CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-892

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-892
Name of drug:	— (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP)
Applicant:	InKine Pharmaceutical Company, Inc.
Indication:	Cleansing of the bowel as a preparation for colonoscopy in adults.
Documents reviewed:	Electronic, dated May 17, 2005
Project manager:	Tanya Clayton
Clinical reviewer:	Eric Brodsky, M.D.
PDUFA Goal Date:	March 17, 2006
Statistical reviewer:	Mushfiqur Rashid, Ph.D.
Statistics team leader:	Stella Grosser, Ph.D.
Biometrics division director:	S. E. Nevius, Ph.D.
Keywords:	NDA review, Clinical studies, Safety studies, Noninferiorty test, ANCOVA

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this submission, the applicant studied the effectiveness of INKP-102 in colon cleansing prior to colonoscopy using Visicol as an active control.

The efficacy data reviewed indicates that both INKP102 dosing regimens were non-inferior to the Visicol treatment regimen with respect to the primary endpoint. There were some safety advantages of the lower dose of INKP102 compared to the higher dose and Visicol. Patient acceptance of the lower dose of INKP102 was better or comparable to acceptance of Visicol for all items in the patient questionnaire.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Visicol is the applicant's currently marketed sodium phosphate tablet purgative, which is indicated for cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age or older. INKP-102 tablets contain the same active ingredients as Visicol, but are smaller in size and easier to swallow. Also, the new tablets contain no microcrystalline cellulose (MCC), an inert but highly insoluble tablet binder that is present in Visicol.

In this submission, the sponsor reported results of two randomized, multicenter, investigator-blinded clinical trials comparing various dosing regimens of INKP-102 to 40 Visicol tablets in adults undergoing colonoscopy. One of the two studies was a Phase II dose-ranging trial. The other study is a Phase III study which compared two doses of INKP-102 tablets with Visicol. The two doses used in the Phase III study were chosen based on the results of the Phase II study.

Brief overview of the Phase II trial:

In the Phase II dose ranging study, the applicant compared six dose regimens of INKP-102 to Visicol tablets to determine the appropriate dosing regimen for colon cleansing. The Phase II trial was a randomized, investigator-blinded, multicenter trial of 214 assessed colonoscopy patients. Two primary endpoints, assessed via endoscopy, were evaluated. Each endpoint was an assessment of colonic cleansing. One was based on the amount of "stool" retained in the colon, while the other was based on the amount of retained "colonic contents." The results for the two endpoints were similar. The six INKP-102 dosing regimens were designed to compare the effect of 1) dose of sodium phosphate (40, 32 or 28 tablets), 2) timing of dosing (administered in doses the evening prior to and the morning of the procedure/"split" or administered in doses the evening prior to the procedure/"evening only") and 3) number of tablets per dose (3 or 4 tablets). Generally, INKP-102 treatment groups had higher response rates than those of Visicol treatment groups. Five of the INKP-102 tablet treatment groups - 40 tablets and 32

tablets, taken 3 or 4 at a time, and 28 tablets/split dose - had higher response rates than those of Visicol. There were no evident differences between INKP-102 40 tablet treatment groups related to whether 3 or 4 tablets were taken at a time. Adverse events occurred with less or the same frequency in the INKP-102 treatment groups compared with the Visicol treatment group. Gastrointestinal disorders accounted for over 95% of adverse events. No adverse events were considered serious, and 97% of the adverse events were considered mild or moderate.

Based on this phase II study, the sponsor has chosen two doses (32 and 40 tablets) of INKP-102 for the phase III trial in this submission. See medical review for further information about this dose finding Phase II study.

Brief overview of the Phase III trial:

The Phase III trial was a multi-center, investigator-blinded Phase III trial, initiated in September 2004, compared two dosage regimens (32 and 40 tablets) of INKP102 to 40 tablets of Visicol. The trial was a randomized, investigator blinded, non-inferiority study in 704 patients. Over 94% of patients in each study arm were responders (i.e. had an overall colon cleansing rating of "excellent" or "good"). The safety, efficacy, and patient acceptance of the regimens were evaluated in adult patients scheduled for colonoscopy.

1.3 STATISTICAL ISSUES AND PRINCIPAL FINDINGS

The primary objective of the Phase III study was to evaluate, by direct visualization, the colon cleansing efficacy of 2 dosing regimens of a new formulation of sodium phosphate (INK-102) compared to Visicol tablets in patients undergoing colonoscopy.

Principal Findings:

The overall colon cleansing rates for Visicol, INKP-102 60 mg group and INKP 40 mg group are 94.5%, 97.0% and 95.3% respectively. The sequential analysis criteria (according to the protocol) for comparing the non-inferiority of the INKP-102 102 arms to Visicol were met. The lower limit of the one-sided 97.5% confidence interval for INKP -102 60 when compared with Visicol, was greater than -10% (lower limit =-1%), and the corresponding p-value was <0.0001, satisfying the non-inferiority test. These results were comparable in the subsequent comparison of the 48g dose of INKP-102 with Visicol, with a lower limit of the 97.5% CI being -2.8 and an associated non-inferiority P-value of <0.0001.

