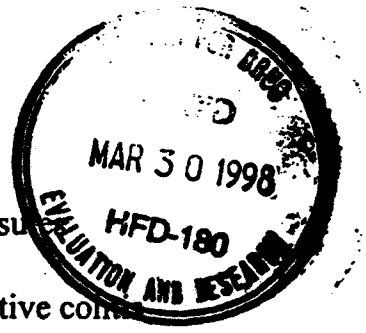
CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-610

STATISTICAL REVIEW(S)

MAR 19 1998



NDA Statistical Review and Evaluation (Stability Analysis)

NDA#:	20-610
Drug Product:	[redacted] (Balsalazide disodium) 0.75 mg capsu[redacted]
Sponsor:	Salix Pharmaceuticals, Inc.
Indications:	Treatment of mildly to moderately active ulcerative co[redacted]
Received Date:	December 1, 1997
Documents Reviewed:	Amendment - Response to FDA request on stability analysis
CSO:	Melodie McNeil
Complete Date:	March 24, 1998
Chemical Reviewer:	Maria E. Ysern, Ph.D.
Primary Reviewer:	Yi Tsong, PhD
Secondary Reviewer:	Abdul J. Sankoh, PhD, Michael Welch, PhD

I. Introduction

The statistical analysis for the stability data of Colazide 0.75 mg capsule submitted by the sponsor as requested by FDA chemist was carried out and reported in this document. Based on FDA's stability analysis of assay and dissolution, the reviewer recommends a 30 month expiration date for packaging of 40cc child resistant cap manufactured by [redacted], 24 month for packaging of 600 cc CRC manufactured by [redacted] and 18 months for the 600 cc CRC packaging manufactured by [redacted] All the stability analysis results are based on storage condition of 25°C and 60% relative humidity.

II. Data and Sponsor's Results

The data submitted by the sponsor are described in the following table. Batches in each group were of the same manufacturer, same strength. Each batch was measured repeatedly at every time point.

Table 1 Stability study data description

Analysis Group	Study No.	Drug Substance Lot	Date of manufacture	Date of last observation (mo)	
				Assay (mean)	Dissolution (individual)
Group 1 Mfg: [redacted] 40cc CRC	DSTAB069	F6832.7D-12 /F6832.7D-14	March 4, 1994	24	24
	DSTAB142	F6290E01	June 7, 1995	18	18
	DSTAB144	P6290D01 /P6290E02	June 14, 1995	18	18

Analysis Group	Study No.	Drug Substance Lot	Date of manufacture	Date of last observation (mo)	
				Assay (mean)	Dissolution (individual)
Group 2 Mfg: — 600cc CRC	DSTAB072	F6832.7D-12 /F6832.7D-14	March 4, 1994	24	24
	DSTAB145	N6290E01	June 7, 1995	18	18
	DSTAB147	P6290D01 /P6290E02	June 14, 1997	18	18
Group 3 Mfg: — 40 cc CRC	DSTAB070	516/535	March 17, 1994	24	24
	DSTAB174	61620001	Nov. 7, 1995	12	12
	DSTAB175	61620001	Nov. 7, 1995	12	12
	DSTAB176	61620001	Nov. 7, 1995	12	12
Group 4 Mfg: — 600 cc CRC	DSTAB177	61620001	Nov. 7, 1995	12	12
	DSTAB178	61620001	Nov. 7, 1995	12	12
	DSTAB179	61620001	Nov. 7, 1995	12	12
	DSTAB073	516/533	March 17, 1994	24	24
Other Mfg: — chem 40 cc CRC	DSTAB071	F6832.7D-10 /F6832.7D-12/535	March 17, 1994	24	24
Other Mfg: — chem 600 cc CRC	DSTAB074	F6832.7D-10 /F6832.7D-12/535	March 17, 1994	24	24

The sponsor used a modified FDA Stability Analysis program for the shelf life estimation. In the sponsor's analysis, degradating models were identified for batches in group 1 to 4. For the remaining two batches, the sponsor selected models by considering all batches in one group called group 5 which consists of batches in groups 1 and 2. The specification for assay is to have batch mean within — of the labeled strength. The specification for dissolution is to have — of the individual tablets dissolved no less than — Sponsor's estimation of expiration dates are given in the table in the next section.

