CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-097

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION — NDA

NDA #: 21-097

Drug Class: 7/S

AUG 1 0 2000

Applicant: InKline Pharmaceutical Company, Inc.

Name of Drug: Diacol (sodium phosphate dibasic anhydrous/sodium phosphate monobasic monohydrate) 2.0 mg tablet

Indication: Cleaning of the bowel when required as a preparation for certain diagnostic procedures, such as colonoscopy, in adults 18 years of age or older

Documents Reviewed: NDA 1.1, 1.6-1.13 Dated November 22, 1999
Amendment 09 Dated March 22, 2000
Amendment 12 Dated April 06, 2000
Supplement 18, Dated June 22, 2000
Amendment 24 Dated July 27, 20000

User Fee Date: 9/23/00 (10 mos)

Statistical Reviewer: Milton C. Fan, Ph.D.

Medical Reviewer: This review has been discussed with medical officer, Robert Prizont, MD

Key Words: Single blind, imputation, equivalence trial

A. Background

DIACOL is solid oral dosage form (tablet) of sodium phosphate. In this NDA, the applicant is seeking approval of DIACOL (sodium phosphate dibasic anhydrous/sodium phosphate monobasic monohydrate) for the indication of colonic purgation in adult patient prior to colonoscopy or similar procedures.

Two pivotal identical multicenter randomized Phase III studies (INKP-100-301and INKP-100-302) were submitted for supporting the efficacy of DIACOL for the indication of colonic purgation in adult patient prior to colonoscopy.

B. Study INKP-100-301

1. Description of Study

This trial was a randomized, single-blind, parallel-group, multicenter (16 investigators) study. The objective was to evaluate, by direct visualization, the purgative effect of

DIACOL compared with a commercially available purgative product (NuLYTELY) in patients undergoing colonoscopy.
The study was designed to demonstrate equivalence in colon cleansing between DIACOL and NuLYTELY.

Eligible patients were randomized to receive one of the following study products before colonoscopy:

1. 4 liter of Cherry Flavor NuLYTELY administered orally beginning the afternoon prior to colonoscopy in accordance with its package insert
2. 30 gram of DIACOL administered on 2 occasions: the evening prior to and the morning of (3-5 hours before) colonoscopy.

DIACOL was administered as 3 tablets with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets beginning at 6:00 PM on the evening prior to colonoscopy. This schedule was repeated at 6:00 AM on the morning of colonoscopy (or 3-5 hours before the procedure) when again 3 tablets of DIACOL were administered with 8 ounces of clear liquids every 15 minutes for a total of 20 tablets.

Individual patients were to be screened within 7 days prior to colonoscopy and discharged within 48-72 hours after colonoscopy.

Patients were to self-administer study product according to the instructions provided and were asked to observe whether undigested or partially digested white tablets appeared in their bowel movements.

Randomization was done using a central randomization schedule with a block size of 4.

Patients completed a questionnaire regarding their bowel-cleansing regimen about tolerance of the study product. Patients were instructed not to discuss with the investigator (colonoscopist) their treatment group assignment or the information recorded on their Patient Questionnaire.

The effectiveness of the study products was assessed by a colonoscopist (investigator) who was blinded as to the identity of the study product assigned to and taken by each patient. Investigators used a 4-point scale to score the overall quality of colonic cleansing and the quality of cleansing of the ascending colon. In addition, investigators recorded the presence or absence of the following: bleeding, superficial mucosal aphthous ulcerations, and undigested or partially digested white DIACOL tablets.

The primary efficacy variable was the overall quality of colonic purgation, measured using a 4-point scale as follows:

1. Excellent >90% of mucosa seen, mostly liquid stool, minimal suction needed for adequate visualization

2. Good >90% of mucosa seen, mostly liquid stool, slightly significant suctioning required for adequate visualization

3. Fair >90% of mucosa seen, mixture of liquid and semisolid stool, could be suctioned and/or washed

4. Inadequate/ <90% of mucosa seen, mixture of semisolid and solid stool which could not be suctioned or washed

The equivalence in quality of colonic purgation between the two study product groups was assessed using two one-sided t-tests procedure, comparing mean scores assigned by the investigator for cleansing.

A total of 400 patients would be required to show equivalence in the equality of colonic cleansing between the two study-product groups. Equivalence was defined as a maximum difference in mean quality of colonic cleansing rating of 0.3. There was an assumption of no true difference between the study-product groups and 5% dropout rate. This sample size required 382 patients with assessments provided 90% power, with an overall type I error of 0.05, for each test, a standard deviation of 1.0 and using two one-sided t-tests procedure to determine equivalence of the 2 study products.

2. Applicant's Analysis

There were 432 patients randomized: 216 patients to receive DIACOL and 216 patients to receive NuLYTELY. A total of 10 patients (3 DIACOL and 7 NuLYTELY) were discontinued from the study prior to treatment with study product. The remaining 422 patients (213 DIACOL and 209 NuLYTELY) treated with study product were analyzed for safety. A total of 415 patients (208 DIACOL and 207 NuLYTELY) had assessment of colon cleansing.