The difference in response rate for the primary efficacy parameter, its lower limit of 97.5% one sided confidence interval, and p-value for non-inferiority test between each INKP-102 treatment arm and Visicol were presented using a Mixed (with the GLIMMIX

SAS macro for binary data) model with fixed effect for treatment, covariates age and sex, and the random effect for endoscopist. To see the robustness of the primary efficacy analysis, this reviewer has conducted ANCOVA (adjusted for age, sex, and fixed investigator) assuming the investigator effect is fixed effect rather than random. This reviewer also has conducted an unadjusted analysis. All these analyses showed that both INKP-102 treated groups were not inferior to Visicol.

This reviewer also conducted additional analyses by redefining (primary endpoint) responder as excellent and non-responder as good or fair or adequate. Both adjusted and unadjusted analyses (based on new definition of responder) showed that the two INKP-102 treated-group were not inferior to Visicol.

Subgroup Analyses:

This reviewer performed subgroup analyses by gender, ethnicity, and age for the overall colon cleansing response rate. The results are summarized below.

The males in INKP-102 treatment arm 60 g (98%) demonstrated an improved responder frequency over males in the Visicol arm (96 %). However, males in INKP-102 treatment arm 48 g (96%;) demonstrated similar rates males in the Visicol arm (96%). For female patients, the responder frequencies for colon cleansing were numerically lower in the treatment groups than the Visicol group.

For both treatment groups, the response rates are numerically higher than the control group in Caucasian and Black patients. Because of small sample sizes in Asian and other groups, the response rates are not interpretable.

For both treatment groups, the response rates are numerically higher than the control group in either age group.

2. *INTRODUCTION*

2.1 *Overview*

INKP-102, a colon cleansing agent, is a new sodium phosphate tablet formulation with no microcrystalline cellulose (MCC). This formulation was expected to result in enhanced mucosal visualization during colonoscopy compared to prior product formulations. The applicant conducted a Phase III, randomized, investigator-blinded, multicenter trial of 704 patients. Patients received either INKP-102 40 tablets (60 gm), INKP-102 32 tablets (48 gm) or Visicol 40 tablets (60 gm) administered in a split dose given the evening prior to and the morning of the procedure. Overall colon cleansing response rate was the primary endpoint.

2.2 **Data Sources**

The reviewed documents were paper, and the data from these studies were archived in the FDA internal electronic document room under network path \\CDSESUB1\N21892\N_000\2005-04-29.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Applicant's Results and Conclusions

Primary endpoint:

The sponsor reported that the test of non-inferiority for each INKP arm (48 or 60 g) versus Visicol was met, satisfying the primary endpoint of the study, which was the overall colon cleansing response rate.

Secondary endpoints:

The INKP-102 arms (48 g or 60 g) had significantly higher ascending colon cleansing response than did Visicol.

Patients who received INKP-102 (48 or 60 g) had significantly better mean overall and ascending colon cleansing scores than did the patients who received Visicol

Patients in the INKP-102 arms (48 or 60 g) required the use of significantly less irrigation fluid during the colonoscopy procedure than the patients in Visicol arm; at east three quarters of all INKP-102 patients needed no irrigation compared to approximately half of Visicol patients who needed no irrigation.

Subgroup Analyses:

The sponsor reported that while a small number of differences were evident in the efficacy analysis of subgroup populations, these differences were clinically meaningful.

3.1.2 Statistical Methodologies

Statistical Analysis:

The primary efficacy parameter, overall colon-cleansing response rate (treatment success) was summarized by the number and percent of responders (overall colon-cleansing response of "good" or "excellent") by treatment arm, with a test of inferiority performed between each INKP-102 arm and the Visicol arm for the all assessed population.

The test of noninferiority was conducted in a sequential manner:

a) The response rate for INKP-102 60 g was first compared to Visicol. If the lower limit of the 97.5%% one-sided CI of the difference in response rate (INKP-102 minus Visicol) was $\geq$ -10%, then INKP-102 60 g was considered noninferior to Visicol.

b) If and only if the non-inferiority of INKP-102 60 g to Visicol was previously established, the lower dose of INKP-102 (48g) was then compared to Visicol (using the non-inferiority analysis with the same parameter described above).

The sequential plan described here does not increase the type I error and no adjustment of the confidence interval for either non-inferiority analysis is required. A p-value for the difference between each INKP-102 arm and Visicol was presented.

The difference in response rate for the primary efficacy parameter, its lower limit of 97.5% one sided confidence interval , and P-value for non-inferiority test between each INKP-102 treatment arm and Visicol were presented using a Mixed (with the GLIMMIX SAS macro for binary data) model with fixed effect for treatment, covariates age and sex, and the random effect for endoscopist.

For secondary efficacy parameters, summary statistics (n, mean, median, Standard deviation [sd]), minimum, and maximum) were presented for the overall and ascending – colon scores for colon cleansing, length of procedure time, and the amount of irrigation fluid used. Contrast statements of ANOVA model with effect for treatment were used to compare each INKP -102 treatment arm with Visicol. The number and percent of ascending colon responders as well as between group comparisons and differences in response rates were summarized by treatment in the manner described for demographics.

For safety parameters, categorical data were summarized as number and percent by each treatment arm; continuous data were summarized presenting descriptive statistics for each treatment arm. For laboratory, vital signs, and weight parameters, changes from screening values to Visit 1 were summarized and compared for each parameter (using paired t-test and contrast statement of an ANOVA model with an effect for treatment.) Based on categorization of normal or abnormal, physical examination changes from screening visit 0 to visit 1 were categorized and presented as no change, improved, or worsened for each body stream. Patient questionnaire responses were summarized (number and percent of

patients by response to each question) and a P-value was presented for the categorical data using a Fisher's exact test to compare the percentages between each INKP-102 treatment arm and Visicol.

