopy and 1 liter of MOVIPREP and 0.5 liters of water taken the next day	2 liters of GoLYTELY solution in the evening before the colonoscopy and 2 liters of GoLYTELY on the day of the colonoscopy	90 mL of OSPS (60 grams of sodium phosphate) and 2 liters of water on the day before the colonoscopy
Number in MOVIPREP studies	**413**	**199**	**214**	**179**	**171**
Number in controlled MOVIPREP trials	**349**	**169**	**180**	**179**	**171**
Compliance Mean % (SD)	**N/A**	**99.4 (3)**	**85.8**	**98.6 (4.6)**	**97.2**
Minimum %/ Maximum % compliance	**N/A**	**75/100**	**N/A**	**75/100**	**N/A**

N/A is not available
Reference: Adapted from the final study reports: Volume 37.1, Section 11.3, Table 9, Page 58 and Volume 66.1, Section 4.1, Table 66, Page 129

Medical Reviewer's Comments: **In this MOVIPREP NDA, 349 patients received MOVIPREP in controlled clinical trials. Thus, the number of patients exposed to MOVIPREP was similar to — or greater than — the exposure to GoLYTELY, NuLYTELY, HalfLYTELY, and Visicol in controlled clinical trials submitted in the GoLYTELY, NuLYTELY, HalfLYTELY, and Visicol NDAs.**

In the overwhelming majority of the colon preparation trials (including the MOVIPREP trials), the study treatments were administered within 24 hours of colon preparation.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

In response to an information request, on March 14, 2006 (4 weeks prior to the PUDFA goal date) the sponsor submitted a summary report of a completed phase 3, randomized, investigator-blinded, multi-center, parallel-group, German trial (Study 01/2004) of MOVIPREP in patients scheduled to have an elective colonoscopy for colon cancer screening. Since no final study report was submitted, this phase 3 study was not used as a primary source of information for efficacy or safety.

7.2.2.2 Postmarketing experience

MOVIPREP has never been approved in the United States or any foreign country; therefore, no post-marketing data is available.

7.2.2.3 Literature

MOVIPREP is a new PEG-based colon preparation product and it has not been studied in the literature.

7.2.3 Adequacy of Overall Clinical Experience

Medical Reviewer's Comments: **This medical officer believes that the MOVIPREP safety database is acceptable for a PEG-based colon preparation product. In this MOVIPREP NDA, 349 patients received MOVIPREP in controlled clinical trials. Thus, the number of patients exposed to MOVIPREP was similar to — or greater than — the exposure to GoLYTELY, NuLYTELY, HalfLYTELY, and Visicol in controlled clinical trials submitted in the GoLYTELY, NuLYTELY, HalfLYTELY, and Visicol NDAs.**

In addition, the duration of exposure (over 13 hours of exposure) was similar to the duration of exposure to other colon preparation products. This medical officer believes that the duration of exposure was acceptable.

This medical officer believes that the design of the two MOVIPREP trials (randomized, investigator-controlled, active controlled, and multi-center) submitted in this NDA is consistent with prior colon preparation designs and was adequate to answer critical questions.

This medical officer believes that the exclusion criteria in the two MOVIPREP trials were reasonable and does not limit the relevance of the safety assessments.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The sponsor did not conduct any *in vitro* pharmacology studies of MOVIPREP. However, according to Dr. Zhang, "PEG 3350 along with other ingredients in MOVIPREP can increase the water content

of the stool and produce a voluminous liquid stool when given orally." For more detail please see Dr. Zhang's review.

7.2.5 Adequacy of Routine Clinical Testing

Medical Reviewer's Comments: **This medical officer believes that the vital sign testing in the MOVIPREP studies were adequate for a colon preparation product. Ideally, orthostatic hypotension measurements could have been performed post-dosing to increase the accuracy of hypovolemia testing.**

This medical officer believes that the MOVIPREP trials included a broad array of laboratory testing including CBC, electrolyte, BUN, creatinine, phosphate, calcium, ALT, AST, and serum osmolality testing.