Patient 301-13-022 took the study product incorrectly and was unable to undergo the study-required colonoscopy.

All efficacy analyses were performed for all randomized patients (ARP), all treated patients (ATP) and all assessed patients (AAP).

2.1 Treatment Group Comparability

The demographic characteristics of all randomized patients populations are summarized in Attached Table 1. As seen from Attached Table 1, the demographic and baseline characteristics were similar between two treatment groups with regard to age, sex, race, and weight.

2.2 Applicant's Analysis of Primary Efficacy Variable

The primary efficacy variable was the overall quality of colonic purgation using a validated instrument consisting of a 4-point scale.

Equivalence between DIACOL and NuLYTELY was demonstrated when the lower bound of the 95% confidence interval for the mean score difference (NuLYTELY minus DIACOL) was greater than or equal to –0.3. A one-sided t-test comparing the mean colon cleansing scores was also performed to assess product difference. Statistical significance was defined as $p<0.05$.

Statistical analysis was performed on All Assessed Patients (AAP), i.e., the entire population of patients with an assessment of colon cleansing. This analysis omitted no efficacy data and included no imputed data. The same analysis was also performed on two additional populations: All Randomized Patients (ARP) and All Treated Patients (ATP), i.e., all patients who ingested any amount of study drug. Patients in these latter two populations who did not have an assessment of colon cleansing were given imputed colon cleansing scores. For each population, at least 2 imputation schemes were used.

For both the ARP and ATP efficacy analyses, missing colonoscopy data was imputed in the first analysis as success (Excellent, score=1) and in a second analysis as failure (Inadequate/Reprep, score=4). In addition, for the ARP population only, an additional analysis was performed in which all patients in DIACOL group with missing data were imputed a score of 4 (Inadequate/Reprep) and all patients in the NuLYTELY group with missing data were imputed a score of 1 (Excellent). This "worst case" analysis was performed as a test of the robustness of the efficacy data.

The results of analysis of the overall quality of colonic purgation for AAP population are given below.

Overall Quality of Colonic Purgation
(All Assessed Patients Population)
Study INKP-100-301

DIACOL (n=208)		NuLYTELY (n=207)		Difference		
Mean	S.D.	Mean	S.D.	(NuLYTELY-DIACOL)	95% C. I.	p-value
1.80	0.76	1.82	0.83	0.02	(-0.14, 0.17)	0.4311

Copied from Table 8, page 53, Vol. 1.10
P-value is from 2-sided t test which has been halved to make a one-sided p-value.

As seen from table above, there was no statistically significant difference between treatment groups in the primary efficacy endpoint, overall quality of colonic purgation. The 95% confidence intervals were within the pre-established range. The lower bound of the confidence interval in the mean scores was greater than –0.3 for all assessed patients populations.

The applicant also performed two additional analyses for both All Treated Patients population and All Randomized Patients population. In the first analysis the missing colon assessment were assigned as Excellent (score 1). In the second analysis the missing colon assessment were assigned as Inadequate (score 4). The results of these analyses are given below.

Imputed Mean Scores for All Treated Patients
Study INKP-100-301

	DIACOL (n=213)		NuLYTELY (n=209)		Difference		
Imputed Value	Mean	S.D.	Mean	S.D.	(NuLY-DIACOL)	95% C. I.	P-value
Excellent (score=1)	1.78	0.76	1.81	0.83	0.03	(-0.13, 0.18)	0.375
Inadequate (score=4)	1.85	0.82	1.84	0.85	-0.01	(-0.18, 0.14)	0.583

Copied from Table 9, page 54, Vol. 1.10.
P-value is from 2-sided t test which has been halved to make a one-sided p-value.

Imputed Mean Scores for All Randomized Patients
Study INKP-100-301

	DIACOL (n=216)		NuLYTELY (n=216)		Difference		
Imputed Value	Mean	S.D.	Mean	S.D.	(NuLY-DIACOL)	95% C. I.	P-value
Excellent (score=1)	1.77	0.76	1.78	0.83	0.01	(-0.14, 0.16)	0.452
Inadequate (score=4)	1.88	0.85	1.91	0.92	0.03	(-0.14, 0.19)	0.393

Copied from Table 9, page 54, Vol. 1.10.
P-value is from 2-sided t test which has been halved to make a one-sided p-value.

In addition, for the ARP population only, the applicant performed a "worst case" analysis in which all patients in DIACOL group with missing data were imputed a score of 4 (Inadequate/Reprep) and all patients in the NuLYTELY group with missing data were imputed a score of 1 (Excellent). The results of "worst case" analysis of overall quality of colonic purgation is given below.