3.1.3 Detailed Review

Study design:

The sponsor conducted a phase III, investigator-blinded, randomized, multicenter study. Approximately 765 eligible patients were to be randomly assigned (i.e., 255 patients per group) to receive one of 3 sodium phosphate dosing regimens prior to colonoscopy. Patients received either 60 grams of Visicol (control group) or one of 2 dosing regimens of INKP-102 (either a 40 – tablet [60 gram] or 32-tablet [48 gram] regime of MCC-free sodium phosphate)

There were two scheduled visits: a screening visit (Visit 0) and the colonoscopy visit (Visit 1). The screening visit took place up to 14 days prior to visit 1. In addition, there was a follow-up "visit" conducted by telephone that occurred 2 weeks after colonoscopy. After receiving confirmation of eligibility (based on laboratory results) from the study site, patients self-administered trial medication on the evening prior to their colonoscopy, starting 6 P.M., and again beginning to 3 to 5 hours prior to their scheduled colonoscopy. Patients were considered to have completed the study if they (1) were compliant with the study medication, (2) underwent a colonoscopy, and (3) completed the telephone follow-up "visit" (2 weeks after colonoscopy).

Dosage Administration:

Visicol (control group) was taken as recommended in its approved labeling: a total dose of 40 tablets 960 grams with half taken on the evening before the colonoscopy, beginning at 6 PM, and half taken the day of colonoscopy, beginning 3 to 5 hours before the procedure. For each dose of 20 tablets, patients took 3 tablets at once every 15 minutes (over 1.5 hours) with at least 8 oz of any clear liquid.

INKP-102, in one of two dosing regimens:

INKP-102 (40 tablets): a total dose of 40 tablets (60 grams sodium phosphate), half taken evening before colonoscopy (beginning at 6 P.M.) and half taken the day of colonoscopy, beginning 3 to 5 hours prior to the procedure. For each dose of 20 tablets, patients took 4 tablets at a time every 15 minutes (over 1 hour) with 8 oz of any clear fluid.

INKP-102 (32 tablets): A total dose of 32 tablets (48 grams sodium phosphate), 20 tablets taken on the evening before colonoscopy(over 1 hour, beginning at 6 P.M),.and 12 tablets taken over ½ hour the day of colonoscopy, beginning 3 to 5 hours prior to procedure. For each dose of 20 or 12 tablets, patients took 4 tablets at a time every 15 minutes with 8 oz of any clear liquid.

Duration of the Study:

The study duration was approximately 1 month. Individual patients were screened within 14 days prior to colonoscopy, discharged on the day of colonoscopy after completion of the procedure and study assessments, and followed –up via telephone 14 days after colonoscopy.

Criteria of evaluations:

Efficacy:

Colon-cleansing efficacy was based on the investigator's (endoscopist) direct visualization of the colon, whereby the investigator used a 4-point scale based on the amount of retained "colonic contents" (1= excellent; 2 = Good, 3=fair, 4=Inadequate) for evaluation of colonic-cleansing quality.

The primary endpoint was response rate to treatment. A patient was considered to be a responder if overall colon cleansing was rated as "excellent" or "good."

Secondary efficacy variables included assessments of the mean overall colon cleansing score, quality of cleansing in the ascending colon (response rate and t mean colon cleansing score), frequency of reexamination within 3 months due to inadequate preparation, total procedure time, and the amount of irrigation fluid used.]

Safety:

Adverse events, changes in clinical laboratory evaluation, physical examination, vital signs (heart rate, blood pressure, respiratory rate, temperature, and testing for postural hypotension), and patient acceptance of the dosing regimen (assessed by means of compliance with dosing and by responses to the Patient Questionnaire).

Sample Size Estimation:

To determine the sample size, the success rate in all treatment arms was assumed to be 85%. The planned power of the study to accept the hypothesis of non-inferiority of INKP-102 to Visicol was 85%. Using these assumptions and the primary endpoint analysis (non-inferiority analysis) an unadjusted sample size of 225 per arm, or 765

patients for a 3 –arm study (with no multiple comparisons adjustment because none was needed).

Patients' disposition:

A total of 828 patients signed informed consent; of these, 816 were randomized to treatment with either Visicol (n=272), INKP-102 60 g (n=273), or INKP-102 48 g (n=271). Seven hundred thirteen (87%) of the randomized patents took at least one tablet of the study medication and were included in the safety population; 704 (86%) patients took at least one tablet of study medication and had their scheduled colonoscopy, thus comprising the all assessed population (the population used for the evaluation of efficacy). Of the 816 randomized patients, 648 (79%) patients were included in the Per Protocol population (i.e., completed at least 90% of their designated study regimen, were not known to have dosed > 2 hours outside of the recommended time from and had their scheduled colonoscopy).

In general, both the Per protocol and the all assessed populations each had an equitable distribution of patients across the three treatment groups (per protocol range:213-218 patients; all assessed range: 233-236 patients).

Two patients (one in INKP-102 and one in INKP-102, 48g) completed the study, but were excluded from the per protocol populations due to protocol violations: the investigators failed to capture colon-cleansing information on the physical questionnaire. Both patients are included in the safety population only.

The following table shows subject disposition including the number of subjects in each treatment group who were randomized, treated and evaluated for efficacy.