III. Reviewer's Result and Comments

The reviewer used Stable97, an FDA's interactive SAS program for model selection and shelf life estimation. Since the USP specification of assay is set on batch mean and the specification for dissolution is on individual tablet, the 95% confidence interval of assay and dissolution are estimated differently as follows,

the 2-sided 95% confidence band of mean linear regression values of potency:

$$(y_i - t_{mn-1,.025}\{1/mn + (T_i-T)^2/[n\Sigma (T_i-T)^2]\}^{1/2}S_y,\ y_i + t_{mn-1,.025}\{1/mn + (T_i-T)^2/[n\Sigma (T_i-T)^2]\}^{1/2}S_y)$$

the 1-sided 95% confidence band of individual linear regression values of dissolution is:

$$(y_i - t_{mn-1,.05}\{1+1/mn + (T_i-T)^2/[n\Sigma (T_i-T)^2]\}^{1/2}S_y,\ \infty)$$

where y_i is the estimated or predicted mean value, at time T_i, m is the total number of observation time points, n is the number of observations at each time T_i, $t_{mn-1,\alpha}$ is the $(1-\alpha)$x100 th percentile of t- distribution with degrees of freedom mn-1, S_y is the estimate of the standard error and T id the mean time point. Note that for potency stability, a 95% 2-sided confidence band is used for the 2-sided specification on batch mean. But for dissolution stability, a 95% one-sided confidence band for individual tablet is used for the one sided dissolution specification.

The models selected are as stated in the following table

Table 2 expiration date model selection

Analysis Group	Study No.	Date of last observation (mo)	
		Assay (mean)	Dissolution (individual)
Group 1 Mfg: [redacted] 40cc CRC		Separate slope and separate intercept	Separate slope and separate intercept
	DSTAB069	y= 99.36 + 0.041t	
	DSTAB142	y= 101.52 - 0.173t	
	DSTAB144	y= 101.02 - 0.061t	
Group 2 Mfg: [redacted] 600cc CRC		Separate slope and separate intercept	Common slope and separate intercept
	DSTAB072	y= 99.75 - 0.014t	
	DSTAB145	y= 101.07 - 0.115t	
	DSTAB147	y= 100.17 - 0.046t	
Group 3 Mfg: [redacted] 40 cc CRC		Separate slope and separate intercept	Common slope and separate intercept
	DSTAB070	y= 98.06 + 0.038t	
	DSTAB174	y= 102.53 - 0.228t	
	DSTAB175	y= 100.45 + 0.005t	
	DSTAB176	y= 100.43 - 0.002t	
Group 4 Mfg: [redacted] 600 cc CRC		Separate slope and separate intercept	Common slope and separate intercept
	DSTAB177	y= 99.38 - 0.012t	
	DSTAB178	y= 102.42 - 0.209t	
	DSTAB179	y= 100.06 + 0.024t	
	DSTAB073	y= 100.31 - 0.013t	

Analysis Group	Study No.	Date of last observation (mo)	
		Assay (mean)	Dissolution (individual)
Mfg: [redacted] 40 cc CRC	DSTAB071	y=99.30+0.027t	[redacted]
Mfg: [redacted] 600 cc CRC	DSTAB074	y= 99.93 + 0.027t	[redacted]

The 95% confidence band of the degradating line of each batch is plotted up to 48 months for assay and 80 months for dissolution in the attached figures. The model projected expiration date of each batch and the regularily allowable number of months (last observation month +six months) are given in the next table as contrasting to the sponsor's result.