Worst Case Evaluation for ARP Population
Overall Quality of Colonic Purgation
(All Randomized Patients Population)
Study INKP-100-301

DIACOL (n=216)		NuLYTELY (n=216)		Difference		
Mean	S.D.	Mean	S.D.	(NuLYTELY-DIACOL)	95% C. I.	P-value
1.88	0.85	1.78	0.83	-0.101	(-0.26, 0.06)	0.8961

Copied from Tables 9 and 10, page 54-55, Vol. 1.10

As seen from the table above, in this "worst case" analysis, the 95% confidence intervals were within the pre-established range. The lower bound of the confidence in the mean scores was greater than –0.3. Colon cleansing with DIACOL was equivalent to NuLYTELY in terms of overall quality of colonic purgation.

The results were highly robust and the finding of equivalency maintained when the scores were imputed for missing data using a variety of imputation schemes.

2.3 Applicant's Analysis of Secondary Variable

Secondary efficacy variable was the quality of colonic purgation in the ascending colon. The quality of colonic purgation in the ascending colon was measured using the same validated 4-point scale as overall quality of colon purgation.

The results of analysis of the overall quality of colonic purgation in the ascending colon for AAP population are given below.

Overall Quality of Colonic Purgation in the Ascending Colon
(All Assessed Patients Population)
Study INKP-100-301

DIACOL (n=208)		NuLYTELY (n=207)		Difference		
Mean	S.D.	Mean	S.D.	(NuLYTELY-DIACOL)	95% C. I.	p-value
1.89	0.80	1.79	0.83	-0.09	(-0.25, 0.07)	0.8702

Copied from Table 11, page 56, Vol. 1.10

As seen from the table above, there was no statistically significant difference between treatment groups.

Patients completed a questionnaire to address their satisfaction with the study treatment at Visit 1, after completing the administration of the study product and just prior to colonoscopy. The results of tolerance/preference assessment are given in Attached Table 2.

As seen from Attached Table 2, significantly more DIACOL patients reported that they were able to take all the study medication as compared to NuLYTELY patients. More patients who received DIACOL tablets found that it "easy" to take the study product than did the patients who received NuLYTELY liquid. More patients who received DIACOL indicated a preference for taking the same preparation in the future compared to patients who received NuLYTELY.

There was no statistically significant difference between treatment groups with respect to the number of patients who required re-examination for overall inadequate bowel preparation (3 patients treated with DIACOL and 1 patient treated with NuLYTELY).

2.4 Safety

Superficial mucosal aphthous ulcerations were noted in 18 patients (8.7%) in the DIACOL treatment group compared to 9 patients (4.3%) in the NuLYTELY treatment group.

Bloating, abdominal pain, nausea and vomiting were reported significantly more frequently in the NuLYTELY treatment group than in the DIACOL treatment group. Patient questionnaire responses revealed that the severity of these events was consistently less in the DIACOL group.

Hyperphosphatemia, hypocalcemia, hypokalemia, and hypophosphatemia occurred more frequently in the DIACOL treatment group. Hyperkalemia and occurred more frequently in the NuLYTELY treatment group.

3. Reviewer's Evaluation

3.1 Reviewer's Comments on Study Design

This study was designed as single-blind trial. In the protocol patients were instructed not to discuss with the investigator (colonoscopist) their treatment group assignment or the information recorded on their Patient Questionnaire. But, during the colonoscopy, investigators recorded undigested or partially digested white DIACOL tablets. So, investigator was not blinded at all. So, this study should be considered as an open trial.

The entire dose of study product, for all treated patients as reported in the Patient Questionnaire, was ingested by 194 (93%) of 213 DIACOL patients compared with 118 (57%) of 209 NuLYTELY patients (P<0.001).

3.2 Reviewer's Comments on Applicant's Definition of Equivalence

The equivalence in the equality of colonic cleaning defined as a maximum difference in mean rating of 0.3 might not be clinical meaningful. It is more appropriate to define equivalence in terms of the proportion of patients with designated Excellent or designated Excellent or Good.

3.3 Reviewer's Analysis of Colon Clean Scores

Per the medical officer request, this reviewer performed some analyses for colon cleansing using colon clean scores. The overall physician rating of colonic purgation was given below.

Quality of Colon Purgation by Treatment Group
(All Assessed Patients Population)
INKP-100-301

Treatment	Excellent	Good	Fair	Inadequate	Total
DIACOL	81 (38.9%)	90 (43.3%)	34 (16.3%)	3 (1.4%)	208
NuLYTELY	91 (44.0%)	65 (31.4%)	49 (23.7%)	2 (1.0%)	207

Compiled by the reviewer from SAS dataset phyquest.

The results of reviewer's analyses of the number of designated Excellent rating and the number of designated Excellent or Good rating for AAP and ARP are given below.