This medical officer believes that the safety laboratory monitoring was suboptimal. None of the four MOVIPREP studies included a safety follow-up laboratory visit several days after the colonoscopy. In the two Visicol phase 3 trials (which compared the safety and efficacy of Visicol and NuLYTELY in patients referred for an elective colonoscopy), NuLYTELY, a PEG-based colon preparation, was associated with hyponatremia in 31% to 36% of the patients 2-3 days after the colonoscopy. Additionally, in these trials, NuLYTELY was associated with hypocalcemia in 8% to 10% of the patients 2-3 days after the colonoscopy. The overwhelming majority of these patients had no clinical symptoms. Since PEG-based colon preparations are associated with electrolyte changes (several days after the colonoscopy), optimal safety testing of PEG-based colon preparations include post-colonoscopy laboratory testing.

Additionally, this medical officer believes that optimum laboratory testing would include more frequent post-dosing laboratory tests. All four MOVIPREP studies only conducted laboratory tests one time after study drug administration. In addition, coagulation blood tests (including INR and PTT) were not performed in the MOVIPREP studies at baseline, during the treatment period, or post-dosing.

This medical officer believes that the safety follow-up monitoring was suboptimal in the four MOVIPREP studies. All four studies did not have any follow-up safety monitoring visits. Since PEG-based products have been associated with electrolyte disorders that have lasted for several days after the colonoscopy and rare clinical events (including seizures) have occurred, optimal safety follow-up visits should have been conducted in the MOVIPREP studies.

This medical officer believes that routine ECG testing should have been performed in the MOVIPREP trials because ECG testing is standard for phase 3 trials. Additionally, MOVIPREP and PEG-based products have been associated with hypokalemia and hypokalemia increases the risk of QT prolongation. However, in the AERS database from 1996 to 2003, only one post-marketing case of ventricular arrhythmia with hypokalemia occurred in a patient who received a PEG-based colon preparation. Also MOVIPREP was associated with a lower frequency of hypokalemia then the approved colon preparation

comparators in the German and French studies. Even though this medical officer believes that a thorough QT/QTc study should have been performed, this medical officer believes that a thorough QT/QTc study is not required for approval.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

According to Dr. Tien Mien Chen, the biopharmaceutics reviewer, PEG 3350 based products are "essentially not metabolized and mainly excreted unchanged" in the colon. In addition, he states very little PEG 3350 is absorbed.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Medical Reviewer's Comments: A thorough QT/QTc study was not performed in this NDA. According to the October 2005 Guidance for Industry entitled, *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs,* "Drugs are expected to receive a clinical electrocardiographic evaluation, beginning early in clinical development, typically including a single trial dedicated to evaluating their effect on cardiac repolarization ("thorough QT/QTc study")."

Additionally, PEG-based colon preparations have been associated with electrolyte disorders (including hypokalemia and hypocalcemia) on the day of the colonoscopy and several days after the colonoscopy. Since hypokalemia and hypocalcemia have been associated with QT prolongation, PEG-based colon preparations may be more likely to be associated with QT prolongation.

Unfortunately, no thorough QT/QTc study of a PEG-based or sodium phosphate-based colon preparation (including GoLYTELY, NuLYTELY, HalfLYTELY, Visicol, and OsmoPrep) has been performed and submitted to the DGP.

However, several PEG-based colon preparations, on the market for over 20 years, have not been associated with a significant number of post-marketing cases of prolonged QT or arrhythmias.

7.2.8 Assessment of Quality and Completeness of Data

During the NDA review, the sponsor responded to several information requests from the DGP and provided the DGP with necessary data from the MOVIPREP trials. This medical officer believes that the original NDA and the sponsor's responses to our information requests provide sufficient information to assess the safety of MOVIPREP.

7.2.9 Additional Submissions, Including Safety Update

On March 14, 2006, the sponsor submitted a summary report of their completed German, phase 3 colon preparation trial of MOVIPREP in patients who received an elective colonoscopy (Study 01/2004). The sponsor reported no deaths and no drug-related SAEs, and no discontinuations due to AEs. In addition, on March 17, 2006, the sponsor submitted a Safety Update. The Safety Update described the following six unrelated SAEs in Study 01/2004: adenocarcinoma (in a MOVIPREP patient), large intestinal perforation (in a MOVIPREP patient), sigmoidectomy (in a MOVIPREP patient), malignant neoplasm (in an OSPS patient), pneumonia (in an OSPS patient), and rectal cancer (in an OSPS patient).