Table 1: Disposition of Patients

Number of Subjects	Visicol 60 g; 40 tablets N=272	INKP-102		All patients N=816
		60 g; 40 tablets	48 g; 32 tablets	
Randomized	272	273	271	816
All assessed	235	233	236	704
Safety Population	238	236	239	713

Seven (<1%) randomized patients discontinued the study after having taken at least one tablet of study medication.

Demographic Characteristics:

The study population as a whole was predominantly Caucasian, with an average age of 56 years (the majority [60%] of patients was between 45 and 64 years of age). In each of the three treatment arms, there were more females (approximately 55% each) than males (approximately 45% each). Three treatment groups differ significantly with respect to gender, race, or height; however, difference in age were observed, specifically in the comparison of INKP-102 60 g patients (mean 54.7 years) with Visicol patients (mean: 57.1 years) (p-value 0.0178). The following table summarizes the demographic characteristics of the patient population.

Table 2: Patients' Demographic Characteristics

Demographic characteristics	Visicol 60 g: 40 tablets N=235	INKP-102		All patients
		60 g; 40 tablets N=233	48 g; 32 tablets N=236	
Age (years)				
Age < 65	165 (70%)	183 (78%)	181 (77%)	529(75%)
Age ≥ 65	70(29%)	50 (22%)	55(23%)	175(25%)
Gender				
Male	104 (44%)	106 (45%)	104 (44%)	314 (45%)
Female	131 (56%)	127 (55%)	132(56%)	390(55%)
Race:				
Caucasian	199(85%)	208(89%)	210(88%)	615 (87%)
Black	30(13%)	18(8%)	25(11%)	73 (10%)
Asian	2(<1%)	3(1%)	1(<1%)	6(<1%)
Other	4 (2%)	4(2%)	2(<1%)	10(1%)
Hispanic	13 (6%)	15 (6%)	13(6%)	41(6%)

Data Sets Analyzed:
There were three analysis populations used in this study:

1) The safety population - consisted of patients who were randomized and took at least one tablet of study medication;

2) The all assessed population – consisted of patients who took at least one tablet of study medication and had their colonoscopy;

3) and the per protocol population completed at least 90% of their designated study regimen, were not known to have dosed > 2 hours outside the recommended time frame, and had their scheduled colonoscopy/.

Efficacy analyses:

The primary efficacy parameter, overall colon-cleansing response rate (treatment success) was summarized by the number and percent of responders (overall colon-cleansing response of "good" or "excellent") by treatment arm, with a test of inferiority performed between each INKP-102 arm and the Visicol arm for the all assessed population. A summary of the overall Colon cleansing rates was summarized in the following table.

Table 3: Summary of Overall Colon Cleansing Responses (All Assessed Population)

Response status	Visicol 60 g : 40 tablets N=235	INKP-102	
		60 g: 40 tablets N=233	48 g : 32 tablets N=236
Overall Colonic Cleansing: Responder n (%)	222 (94.5%)	226 (97.0%)	225 (95.3%)
Comparison with Visicol:			
Difference in Success rates		2.7	0.9
Two-sided 95% CI of difference		-1.0, 6.5	-2.8, 4.7
P-value for difference		0.1554	0.6198
P-value for noninferiority test (adjusted for age, sex, and random investigator)		<0.0001	<0.0001

It can be seen that from the above table that both INKP-102 doses were non-inferior to the active control Visicol.

Secondary Efficacy Endpoints:

The secondary efficacy analyses were based on responses to the Physician questionnaire and were performed for the all assessed population.

Mean Overall Colon Cleansing score:

The number of patients with excellent overall cleansing scores in the INKP-102 arms exceeded those for theVisicol arm by 50 and 60 patients (22% and 25%), respectively. With all scores (excellent=1, good=2, etc.) built into the parameter, mean (+/-s.d.) scores for patients in the Visicol, INKP-102 60g, and INKP-102 48 g arms were 1.54 (+/-0.60), 1.31 (+/- 0.56), and 1.30 (+/-0.61) respectively.
These mean scores translated to differences of -0.24 for each INKP-102 arm compared with Visicol, with the differences being statistically significant (p-value <0.0001), favoring both INKP-102 48-g and INKP-102 60-g.

Ascending Colon Cleansing Response Rates:

The overall response rate for AC cleansing was 93% with both the INKP-102 60-g (96%) and INKP-102 48-g (94%) having higher response rates than the Visicol arm (89%). As with the primary efficacy endpoint, tests of non-inferiority for AC cleansing response rates were met using a hierarchical analysis. The results are summarized in the Table A.1 in the appendix.

Mean Ascending Colon Cleansing Score:

The mean quality of ascending colon (AC) cleansing was determined from responses to the Physician questionnaire in the same manner, and using the same scoring as that for the mean quality of colon cleansing. P-values and mean differences were obtained using an ANOVA with factor treatment used to compare the means between INKP-102 and Visicol groups. Results showed that patients in both the INKP-102 60 g and INKP-102 48-g arms had "excellent" AC cleansing scores that exceeded those for the Visicol arm by 50 and 54 patients (22% and 23%), respectively. Mean (=/- sd) AC scores for patients in the Visicol, INKP-102 60-g, and INKP-102 48-g arms were 1.59 (+/- 0.69), 1.29 (+/- 0.54), and 1.32 (+/-0.63), respectively. From the ANOVA, these mean scores translated to differences of –0.30 (INKP-102 60 g) and -0.27 (INKP-102 48 g) in the comparison with Visicol; these differences were statistically significant (both cases p-value <0.0001),

favoring both INKP-102 60 g (95% CI=-0.41, -0.19) and INKP-102 48 g (95% CI=-0.38, -.016).