(All Assessed Patients Population)
INKP-100-301

Parameter	DIACOL (N=208)	NuLYTELY (N=207)	Difference (DIACOL-NuLYTELY)	95% CI
Excellent	81 (38.9%)	91 (44.0%)	-5.1%	(-14.5%, 4.5%)
Excellent or Good	171 (82.2%)	156 (75.4%)	6.8%	(-1.0%, 14.7%)

(All Randomized Patients Population)
INKP-100-301

Parameter	DIACOL (N=216)	NuLYTELY (N=216)	Difference (DIACOL-NuLYTELY)	95% CI
Excellent	81 (37.5%)	91 (42.1%)	-4.6%	(-13.9%, 4.6%)
Excellent or Good	171 (79.2%)	156 (72.2%)	6.9%	(-1.1%, 15.0%)

As seen from Table above, the 95% lower confidence limit of the difference of the proportions of the number of designated Excellent was about –14%, much less than –5% for AAP and ARP. However, the lower confidence limit was greater than –5% for the number of designated Excellent or Good for AAP and ARP.

3.4 Reviewer's Analysis of the Ascending Colon Clean Scores

Per the medical officer request, this reviewer performed some analyses for the ascending colon cleansing using colon clean scores. The overall physician rating of colonic purgation was given below.

Quality of Ascending Colon Purgation by Treatment Group
(All Assessed Patients Population)
INKP-100-301

Treatment	Excellent	Good	Fair	Inadequate	Total
DIACOL	74 (36.8%)	79 (39.3%)	45 (22.3%)	3 (1.5%)	201
NuLYTELY	93 (45.6%)	62 (30.4%)	47 (23.0%)	2 (1.0%)	204

Compiled by the reviewer from SAS dataset phyquest.

The results of reviewer's analyses of the number of designated Excellent rating and the number of designated Excellent or Good rating for AAP and ARP are given below.

(All Assessed Patients Population)
INKP-100-301

Parameter	DIACOL (N=201)	NuLYTELY (N=204)	Difference (DIACOL-NuLYTELY)	95% CI
Excellent	74 (36.8%)	93 (45.6%)	-8.8%	(-18.3%, 0.8%)
Excellent or Good	156 (77.6%)	155 (76.0%)	1.6%	(-6.6%, 9.9%)

(All Randomized Patients Population)
INKP-100-301

Parameter	DIACOL (N=216)	NuLYTELY (N=216)	Difference (DIACOL-NuLYTELY)	95% CI
Excellent	74 (34.3%)	93 (43.1%)	-8.8%	(-17.9%, 0.4%)
Excellent or Good	156 (72.2%)	155 (71.8%)	0.5%	(-8.0%, 8.9%)

As seen from Table above, the 95% lower confidence limit of the difference of the proportions of the number of designated Excellent was about –18%, much less than –5% for AAP and ARP. The lower confidence limit was also less than –5% for the number of designated Excellent or Good for AAP and ARP.

C. Study INKP-100-302

1. Description of Study

The design for this study was identical to that for study INKP-100-301. This study was conducted in 18 sites.

2. Applicant's Analysis

There were 454 patients randomized: 229 patients to receive DIACOL and 225 patients to receive NuLYTELY. A total of 17 patients (15 DIACOL and 2 NuLYTELY) were discontinued from the study prior to treatment with study product. The remaining 437 patients (214 DIACOL and 223 NuLYTELY) treated with study product and analyzed for safety. A total of 430 patients (212 DIACOL and 218 NuLYTELY) had assessment of colon cleansing.

Of the 437 patients who received study product, 427 patients (209 DIACOL and 218 NuLYTELY) completed the study. Completed patients were defined as those treated patients completing Visit 2 study specific procedures.

All efficacy analyses were performed for all randomized patients (ARP), all treated patients (ATP) and all assessed patients (AAP).

2.1 Treatment Group Comparability

The demographic characteristics of all randomized patients populations are summarized in Attached Table 3. As seen from Attached Table 3, the demographic and baseline characteristics were similar between two treatment groups with regard to age, sex, race, and weight.

2.2 Applicant's Analysis of Primary Variable

The primary efficacy variable and statistical analyses were the same as used for Study INKP-100-301.
The results of analysis of the overall quality of colonic purgation for AAP population are given below.

Overall Quality of Colonic Purgation
(All Assessed Patients Population)
Study INKP-100-302

DIACOL (n=212)		NuLYTELY (n=218)		Difference		
Mean	S.D.	Mean	S.D.	(NuLYTELY-DIACOL)	95% C. I.	p-value
1.69	0.74	1.80	0.81	0.11	(-0.03, 0.26)	0.0642

Copied from Table 8, page 51, Vol. 1.11
P-value is from 2-sided t test which has been halved to make a one-sided p-value.

As seen from table above, there was no statistically significant difference between treatment groups in the primary efficacy endpoint, overall quality of colonic purgation. The 95% confidence intervals were within the pre-established range. The lower bound of the confidence in the mean scores was greater than –0.3 for all assessed patients populations.

The applicant also performed two additional analyses for both ALL Treated Patients population and All Randomized Patients population. In the first analysis the missing colon assessment were assigned as Excellent (score 1). In the second analysis the missing colon assessment were assigned as Inadequate (score 4). The results of these analyses are given below.