Medical Reviewer's Comments: The sponsor's Safety Update does not change this medical officer's conclusions regarding the safety of MOVIPREP.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The important MOVIPREP-related AEs in the four MOVIPREP studies (the German, the French Study 01/2000, and Study 02/2000) include the following:

1) 60 year old female who developed vomiting and hypokalemia and required hospitalization after receiving MOVIPREP in Study 02/2000 (Section 7.1.2).
2) 37 year old female who developed nausea and required study discontinuation after receiving MOVIPREP in Study 01/2000 (Section 7.1.3.1).
3) 43 year old male who developed nausea and mild malaise and required study discontinuation after receiving MOVIPREP in the German study (Section 7.1.3.1).
4) 77 year old female who developed malaise and required study discontinuation after receiving MOVIPREP in the German study (Section 7.1.3.1).
5) 56 year old female who developed vomiting and required study discontinuation after receiving MOVIPREP in the German study (Section 7.1.3.1).

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Since this NDA only included two controlled MOVIPREP trials (the German and French studies), no pooling of safety or efficacy data was performed in this NDA review.

7.4.1.2 Combining data

Since this NDA only included two controlled MOVIPREP trials (the German and French studies), no pooling of safety or efficacy data was performed in this NDA review.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The two controlled MOVIPREP trials used the identical total dose (2 liters of MOVIPREP with 1 additional liter of water); therefore, explorations for dose dependency are not possible.

7.4.2.2 Explorations for time dependency for adverse findings

Since the two MOVIPREP trials were of short duration (the blinded treatment period was less than 24 hours), and the full post-dosing AE assessments were only taken once (on the day of the colonoscopy), an assessment of time-dependency of adverse findings is difficult.

The French study, compared to the German study, had a higher rate of GI MOVIPREP-related AEs. This may have been due to administration of a greater amount of MOVIPREP over a shorter period of time in the French study (evening only doses) compared to the longer period of time of MOVIPREP administration (over 13 hours) in the German study (split-dosing).

7.4.2.3 Explorations for drug-demographic interactions

Please see Section 8.3 for explorations of drug-demographic interactions.

7.4.2.4 Explorations for drug-disease interactions

There were no clear drug-disease interactions.

7.4.2.5 Explorations for drug-drug interactions

There were no clear drug-drug interactions in this NDA.

7.4.3 Causality Determination

Please see Section 7.3 (Summary of Selected Drug-Related Adverse Events. Important Limitations of Data, and Conclusions) for information about causality

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor proposes the following three MOVIPREP dosing regimens for use in adult patients (all three proposed dose regimens contains a total of 2 liters of MOVIPREP solution with 1 liter of additional liter of clear fluids taken orally):

1) Split MOVIPREP dose regimen: The evening before the colonoscopy, take the first liter of MOVIPREP solution over one hour and then drink 0.5 liters of clear fluid. Then, on the morning of the colonoscopy, take the second liter of MOVIPREP solution over one hour and then drink 0.5 liters of clear liquid at least one hour prior to the start of the colonoscopy;
2) Evening-only MOVIPREP dose regimen: Around 6 PM in the evening before the colonoscopy, take the first liter of MOVIPREP solution over one hour and then about 1.5 hours later take the second liter of MOVIPREP solution over one hour. In addition, take 1 liter of additional clear liquid during the evening before the colonoscopy; or
3) [redacted]

Medical Reviewer's Comments: This medical officer agrees with the sponsor's first two dose and dosage regimens because these two regimens were studied in phase 3 trials. The split MOVIPREP dosage regimen was evaluated in the phase 3, German study and the evening-only MOVIPREP dosage regimen was evaluated in the phase 3, French study. However, the sponsor did not include [redacted] MOVIPREP dosage regimen in any of the MOVIPREP studies. Thus, this medical officer does not recommend [redacted] dosage regimen.