Table 3 Results of statistical analysis

Analysis Group	Study No.	Assay (model expiration date in months)		Dissolution (model expiration date in months)		Obs+6 Mon
		Sponsor's	Reviewer's	Sponsor's	Reviewer's	
Group 1 Mfg: [redacted] 40cc CRC	Group	Common slope and intercept	Separate slope and intercept	Separate slope and intercept	Separate slope and separate intercept	
	DSTAB069	68	>48	55	45	30
	DSTAB142	68	48	63	96	24
	DSTAB144	68	>48	67	54	24
Group 2 Mfg: [redacted] 600cc CRC	Group	Common slope and intercept	Separate slope and intercept	Common slope and intercept	Common slope and separate intercept	30
	DSTAB072	53	>48	43	40	30
	DSTAB145	55	>48	43	43	24
	DSTAB147	55	>48	54	63	24
Group 3 Mfg: [redacted] 40 cc CRC	All	Separate slope and intercept	Separate slope and intercept	Separate slope and intercept	Common slope and separate intercept	
	DSTAB070	84	>48	33	28	30
	DSTAB174	16	37	43	44	18
	DSTAB175	37	>48	40	40	18
	DSTAB176	84	>48	43	44	18

Analysis Group	Study No.	Assay		Dissolution		
		Sponsor's	Reviewer's	Sponsor's	Reviewer's	Obs+6 Mon
Group 4 Mfg [redacted] 600 cc CRC	All	Separateslope and separate intercept	Separate slope and intercept	Separate slope and intercept	Common slope and separate intercept	
	DSTAB177	84	>48	48	32	18
	DSTAB178	22	>48	47	56	18
	DSTAB179	28	36	43	54	18
	DSTAB073	31	>48	36	47	30
Mfg [redacted] 40 cc CRC	DSTAB071	84	>48	65	40	30
Mfg [redacted] 600 cc CRC	DSTAB074	84	>48	58	92	30

As shown in the above table and attached figures on pages 8-24, based on reviewer's analysis, the statistical expiration date (the minimum date among the batches) for the different packaging and manufacturer are as follow

Group 1 40 cc CRC, manufacturer: [redacted]
- 48 months (potency only)
45 months (both potency and dissolution)
last observation + six months = 24

Group 2 600 cc CRC, manufacturer: [redacted]
- greater than 48 months (potency only)
40 months (both potency and dissolution)
last observation +six months = 24

Group 3 40 cc CRC, manufacturer: [redacted]
37 months (potency only)
28 months (both potency and dissolution)
last observation +six months = 18

Group 4 600 cc CRC, manufacturer: [redacted]
- 36 months (potency only)
32 months (potency and dissolution)
last observation + six months = 18

Since DSTAB071 is a combination of study group 1 and 3, the expiration date should be minimum of the batches in group 1 and 3. For the same reason, DSTAB074 is a combination of study group 2 to 4, and the expiration date should be the minimum of all batches in the group 2 and 4.

DSTAB071 potency only = 37
potency and dissolution = 28
last observation + six months = 18

DSTAB074 potency only = 36
potency and dissolution = 32
last observation + six months = 18

However, these statistical estimates are based on the linear degradating assumption with observations of no more than 24 months. In general, assumption on degradation model should not be carried forward to the future prediction for more than six months. Hence, the reviewer will recommend expiration date be no more than 30 months for batches in group 1, 24 months for group 2, 18 months for group 3, 4, batch DSTAB071 and DSTAB074.

Out of Specification Batches

The reviewer's noticed also that some batches used in this stability study do not satisfy the USP dissolution sampling plan. According to USP XXII, the acceptance table requires that

Stage	Number tested	Acceptance criteria
1	6	Each unit is no less than Q+5%
2	6	Average of 12 units is equal to or greater than Q, and no unit is less than Q-15%
3	12	Average of all 24 units is equal to or greater than Q, no more than 2 units are less than Q-15%, and one unit is less than Q-25%

where Q is the specification.