Imputed Mean Scores for All Treated Patients
Study INKP-100-302

Imputed Value	DIACOL (n=214) Mean	S.D.	NuLYTELY (n=223) Mean	S.D.	Difference (NuLY-DIACOL)	95% C. I.	P-value
Excellent (score=1)	1.68	0.74	1.78	0.81	0.10	(-0.04, 0.25)	0.0841
Inadequate (score=4)	1.71	0.77	1.85	0.87	0.14	(--0.01, 0.30)	0.0357

Copied from Table 9, page 52, Vol. 1.11
P-value is from 2-sided t test which has been halved to make a one-sided p-value..

Imputed Mean Scores for All Randomized Patients
Study INKP-100-302

Imputed Value	DIACOL (n=229) Mean	S.D.	NuLYTELY (n=225) Mean	S.D.	Difference (NuLY-DIACOL)	95% C. I.	P-value
Excellent (score=1)	1.64	0.73	1.78	0.81	0.14	(-0.00, 0.28)	0.0269
Inadequate (score=4)	1.86	0.94	1.87	0.88	0.01	(-0.16, 0.18)	0.4496

Copied from Table 9, page 52, Vol. 1.11
P-value is from 2-sided t test which has been halved to make a one-sided p-value..

In addition, for the ARP population only, the applicant performed a "worst case" analysis in which all patients in DIACOL group with missing data were imputed a score of 4 (Inadequate/Reprep) and all patients in the NuLYTELY group with missing data were imputed a score of 1 (Excellent). The results of "worst case" analysis of overall quality of colonic purgation is given below.

Worst Case Evaluation for ARP Population
Overall Quality of Colonic Purgation
(All Randomized Patients Population)
Study INKP-100-302

DIACOL (n=229) Mean	S.D.	NuLYTELY (n=225) Mean	S.D.	Difference (NuLYTELY-DIACOL)	95% C. I.	p-value
1.86	0.94	1.78	0.81	-0.08	(-0.24, 0.08)	0.8420

Copied from Tables 9 and 10, page 52-53, Vol. 1.11

As seen from the table above, in this "worst case" analysis, the 95% confidence intervals were within the pre-established range. The lower bound of the 95% confidence interval in the mean scores was greater than –0.3. Colon cleansing with DIACOL was equivalent to NuLYTELY in terms of overall quality of colonic purgation.

2.3 Applicant's Analysis of Secondary Variable

Secondary efficacy variable was the quality of colonic purgation in the ascending colon. The quality of colonic purgation in the ascending colon was measured using the same validated 4-point scale as overall quality of colon purgation.

The results of analysis of the overall quality of colonic purgation in the ascending colon for AAP population are given below.

Overall Quality of Colonic Purgation in the Ascending Colon (All Assessed Patients Population) Study INKP-100-302

DIACOL (n=211)		NuLYTELY (n=216)		Difference		
Mean	S.D.	Mean	S.D.	(NuLYTELY-DIACOL)	95% C. I.	p-value
1.80	0.80	1.80	0.90	0.00	(-0.15, 0.16)	-0.4538

Copied from Table 11, page 54, Vol. 1.11

As seen from the table above, there was no statistically significant difference between treatment groups.

The results of tolerance/preference assessment are given in Attached Table 4.

As seen from Attached Table 4, significantly more DIACOL patients reported that they were able to take all the study medication as compared to NuLYTELY patients. More patients who received DIACOL tablets found that it "easy" to take the study product than did the patients who received NuLYTELY liquid. More patients who received DIACOL indicated a preference for taking the same preparation in the future compared to patients who received NuLYTELY.
The physician questionnaire data indicated that 2 patients (0.9%) treated with DIACOL and 5 patients treated with NULYTELY (2.2%) required re-examination.

2.4 Safety

Mucosal bleeding was observed at colonoscopy in 12 (5.7%) patients treated with DIACOL and 8 patients (3.7%) treated with NuLYTELY. Superficial mucosal aphthous ulcerations was noted in 17 patients (8.0%) in the DIACOL treatment group compared to 3 patients (1.4%) in the NuLYTELY treatment group.

Bloating, nausea and vomiting were reported significantly more frequently in the NuLYTELY treatment group than in the DIACOL treatment group. Patient questionnaire response indicated that the severity of nausea and vomiting was consistently less in the DIACOL group.

Hyperphosphatemia, hypocalcemia, hypokalemia, and hypophosphatemia occurred more frequently in the DIACOL treatment group. Hyperkalemia occurred more frequently in the NuLYTELY treatment group.

3. Reviewer's Evaluation

3.1 Reviewer's Comments

There was disproportionate number of patients who were not treated (15 in DIACOL and 2 in NuLYTELY, p=0.001). There were 5 patients in NuLYTELY and 2 patients in DIACOL groups, who were not assessed.

The imbalance between the number of patients in the two treatment groups in the All Randomized Patients (ARP) and All Treated Patients (ATP) is due to the fact that by the design, the randomization was done prior to a determination of eligibility. As a result, ten of the patients (9 in DIACOL and 1 in NuLYTELY) had laboratory results at baseline that were outside the range defined by the inclusion criteria in the protocol. 3 patients (2 in DIACOL and 1 in NuLYTELY) did not have laboratory results available at the time of dosing; 2 patients (DIACOL) were discontinued because the sponsor closed the study due to adequate enrollment; 1 patient (NuLYTELY) was identified as being pregnant.