8.2 Drug-Drug Interactions

The MOVIPREP trials did not have any unequivocal drug-drug interactions. In addition, according to Dr. Chen, MOVIPREP should have similar drug-drug interactions as the other approved PEG-based colon preparation products. According to the **Drug Interactions** subsections of the **PRECAUTIONS** sections of the GoLYTELY, NuLYTELY, and HalfLYTELY labels, "Oral medication administered within one hour of the start of administration of the solution may be flushed from the gastrointestinal tract and not absorbed."

Medical Reviewer's Comments: Thus, this medical officer believes that a similar statement should be placed in the Drug Interactions subsection of the PRECAUTIONS section of the MOVIPREP label.

8.3 Special Populations

Gender — Efficacy: There were no consistent differences in the proportion of patients who responded to the Overall Colon Cleansing Scale (the primary efficacy assessment) based upon gender. In the German study, the Overall Colon Cleansing response rate was 86% and 92%, respectively for men and women taking MOVIPREP; and 93% and 96%, respectively, for men and women taking GoLYTELY. In the French study, the Overall Colon Cleansing response rate was 77% and 69%, respectively for men and women taking MOVIPREP; and 55% and 74%, respectively, for men and women taking OSPS.

Gender — Safety: Overall, there were no appreciable differences in the safety of MOVIPREP in men and women.

Medical Reviewer's Comments: This medical officer does not recommend dose adjustment based on gender.

Geriatrics — Efficacy: There were no consistent differences in the proportion of geriatric patients and patients less than 65 years old who responded to the Overall Colon Cleansing Scale (the primary efficacy assessment). In the German study, the Overall Colon Cleansing response rate was 84% and 91%, respectively, for geriatric patients and patients less than 65 years old taking MOVIPREP; and 92% and 97%, respectively, for geriatric patients and patients less than 65 years old taking GoLYTELY. In the French study, the Overall Colon Cleansing response rate was 78% and 72%, respectively for geriatric patients and patients less than 65 years old taking MOVIPREP; and 65% and 64%, respectively, for geriatric patients and patients less than 65 years old taking OSPS.

Geriatrics — Safety: There were no appreciable differences in the proportion of patients less than 65, patients between 65 and 75, and patients over 75 years old who received MOVIPREP in the German study who had drug-related AEs including drug-related GI AEs (such as abdominal pain, nausea, and vomiting).

Medical Reviewer's Comments: This medical officer does not recommend dose adjustment based on age.

Race — Efficacy and Safety: In the sponsor's March 14, 2006 response to DGP's information request, the sponsor stated that it did not prospectively collect race and ethnicity data in the MOVIPREP development program including the German and French studies. According to the sponsor, all of the MOVIPREP studies were conducted in Europe and predominantly enrolled Caucasian patients of European decent. According to the sponsor, MOVIPREP "exhibits several intrinsic properties that reduce the probability that ethnicity may effect its use as a bowel-cleansing agent. The active ingredients in MOVIPREP are not absorbed, distributed, metabolized or excreted to any appreciable extent in the human body." The sponsor stated that "the pharmacodynamic and clinical behavior of MOVIPREP in the ethnically diverse region of the United States will be similar to that observed in the clinical trials conducted in Europe."

Medical Reviewer's Comments: Since MOVIPREP is similar to many PEG-based colon preparations approved in the United States since 1984, this medical officer does not believe that the lack of race and ethnicity data impairs the approvability of this application. This medical officer recommends that the sponsor prospectively collect ethnicity and race data in future MOVIPREP clinical trials.

8.4 Pediatrics

All of the MOVIPREP studies excluded subjects/patients less than 18 years old and no pediatric subject/patient has received MOVIPREP. In this NDA, the sponsor requested a full deferral to conduct pediatric studies of MOVIPREP until there is adequate post-marketing experience in adults. The sponsor states that NuLYTELY, an approved PEG-based colon preparation, is approved for use in pediatric patients.