Frequency of Re-examination within 3 months (Due to Inadequate Preparation):

Following their assessment of colon-cleansing effectiveness, investigators were asked for their estimation on the adequacy of the preparation by answering "yes" or "no" to their question: Does the patient require re-examination within 3 months due to inadequate preparation: one patient in the INKP-102 60-g arm, and 2 patients in the INKP-102 48-g arm.

Table A.2 presents a summary of patients requiring re-examination within 3 months due to inadequate preparation. All the treatments groups were comparable with respect to frequency of re-examination within 3 months.

Amount of Irrigation Used:

In response to the question, *was irrigation required to clear material from colon,* investigators marked their response in one four boxes correlating to no=0, <50 cc=1, 50-100 cc=2, or >100 cc=3.

More patients in the INKP-102 60-g and 48-g arms (79% and 75%, respectively) required no irrigation when compared with patients in the Visicol arm (56%). For those patients who required >100 cc of irrigation during the study (n=72), Visicol patients accounted for half (n=350 – nearly twice as many as those requiring > 100 cc of irrigation in the INKP-102 60-g (n=19) and 48-g (n=18) arms.

Mean (+/-sd) irrigation scores were 0.86 (+/- 1.13)m for Visicol patients, 0.42 (+/-0.91) for INKP-102 60-g patients, and 0.47 (+/- 0.92) for INKP-102 48-g patients. Differences of the treatment means were statistically significant (P-value <0.0001) using the ANOVA model for the amount of irrigation required to clear material from the colon, favoring patients in both INKP-102 arms over patients in Visicol arm.

3.2 Other Analyses

Fixed Effects Analysis:

To see the robustness of the primary efficacy analysis, this reviewer has conducted ANCOVA (adjusted for age, sex, and fixed investigator) assuming the investigator effect is fixed effect rather than random. This reviewer also has conducted an unadjusted analysis. These efficacy analyses are summarized in the following table:

Table 7: Summary of Overall Colon Cleansing Response (all assessed population: reviewer's analysis: fixed effects model and investigator effect is a fixed effect)

Response status	Visicol 60 g : 40 tablets N=235	INKP-102	
		60 g: 40 tablets N=233	48 g : 32 tablets N=236
Overall Colonic Cleansing: Responder n(%)	222/235(94.5%)	226/233 (97%)	225/236 (95.3%)
Comparison with Visicol: Difference in Success (adjusted) rates (s.e.)		0.42(.02)	2.6 (.02)
95% CI of difference (adjusted for age, sex, and fixed investigator)		(0.005, 0.08)	(-0.01 , 0.07)
Difference in Success (not adjusted) rates (s.e.)		0.03(0.02)	0.009 (0.02)
95% CI of difference (not adjusted for covariates)		(-0.01, 0.06)	(-0.03 , 0.05)

It can bee seen that fixed effect ANCOVA produced results which are consistent with the ANCOVA assuming the investigator affects are random. Also the unadjusted analysis showed the both INKP-102 treated groups were not inferior to Visicol.

Redefined Primary Endpoint (when responder=excellent and non-responder= [good, fair, inadequate]):

This reviewer conducted analyses by redefining responder as excellent and non-responder as good or fair or adequate. The results are summarized in the following table:

Table 8: Summary of Overall Colon Cleansing Response (all assessed population: reviewer's analysis: fixed effects and not adjusted) When Responder=excellent and Non-responder= (good, fair, inadequate)

Response status	Visicol 60 g : 40 tablets N=235	INKP-102	
		60 g: 40 tablets N=233	48 g : 32 tablets N=236
Overall Colonic Cleansing: Responder n(%)	120/135(51%)	170/233 (73%)	180/236 (76%)
Comparison with Visicol: Difference in Success (adjusted) rates (s.e.)		25%(0.0431)	28% (0.0425)
One-sided 97.5% CI of difference (adjusted for age, sex, and fixed investigator)		(17% 34%)	(19% 36%)
Difference in Success (not adjusted) rates (s.e.)		21.90% (0.0437)	25.21% (0.0428)
One-sided 97.5% CI of difference (not adjusted for covariates)		(13.33% 30.47%)	(16.33% 33.59%)

Both adjusted and unadjusted analyses (based on new definition of responder) showed that two INKP-102 treated group were not inferior to Visicol.

3.2 Evaluation of Safety

Adverse Events:

The sponsor reported that nearly all adverse events (AEs) experienced by patients in this study were related to the system organ class of gastrointestinal disorders, regardless of dosage or treatment.

A dose-effect appeared evident in the frequency of AEs across treatment arms, with more patients in the gastrointestinal disorders (the body system accounting for approximately 91% of all AEs) than patients in either of the higher dose groups. (Visicol and INKP-102 60 g).

Most AEs were considered by the investigator to be mild to moderate in intensity and were considered to be related to study medication, regardless of dosage treatment.

Adverse events led to discontinuation of study medication in 5 patients, all occurring in INKP-102 60g patients; all 5 patients remained in the study and had a colonoscopy.

There were 2 serious adverse events and 1 withdrawal from the study due to an AE.