The entire dose of study product, for all treated patients as reported in the Patient Questionnaire, was ingested by 201 (95%) of 214 DIACOL patients compared with 123 (57%) of 223 NuLYTELY patients (P<0.001).

Superficial mucosal aphthous ulcerations were significantly more in the DIACOL group (p<0.001).

3.2 Reviewer's Analysis of Colon Clean Scores

Per the medical officer request, this reviewer performed some analyses for colon cleansing using colon clean scores. The overall physician rating of colonic purgation was given below.

Quality of Purgation Treatment Group
(All Assessed Patients Population)
INKP-100-302

Treatment	Excellent	Good	Fair	Inadequate	Total
DIACOL	98 (46.2%)	85 (40.1%)	26 (12.3%)	3 (1.4%)	212
NuLYTELY	94 (43.1%)	76 (34.9%)	45 (20.6%)	3 (1.4%)	218

Compiled by the reviewer from SAS dataset phyquest.

The results of reviewer's analyses of the number of designated Excellent rating and the number of designated Excellent or Good rating for AAP and ARP are given below.

(All Assessed Patients Population)
INKP-100-302

Parameter	DIACOL (N=212)	NuLYTELY (N=218)	Difference (DIACOL-NuLYTELY)	95% CI
Excellent	98 (46.2%)	94 (43.1%)	3.1%	(-6.3%, 12.5%)
Excellent or Good	183 (86.3%)	170 (78.0%)	8.3%	(1.2%, 15.5%)

(All Randomized Patients Population)
INKP-100-302

Parameter	DIACOL (N=229)	NuLYTELY (N=225)	Difference (DIACOL-NuLYTELY)	95% CI
Excellent	98 (42.8%)	94 (41.8%)	1.1%	(-8.1%, 10.1%)
Excellent or Good	183 (79.9%)	170 (75.6%)	4.4%	(-3.3%, 12.0%)

As seen from Table above, the lower bound of the 95% confidence interval in the difference of the proportions of the number designated Excellent was –6% and –8% for AAP and ARP respectively, less than –5%. However, the lower bound was greater than –5% for the number of designated Excellent or Good for AAP and ARP.

3.3 Reviewer's Analysis of the Ascending Colon Clean Scores

Per the medical officer request, this reviewer performed some analyses for the ascending colon cleansing using colon clean scores. The overall physician rating of colonic purgation was given below.

Quality of Ascending Colon Purgation by Treatment Group
(All Assessed Patients Population)
INKP-100-302

Treatment	Excellent	Good	Fair	Inadequate	Total
DIACOL	85 (40.3%)	87 (41.2%)	35 (16.6%)	4 (1.9%)	211
NuLYTELY	99 (45.8%)	64 (29.6%)	48 (22.2%)	5 (2.3%)	216

Compiled by the reviewer from SAS dataset phyquest.

- The results of reviewer's analyses of the number of designated Excellent rating and the number of designated Excellent or Good rating for AAP and ARP are given below.

(All Assessed Patients Population)
INKP-100-302

Parameter	DIACOL (N=211)	NuLYTELY (N=216)	Difference (DIACOL-NuLYTELY)	95% CI
Excellent	85 (40.3%)	99 (45.8%)	-5.5%	(-14.9%, 3.8%)
Excellent or Good	172 (81.5%)	163 (75.5%)	6.1%	(-1.7%, 13.8%)

(All Randomized Patients Population)
INKP-100-302

Parameter	DIACOL (N=229)	NuLYTELY (N=225)	Difference (DIACOL-NuLYTELY)	95% CI
Excellent	85 (37.1%)	99 (44.0%)	-6.9%	(-15.9%, 2.1%)
Excellent or Good	172 (75.1%)	163 (72.4%)	2.7%	(-5.4%, 10.8%)

As seen from Table above, the 95% lower confidence limit of the difference of the proportions of the number of designated Excellent was about –15%, much less than –5% for AAP and ARP. The lower confidence limit was also less than –5% for the number of designated Excellent or Good for AAP but not for ARP.

D. Reviewer's Evaluation of Integrated Efficacy Analysis

1. Unblinding

Of the 420 DIACOL patients with assessments of colon cleansing, there were 256 (61%) with one or more indicia of possible unblinding. The most common reason for potential unblinding was a physician response indicating the presence of undigested or partially digested white tablets in the colon. Of the 425 NuLYTELY patients, 46 (11%) had one or more indicia of unblinding. Even in the group who received NuLYTELY, the most common reason for unblinding was the presence of undigested or partially digested white tablets in the colon.

So, both studies (301 and 302) were open and not blinded. The results from open studies might not be reliable. It could cast doubt about the applicant's finding of equivalence of DIACOL to NuLYTELY.