Medical Reviewer's Comments: This medical officer believes that our division should grant a full waiver to the sponsor of MOVIPREP to conduct pediatric studies. Currently, NuLYTELY, a PEG-based colon preparation, is approved for "bowel cleansing prior to colonoscopy" in pediatric patients ≥ six months of age. Furthermore, OSPS is professionally labeled OTC for colon cleansing in pediatric patients ≥ 12 years of age. Therefore, multiple colon preparations are available for pediatric patients ≥ 12 months of age and one colon preparation is available for pediatric patients ≥ six months of age.

PEG-related products containing similar amounts of PEG 3350 are likely to be equally efficacious and safe in pediatric patients. Therefore, MOVIPREP is not likely to "represent a meaningful therapeutic benefit over existing treatments for pediatric patients". In addition, colon preparation is not performed in a substantial number of pediatric patients. According to 21 CFR 314.55(c)(2)(i), a full waiver can be satisfied if the "drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients." Therefore, this medical officer recommends a full pediatric waiver for the study of MOVIPREP in pediatric patients.

8.5 Advisory Committee Meeting

There were no Advisory Committee meetings related to MOVIPREP

8.6 Literature Review

There were no literature reports of MOVIPREP.

8.7 Postmarketing Risk Management Plan

This medical officer does not recommend a post-marketing risk management plan.

8.8 Other Relevant Materials

There are no additional relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

Two well-controlled, randomized, investigator-blinded, parallel-group, multi-center, European trials (the German and French studies) of MOVIPREP demonstrated substantial evidence of effectiveness and safety for the intended use of MOVIPREP as a colon preparation prior to a colonoscopy in adult patients.

9.2 Recommendation on Regulatory Action

From a clinical perspective, this medical officer recommends **approval** of the MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) oral solution for **cleansing of the colon as a preparation for colonoscopy in adults** if the sponsor agrees to important labeling changes. If the sponsor does not agree to the important labeling changes, then this medical officer recommends an **approvable** action.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Risk management activities are not indicated.

9.3.2 Required Phase 4 Commitments

This medical officer does not recommend any phase 4 commitments.

9.3.3 Other Phase 4 Requests

There are no additional phase 4 requests.

9.4 Labeling Review

Nora Roselle, PharmD, a drug safety office reviewer in the Division of Medication Errors and Technical Support (DMETS), stated that "DMETS has no objections to the use of the proprietary name, MOVIPREP. This is considered a final decision." For more information, please see her review.

This medical officer recommends adding **WARNINGS** to the MOVIPREP label about the risk of generalized tonic-clonic seizures and electrolyte changes associated with use of polyethylene glycol (PEG) colon preparation products in patients with no prior history of seizures. In addition, this medical officer added a **CLINICAL STUDIES** section to the MOVIPREP label. In the **CLINICAL STUDIES** section, this medical officer described the designs, the primary efficacy endpoints, and the results of the primary efficacy endpoints in the German and French phase 3 studies. Finally, this medical officer added a table in the **ADVERSE REACTIONS** section of the label detailing the most common drug-related adverse events.

9.5 Comments to Applicant

This medical officer does not have any comments to the applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

The individual study reports are in Section 6.1.3.

10.2 Line-by-Line Labeling Review

For this labeling review, words underlined and **bolded** signify an addition and words formatted with a ~~strikethrough~~ indicate a deletion to the sponsor's proposed MOVIPREP label. Below is the MOVIPREP label that will be sent to the sponsor before labeling negotiations. The overwhelming majority of changes in this labeling review is from this medical officer.

DESCRIPTION

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_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

10.3 Abbreviations

Please see Table 33 for a list of abbreviations and definitions used in this review.