Laboratory values:

Patients who received INKP-102 tended to have comparable laboratory change values or values exhibiting less variation from screening values than patients who received either Visicol or INKP-102 60 g.

INKP-102 48 g was associated with significantly smaller increases in serum inorganic phosphorous than 60 g of INKP-102 or Visicol

The expected reductions in serum potassium and calcium were observed in this study; the differences between INKP-102 48 g and Visicol were unimportant.

Vital Signs and physical examinations:

The sponsor reported that changes from screening values in vital signs were modest, clinically unimportant, did not differ among treatment groups.

The sponsor also reported that changes in physical examination findings did not indicate a clinically meaningful difference from the screening examination.

Other Adverse Events:

Only two patients, one in the Visicol arm and one in the INKP-102 arm, had symptomatic postural hypotension; none had syncope.

See medical review for further safety information.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS and OTHER ANALYSES

4.1 Gender, Race and Age

This reviewer examined treatment benefits among the following subgroups:

Male versus Female;

Race (Caucasian, Black, Hispanic and Asian);

Age < 65 years versus ≥ 65 years.

Sub-group analyses are summarized below.

Gender

The Overall Colon Cleansing response rates by gender are summarized in the following table:

Table 4: Summary of Overall Colon Cleansing Response (all assessed population: reviewer's analysis) by Gender

Response status	Visicol 60 g : 40 tablets N=235	INKP-102	
		60 g: 40 tablets N=233	48 g : 32 tablets N=236
Overall Colonic Cleansing:			
Male: Responder n/N(%)	95/104 (96%)	104/106 (98%)	100/104 (96%)
Female: Responder n/N(%)	127/131 (97%)	122/127 (96%)	125/132 (94%)

It can be seen from the above table that males in INKP-102 treatment arm 60 g (98%) demonstrated an improved responder frequency over males in the Visicol arm (96 %). However, males in INKP-102 treatment arm 48 g (96%;) demonstrated similar rates males in the Visicol arm (96%). For female patients, the responder frequencies for colon cleansing were numerically lower in the drug groups than the control group.

Race
The Overall Colon Cleansing response rates by race are summarized in the following table:

Table 5: Summary of Overall Colon Cleansing Response (all assessed population: reviewer's analysis) by Race

Response status	Visicol 60 g : 40 tablets N=235	INKP-102	
		60 g: 40 tablets N=233	48 g : 32 tablets N=236
Overall Colonic Cleansing: Responder n/N(%)			
Caucasian	188/199 (94%)	203/208(98%)	198/208(95%)
Black	28/30(93%)	17/18(94%)	24/25 (96%)
Asian	2/2 (100%)	3/3 (100%)	1/1(100%)
Other	4/4 (100%)	¾ (75%)	2/2 (100%)

It can be seen from the above table that in both treatment groups the response rates are numerically higher than the control group in Caucasian and Black patients. Because of small sample sizes in Asian and other groups, the response rates are not interpretable.

Age-group:

The Overall Colon Cleansing response rates by age-group are summarized in the following table:

Table 6: Summary of Overall Colon Cleansing Response (all assessed population: reviewer's analysis) by Age-group

Response status	Visicol 60 g : 40 tablets N=235	INKP-102	
		60 g: 40 tablets N=233	48 g : 32 tablets N=236
Age-group < 65: Responder n/N(%)	154/165 (93%)	176/183 (96%)	170/181 (94%)
Age-group > 65: Responder n/N(%)	68/70 (97%)	50/50 (100%)	55/55(100%)

It can be seen from the above table that in both treatment groups the response rates are numerically higher than the control group in either age group.

5. SUMMARY AND CONCLUSIONS

5.2 CONCLUSIONS AND RECOMMENDATIONS

Efficacy:

Primary endpoint:

The efficacy data in this submission showed that each INKP-102 (48 g or 60 g) was not inferior to Visicol in colon cleansing prior to colonoscopy.

Secondary Endpoints:

The INKP-102 arms (48 g or 60 g) had advantage over Visicol with respect to secondary endpoints (e.g., ascending-colon cleansing response rates, mean overall colon cleansing scores, ascending colon cleansing scores, and irrigation fluid). Patient acceptance of the lower dose of INKP102 was better or comparable to acceptance of Visicol for all items in the patient questionnaire.

Safety:

The incidence of any specific treatment related adverse events were comparable between the two groups.

Mushfiqur Rashid, Ph.D.
Mathematical Statistician

Concur:

Dr. Stella Grosser

Table A.1: Summary of Ascending Colon Cleansing Responses (All Assessed Population)

Response status	Visicol 60 g : 40 tablets N=235	INKP-102	
		60 g: 40 tablets N=233	48 g : 32 tablets N=236
Overall Colonic Cleansing:			
Responder n(%)	208 (89%)	220 (96%)	220 (94%)
Comparison with Visicol:			
Difference in Success rates		8.0	5.0
One-sided 97.5% CI of difference		(2.8, 12.3)	(0.6, 10.0)
P-value for difference		0.0019	0.0272
P-value for noninferiority test (adjusted for age, sex, and random investigator)		<0.0001	<0.0001

Table A.2: Summary of Requirements of Re-examination Within 3 Months Due to Inadequate Preparation (All Assessed Population)

	Visicol 60 g : 40 tablets N=235	INKP-102	
		60 g: 40 tablets N=233	48 g : 32 tablets N=236
Required re-examination due to inadequate preparation			
No	235	232	234 (99%)