2. Under treated Comparator (NuLYTELY)

The entire dose of study product, for all treated patients as reported in the Patient Questionnaire was ingested by 241 (54%) of 443 NuLYTELY patients compared with 395 (93%) of 427 DIACO patients ($p<0.001$). About one half of NuLYTELY patients (46%) were under treated and did not ingest the entire dose of study product. This might introduce bias against NuLYTELY group.

The amount of medication left for those patients did not take the entire dose was summarized below.

Summary of the Amount of Medication Left

Study	Treatment	¼ - ½	<1/4	>3/4
301	DIACOL	3	8	3
	NuLYTELY	30	48	10
301	DIACOL	1	6	0
	NuLYTELY	21	58	8

Compiled by the reviewer from SAS dataset patquest.

As seen from the table above, there were 51 (11.5%) NuLYTELY patients had ¼ to ½ amount of medication left. There were 106 (23.9%) NuLYTELY patients had less than ¼ amount of medication left. About 4% (18) NuLYTELY patients had more than ¾ amount of medication left. Since the applicant did not collect all data for the medication left, no statistical analysis could be done for adjusting for imbalance of amount of medication left.

However, the applicant's finding might only show that DIACOL was equivalent to under treated NuLYTELY. This could cast doubt about the applicant's finding on the equivalence of DIACOL to the approved fully dosed NuLYTELY.

E. Reviewer's Evaluation of Integrated Safety Analysis.

1. Mucosal Ulcerations Observed

The presence of superficial mucosal aphthous ulcerations was reported in two Phase III studies. This reviewer performed an integrated analysis of the incidences of reported mucosal ulcerations by combining two studies (301 and 302) using the Cochran-Mantel-Haenszel method. The results are given below.

Superficial Mucosal Aphthous Ulcerations Observed in Studies 301 and 302

Study	DIACOL	NuLYTELY	Between treatment p-value	CMH p-value
301	18/208 (8.7%)	9/207 (4.3%)	0.075	0.001
302	17/212 (8.0%)	3/218 (1.4%)	0.001	

Copied from Table 15 pages 65 and pages 62, vol. 1.10 and 1.11, respectively.
Between treatment p-values were obtained by this reviewer using Chi-square test.
CMH p-value for combined studies was obtained this reviewer using CMH method.

As seen from the table above, in the integrated analysis, superficial mucosal aphthous ulcerations were statistically significantly more in the DIACOL group than in the NuLYTELY.

2. QTc Interval Changes > 450 milliseconds

Per FDA medical officer's request, the sponsor submitted a tabular list of patients whose QTc interval on ECG changed from baseline and exceeded a value of 450 milliseconds on treatment. This reviewer performed an integrated analysis of the number of patients

whose QTc interval on ECG changed from baseline and exceeded a value of 450 milliseconds on treatment by combining two studies (301 and 302) using the Cochran-Mantel-Haenszel method. The results are given below.

Patients with QTc Interval Changes > 450 milliseconds in Studies 301 and 302

Study	DIACOL	NuLYTELY	Between treatment p-value	CMH p-value
301	19/208 (9.1%)	7/207 (3.4%)	0.016	0.001
302	31/212 (14.6%)	17/218 (7.8%)	0.025	

Copied from pages 4, Amendment 09, dated March 22, 2000.
Between treatment p-values were obtained by this reviewer using Chi-square test.
CMH p-value for combined studies was obtained this reviewer using CMH method.

As seen from the table above, in the integrated analysis, patients with QTc interval on ECG changed from baseline and exceeded a value of 450 milliseconds were statistically significantly more in the DIACOL group than in the NuLYTELY.

F. **Overall Summary and Recommendation**

Due to the fact that both studies 301 and 302 were open label trials. There were 256 (61%) of the 420 DIACOL patients with one or more indicia of possible unblinding and about 46% NuLYTELY patients did not ingest the entire dose of study product, the results were highly biased in favor of DIACOL and might not be reliable. They cast doubt that DIACOL was equivalent to NuLYTELY.

Furthermore, for quality of colonic purgation, in both studies (301 and 302), the 95% lower confidence limit of the difference of the proportions of the number of designated Excellent was less than –5% for AAP and ARP. However, the lower confidence limit was greater than –5% for the number of designated Excellent or Good for AAP and ARP.

For quality of colonic purgation in the ascending colon, in both studies (301 and 302), the 95% lower confidence limit of the difference of the proportions of the number of designated Excellent was less than –5% for AAP and ARP. The lower confidence limit was also less than –5% for the number of designated Excellent or Good for AAP and ARP for study 301. For 302, The lower confidence limit was less than –5% only for ARP.

The applicant's finding is not statistically persuasive to claim that DIACOL was equivalent to NuLYTELY.

Superficial mucosal aphthous ulcerations and patients with QTc interval on ECG changed from baseline and exceeded a value of 450 milliseconds were statistically significantly higher in the DIACOL treatment group than in the NuLYTELY treatment group.