Table 33: List of abbreviations and definitions

ACE inhibitor	Angiotensin converting enzyme inhibitor
AERS	Adverse Event Reporting System
AEs	Adverse events
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
BM	Bowel Movement
DB	Double-blind
DGP	Division of Gastroenterology Products
ITT	Intent-to-treat
LDH	Lactate Dehydrogenase
MC	Multi-centered
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeters
NSAID	Non-steroidal anti-inflammatory drug
PC	Placebo-controlled
R	Randomized
SAE	Serious adverse event
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase

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CLINICAL MOVIPREP® NDA REVIEW (SECOND CYCLE)

Application Type	NDA
Submission Number	21-881
Submission Code	000
Letter Date	6/2/06
Stamp Date	6/2/06
PDUFA Goal Date	8/2/06
Reviewer Name	Eric Brodsky, MD
Review Completion Date	7/27/06
Established Name	PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid for oral solution
Trade Name	MoviPrep®
Therapeutic Class	Purgative
Applicant	Norgine B.V.
Priority Designation	Standard
Formulation	Oral solution
Proposed Indication	Cleaning of the colon as a preparation for colonoscopy in adults 18 years of age or older
Intended Population	Adults
Proposed Dosing Regimen	Two administration options:

1) Evening-only regimen – around 6 PM in the evening before the colonoscopy, take the first liter of MoviPrep solution over one hour and then about 1.5 hours later take the second liter of MoviPrep solution over one hour. In addition take 1 liter of additional clear liquids during the evening prior to the colonoscopy; or
2) Split-dose regimen – during the evening before the colonoscopy, take the first liter of MoviPrep solution over one hour and then drink 0.5 liters of clear liquid. Then, on the morning of the colonoscopy, take the second liter of MoviPrep solution over one hour and then drink 0.5 liters of clear liquid at least one hour prior to the start of the colonoscopy.

1.0 BACKGROUND:

Norgine originally submitted the MoviPrep® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid for oral solution) application (NDA 21-881) on June 10, 2005 for bowel cleansing prior to colonoscopy ——————————————— On April 10, 2006, the Division of Gastroenterology Products (DGP) took an approvable action on this NDA because:

> "During recent inspections of the manufacturing facilities for this application, our filed investigator conveyed deficiencies to the facilities' representatives. Satisfactory resolution to these deficiencies is required before this application may be approved."

During the initial MoviPrep NDA review, this medical officer, from a clinical perspective, recommended approval of the original application for cleansing of the colon as a preparation for colonoscopy in adults if the sponsor agreed to important labeling changes (please see this medical officer's April 2006 MoviPrep NDA review). During the initial cycle, the sponsor and the DGP came to an agreement on the overwhelming majority of the labeling. At the end of the last cycle, there were two outstanding labeling issues involving language under the two tables (Tables 1 and 2) in the **CLINICAL STUDIES** section:

1) The translation of the colonoscopy case reports forms into English; and
2) The statistical language comparing the MoviPrep group with its active comparator.

On June 6, 2006, the sponsor resubmitted the MoviPrep NDA with new labeling with the following indication: "MoviPrep® is indicated for cleansing of the colon as a preparation for colonoscopy in adults 18 years of age or older." The sponsor and the Division of Gastroenterology agreed to this language during last cycle. Furthermore, the sponsor said that since the last Safety Update there have not been any new safety findings that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions.

On July 25, 2006, the sponsor submitted the following proposed labeling change: to move the sentence regarding glucose-6-phosphodehydrogenase (G-6-PD) deficiency from the **CONTRAINDICATIONS** section to the **General** subsection of the **PRECAUTIONS** section and to modify the language.

2.0 LABELING REVIEW:

For this medical officer's labeling review, words **bolded** and underlined signify this medical officer's recommendation to add to the sponsor's proposed MoviPrep label and words with a ~~strikethrough~~ indicate this medical officer's recommendation to delete to part of the sponsor's proposed MoviPrep label. To improve the clarity of the FDA's suggested changes to Tables 1 and 2 in the **CLINICAL STUDIES** section, this medical officer included two versions (the FDA's proposal and the sponsor's proposal) of both tables.

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__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

[redacted]

3.0 CONCLUSIONS

This medical officer believes that MoviPrep is safe and effective for cleansing of the colon as a preparation for colonoscopy in adults. Please see this medical officer's original MoviPrep NDA review for more details.

4.0 RECOMMENDATIONS FOR REGULATORY ACTION:

From a clinical perspective, this medical officer recommends approval of the MoviPrep® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) oral solution for cleansing of the colon as a preparation for colonoscopy in adults if the Division of Gastroenterology Products and the sponsor agreed to the labeling.

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