Table A.3: Summary of Irrigation Requirements (All Assessed)

	Visicol 60 g : 40 tablets N=235	INKP-102	
		60 g: 40 tablets N=233	48 g : 32 tablets N=236
Irrigation required to clear material from colon			
(0) None	132(56%)	183(79%)	176 (75%)
(1) <50 cc	38(16%)	21(9%)	27 (11%)
(2) 50-100 cc	30 (13%)	10(4%)	15(8%)
(3) >100 cc	35(15%)	19 (8%)	18(8%)

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/s/

Mushfiqur Rashid
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Stella Grosser
3/2/2006 04:58:30 PM
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STATISTICAL REVIEW AND EVALUATION

Stability

Medical Division: Division of Gastroenterology Products
Biometrics Division: Division of Biometrics I

NDA NO.:	21-892
SERIAL NO.:	S_000
DATE OF RECEIVED BY THE CENTER:	December 12, 2005
DRUG NAME:	[redacted] Tablets (sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP)
DOSAGE:	1500 mg Tablet
INDICATION:	Cleansing of Bowel as Preparation for Colonoscopy
SPONSOR:	Salix Pharmaceuticals, Inc.
DOCUMENTS REVIEWED:	12-Month Stability Data
NAME OF PROJECT MANAGER:	Tanya Clayton (DGP)
NAMES OF STATISTICAL REVIEWERS:	Roswitha Kelly, M.S. (OB/DBI)
NAME OF CHEMISTRY REVIEWER:	Ali H Al Hakim, Ph.D. (ONDQA/DPAMS)

Roswitha Kelly, M.S.
Mathematical Statistician

Concur:

James Hung, Ph.D.
Director, DBI

Distribution: NDA 21892/ [redacted]
ONDE/ODE3/T.Clayton
ONDQA/A. Al Hakim, Ph.D.
OPSS/OB/DBII/S. Grosser, Ph.D.
OPSS/OB/DBI/K.Mahjoob, Ph.D.
OPSS/OB/DBI/J. Hung, Ph.D.
OPSS/OB/QMRS/Y. Tsong, Ph.D.
OPSS/OB/QMRS/S.Machado Ph.D.
OPSS/OB/DBI/Roswitha Kelly, M.S.
OPSS/OB/R. O'Neill, Ph. D.
OPSS/OB/L. Patrician, M.S.

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

All attributes which had associated specification limits supported an extrapolation of shelf life to 24 months for [redacted] 1.5 g tablets packaged into [redacted] count or 100 count [redacted] bottles and stored at room temperature.

The sponsor appropriately analyzed the 12-month stability data for sodium phosphate monobasic monohydrate, USP, sodium phosphate dibasic anhydrous, USP, dissolution at 1 hour, disintegration, friability, and [redacted] The analysis of each attribute supported a 24-month shelf life for both the product in [redacted] count bottles and the product in 100 count bottles when stored at room temperature. The results for tablet hardness were also statistically analyzed but no shelf life estimate was computed.

The reviewer independently analyzed the stability data for sodium phosphate dibasic anhydrous of the product in [redacted] count bottles, for sodium phosphate monobasic monohydrate of the product in 100 count bottles, and for friability of the product in either package type. The results matched the sponsor's closely. Therefore, the reviewer accepted the sponsor's analysis results for the remaining attributes. She also concluded that an extension of the product's shelf life to 24 months was warranted.

1.2 Overview of the Submission

The December 12, 2005, submission contained the stability data listings, the statistical analysis results and the sponsor's conclusions. Three validation batches per package type had stability data for 12 months under the room temperature condition and for 6 months under the accelerated storage condition. The sponsor requested a 24-month shelf life based on the analysis of the room temperature stability data.

1.3 Principal Findings

1.3.1 Sponsor's Results and Conclusions

The sponsor provided detailed statistical analysis results for each attribute of the three batches when packaged into [redacted] count bottles or into 100 count bottles and stored under room temperature and accelerated conditions. Statistical analysis followed the ICH Q1E guideline. For the stability data collected under room temperature conditions, all attributes except hardness were analyzed and found to support extrapolated shelf life estimates of 24 months. Hardness did not have a specification limit and the sponsor did not estimate an expiry for this attribute. The data collected under the accelerated

condition did not show any significant change. Hence, the sponsor concluded that an extrapolated shelf life of 24 months was warranted.

1.3.2 Reviewer's Results and Conclusions

The sponsor's statistical analyses were appropriate and detailed, such that spot checking could confirm their correctness. The reviewer independently analyzed sodium phosphate dibasic assay for the product in — count bottles, sodium phosphate monobasic assay for the product in 100 count bottles, and friability for either package. Results closely matched those of the sponsor and the reviewer accepted the sponsor's findings for the remaining attributes. She agreed with the sponsor that an extrapolated shelf life of 24 months is supported based on the submitted data and analysis results.

1.3.3 Extent of the Evidence in Support of the Requested Shelf Life

There were 12-month stability data from three validation batches packaged into — count — bottles and into 100 count bottles and stored at 25°C/60%RH. For each package type, the reviewer confirmed some of the sponsor's analyses and agreed that all attributes with specification limits supported an extrapolated shelf life of 24 months.

1.3.4 Statistical Issues

There were no statistical issues related to the sponsor's analyses or findings. The reviewer spot checked some of the sponsor's output and was able to reproduce the p-values for pooling slopes. The p-values for pooling intercepts were somewhat different but still led to the same conclusions. Hence the reviewer accepted as correct all statistical output provided by the sponsor.