Hyperphosphatemia, hypocalcemia, hypokalemia, and hypophosphatemia occurred more frequently in the DIACOL treatment group. Hyperkalemia occurred more frequently in the NuLYTELY treatment group.

/S/

Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 18 pages of text and 4 pages of tables.

concur: Dr. Permutt /S/ 8/1/00
Dr. Welch /S/ 8/10/00

cc:
Archival NDA 21-097
HFD-180
HFD-180/Dr. Talarico
HFD-180/Dr. Aurecchia
HFD-180/Dr. Gallo-Torres
HFD-180/Dr. Prizont
HFD-180/Ms. Kacuba
HFD-715/Chronicle
HFD-715/Dr. Nevius
HFD-715/Dr. Welch
HFD-715/Dr. Permutt
HFD-715/Dr. Fan
Dr. Fan/x73088/mcf/07/31/00

Table 1 Summary of Demographic and Baseline Characteristics— INKP 100-301

Characteristics	ALL Randomized Patients DIACOL (N=216)	NuLYTELY (N=216)	Between Treatment p-value
Sex			
Male	112 (52%)	101 (47%)	0.3359
Female	104 (48%)	115 (53%)	
Race			
White	195 (90%)	183 (85%)	0.183
Black	14 (6%)	21 (10%)	
Oriental	0 (0%)	3 (1%)	
Other	7 (3%)	9 (4%)	
Age (yr)			
Mean (SD)	56.4 (13.8)	6.7 (13.6)	0.8059
Age			0.756
< 65	150 (69%)	146 (68%)	
≥ 65	66 (31%)	70 (32%)	
Weight (lb)			
N	215	215	
Mean (SD)	185.1 (39.1)	181.8 (43.2)	0.4125

P-values for categorical variable obtained using Fisher's Exact Test.
P-values for continuous variables obtained using a the analysis of variance..
Compiled by this reviewer from Tables 2.1.0 and 2.1.1, pages 98-101, Vol. 1.10.

Table 2 Summary of Tolerance/Preference Assessments--- INKP 100-301

	ALL Treated Patients		
Parameter	DIACOL (N=213)	NuLYTELY (N=209)	Between Treatment p-value
Able to take study preparation	194/209 (93%)	118/206 (57%)	<0.0001
Ease/difficulty of taking study preparation			<0.0001
Easy	126 (60%)	60 (29%)	
Slightly difficult	63 (30%)	63 (30%)	
Mod. difficult	17 (8%)	66 (32%)	
Extreme difficult	4 (2%)	18 (9%)	
Taste of study preparation			<0.0001
No taste	154 (74%)	23 (11%)	
Not good, but tolerable	53 (24%)	142 (69%)	
Bad, barely tolerable	2 (1%)	36 (17%)	
Very bad, not tolerable	0 (0%)	6 (3%)	
Take study preparation In future	188/207 (91%)	142/205 (69%)	<0.0001

Copied from Table 12, page 58, Vol. 1.10

Table 3 Summary of Demographic and Baseline Characteristics— INKP 100-302

Characteristics	ALL Randomized Patients DIACOL (N=229)	NuLYTELY (N=225)	Between Treatment p-value
Sex			
Male	107 (47%)	110 (49%)	0.7071
Female	122 (53%)	115 (51%)	
Race			
White	198 (87%)	194 (86%)	0.0951
Black	12 (5%)	20 (9%)	
Oriental	0 (0%)	1 (<1%)	
Other	19 (8%)	10 (4%)	
Age (yr)			
Mean (SD)	56.3 (13.7)	57.5 (13.6)	0.3391
Age			0.491
< 65	153 (67%)	143 (64%)	
≥ 65	76 (33%)	82 (36%)	
Weight (lb)			
N	227	221	
Mean (SD)	182.5 (43.6)	183.8 (41.3)	0.7559

P-values for categorical variable obtained using Fisher's Exact Test.
P-values for continuous variables obtained using a the analysis of variance..
Compiled by this reviewer from Tables 2.1.0 and 2.1.1, pages 94-97, Vol. 1.11.

Table 4 Summary of Tolerance/Preference Assessments— INKP 100-302

Parameter	ALL Treated Patients DIACOL (N=214)	NuLYTELY (N=223)	Between Treatment p-value
Able to take study preparation	201/211 (95%)	123/215 (57%)	<0.0001
Ease/difficulty of taking study preparation			<0.0001
Easy	119 (56%)	66 (30%)	
Slightly difficult	65 (31%)	69 (32%)	
Mod. difficult	21 (10%)	54 (25%)	
Extreme difficult	7 (3%)	30 (14%)	
Taste of study preparation			<0.0001
No taste	145 (69%)	14 (7%)	
Not good, but tolerable	64 (30%)	145 (67%)	
Bad, barely tolerable	2 (1%)	46 (21%)	
Very bad, not tolerable	0 (0%)	12 (6%)	
Take study preparation In future	191/211 (91%)	138/212 (65%)	<0.0001

Copied from Table 12, page 58, Vol. 1.1