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

— is a 1.5 gram tablet where sodium phosphate monobasic monohydrate constitutes 1102 mg/tablet and sodium phosphate dibasic anhydrous the remaining 382 mg/tablet. The product is indicated for the cleansing of the bowel as a preparation for colonoscopy in adults 18 years or older. It is packaged into — count — bottles and into 100 count — bottles which is the trade line. The reviewer received the consult on January 17, 2006 with a requested completion date of the first week of February. The PDUFA date is March 17, 2006.

The consult requested a statistical analysis of the submitted 12-month long-term stability data to establish whether an extrapolated shelf life can be granted. Dissolution, assay, and friability were identified as being important attributes. The sponsor's data, analyses and report could be found in the 12/12/2005 electronic submission to the EDR, but the stability data were not available as an electronically analyzable data set.

2.2 Overview of the Stability Program and Studies Reviewed

NDA 21-892 was submitted on March 17, 2005 with only three months of stability data. Subsequently, the submission was amended with six- and nine-month data and finally on December 12, 2005 with the 12-month update. Three validation batches had been packaged into — count [redacted] bottles and also into 100 count [redacted] bottles. The latter represented the commercial package. Stability data were collected for 12 months at room temperature and for six months at the accelerated condition. The stability commitment was updated to include the 18, 24, and 36 months time points for the validation batches and all time points for the future annual batches, which will be packaged into both bottle sizes as well.

2.3 Data Analyzed and Sources

Specification limits and 12-months raw data when the product was stored at 25°C/60%RH were provided for appearance, sodium phosphate monobasic monohydrate, USP, sodium phosphate dibasic anhydrous, USP, dissolution, disintegration, friability, and [redacted] In addition, the measurements for hardness were provided but no associated specification limit. Hence this attribute was not used to estimate a shelf life. The sponsor also provided the details of their statistical analyses used to estimate the shelf life.

2.4 Stability Study

2.4.1 Sponsor's Analysis, Results and Conclusions

The sponsor provided a detailed report and statistical analyses of the stability data. For each attribute the sponsor reported the method of statistical analysis, final modeling results, and graphs. These followed the ICH Q1E guideline and each attribute estimated an expiry of at least 24 months for either package type. The sponsor also provided similar regression analyses for the data for hardness but did not estimate a shelf life as no specification limit is available. The sponsor also stated that these findings and conclusions were supported by the stability data collected under the accelerated condition. These showed no significant change in the assays and no Stage 2 testing for dissolution.

2.4.2 Reviewer's Analysis, Results and Conclusions

As the sponsor provided suitable detail of their statistical analyses (modeling approach, p-values), the reviewer chose to spot-check some results and to accept the remaining results if good overlap of findings was observed. The reviewer independently analyzed sodium phosphate dibasic anhydrous assay for the product in the [redacted] count bottles, sodium phosphate monobasic monohydrate assay for the product in the 100 count bottles (Tables 1 and 2, Figures 1 and 2), and friability for the product in either package configuration (Tables 3 and 4, Figures 3 and 4). She applied the standard stability software used by the Office of Biostatistics. The modeling steps and computation of shelf life proved to be the same as the sponsor had performed. The reviewer obtained the same p-values as the sponsor had reported for testing the poolability of slopes. The p-values for pooling of intercepts were numerically somewhat different but resulted in the same final model. Hence the reviewer accepted the sponsor's analysis results for the remaining attributes for the product in either package type.

The sponsor reported and analyzed mean dissolution. In general, the individual dissolution values are preferred to give an estimate of their variability and to document excursions to Stage 2 testing. However, the sponsor reported that no Stage 2 testing had been required at either the room temperature or the accelerated conditions and therefore the use of mean dissolution in the analyses was acceptable.

2.5 Statistical and Technical Issues

There were no statistical issues with this submission. The sponsor used the same analysis approach as the reviewer and provided sufficient detail to permit verification of results. Spot-checking of the sponsor's findings confirmed sufficient overlap in p-values that the reviewer accepted the numeric accuracy of all of the sponsor's analyses.

2.6 Statistical Evaluation of Collective Evidence

The sponsor provided 12-month stability data for [redacted] 1.5 g tablets when stored at 25°C/60%RH and 6-month data when stored under the accelerated condition. The sponsor provided detailed analysis results which permitted verification of appropriateness and accuracy. Independent analyses by the reviewer confirmed the sponsor's results and conclusions for several attributes. Therefore, the reviewer also concluded that all attributes which had specification limits support an extrapolated shelf life of 24 months. In addition, the sponsor reported no significant change in the attributes when the product was stored under the accelerated storage condition and no Stage 2 testing for dissolution.

2.7 Conclusions and Recommendations

Three batches of 1.5 g [redacted] tablets were packaged into [redacted] count [redacted] bottles and also into 100 count [redacted] bottles and stored at room temperature for 12 months. The sponsor provided the data, a thorough description of their analysis approach, and sufficient numeric detail to permit verification of their results. Comparing the sponsor's results with those obtained from the standard Office of Biostatistics software the reviewer found good overlap and could accept the numeric results of the sponsor's remaining analyses. She also concluded with the sponsor that the requested shelf life of 24 months is supported by all attributes which had specification limit(s). Hardness was the only attribute which did not have a specification limit. It was therefore not used to estimate the product's shelf life.

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