Each of the batches submitted for stability evaluation consists of six units tested at each time point. The following is a list of batches that do not comply with the USP XXII acceptance table during the observation period.

Batch	Time point in weeks	Dissolution fail to satisfy the Acceptance criteria
DSTAB071	0	
DSTAB072	3	
DSTAB145	12	
DSTAB074	0	

Summary

The sponsor requested [redacted] month expiration date for all batches. The reviewer's analysis result in statistical expiration date as indicated in the following

based on potency only
Group 1 40 cc CRC, manufacturer: [redacted]

Group 2 600 cc CRC, manufacturer: —
Group 3 40 cc CRC, manufacturer: —
Group 4 600 cc CRC, manufacturer: —

based on potency and dissolution
Group 1 40 cc CRC, manufacturer: —
Group 2 600 cc CRC, manufacturer: —
Group 3 40 cc CRC, manufacturer: —
Group 4 600 cc CRC, manufacturer: —

If the expiration date can't be extended to more than six months beyond the last observation date then the expiration date for the batches would be recommended as follow

Group 1 40 cc CRC, manufacturer: —
Group 2 600 cc CRC, manufacturer: —
Group 3 40 cc CRC, manufacturer: —
Group 4 600 cc CRC, manufacturer: —

Batches DSTAB071 and DSTAB074 assume the minimum expiring period of the original study groups. In addition, Study batches DSTAB071 and DSTAB074 failed to satisfy the USP XXII dissolution acceptance criteria at baseline time point, 0 month. Study batches DSTAB072 and DSTAB145 failed at 3 and 12 month time point respectively.

/S/

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/S/ 3/12/98

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/S/ 3/19/98

Michael Welch, PhD, Acting Division Director, HFD-720

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THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

18 pages

McNeil

Statistical Review and Evaluation

NDA 20-610
Name of drug: [redacted] (balsalazide disodium) capsules
Applicant: Salix Pharmaceuticals, Inc.
Indication: ulcerative colitis
Documents reviewed: Statistics volumes 1; Label and package insert
Project manager: Melodie McNeil, R. Ph.
Medical officer: Robert Prizont, M.D.
Dates: received 2 May, 2000

Reviewer: Yi Tsong, Ph.D.

Statistical Review of Label of NDA20-610 Colazal

The changes are needed for the following lines.

1. Lines 110 and 111.

   Comment: Review comparison was based on intent-to-treat analysis instead of per protocol analysis.

   Recommended change: Results demonstrated a statistically significant difference between high and low dose of Colazal® in improvement of rectal bleeding (p=0.004), stool frequency (p=0.012) and sigmoidoscopy (0.024) (See attached Figure 1).

2. Figure 1

   Comment: Y-axis was misleading. Show intent-to-treat results.

   Recommended changes: The y-axis needs to start from 0% instead of 20% (See revised Figure 1). Sample size may be added to the chart as follow,

   n=49 for both Colazal 2.25g and Colazal 6.75g in rectal bleeding and stool frequency
   n= 50 for Colazal 2.25g and n=53 for Colazal 6.75g in improved sigmoidoscopy

3. Figure 2

   Comment: Figure 2 is misleading and with errors.

Recommended changes:

a. The y-axis needs to start from 0% instead of 20% (please refer to revised Figure
b. Sample size n on chart needs to be corrected
c. There was no planned statistical comparison at individual visit. Using Figure 2 to illustrate statement in lines 112-114 maybe misleading to statistically significant interpretation of the differences. Reviewer's recommendation: to delete Figure 2.

4. Lines 121 to 127 and Figure 3.
Comment: The statement "A second study, conducted in Europe, confirmed findings of symptomatic improvement" is misleading as a reproduction of the finding in the first study.

Recommended change: "A second study, conducted in Europe, provided supporting findings of treatment effect in remission rates improvement".

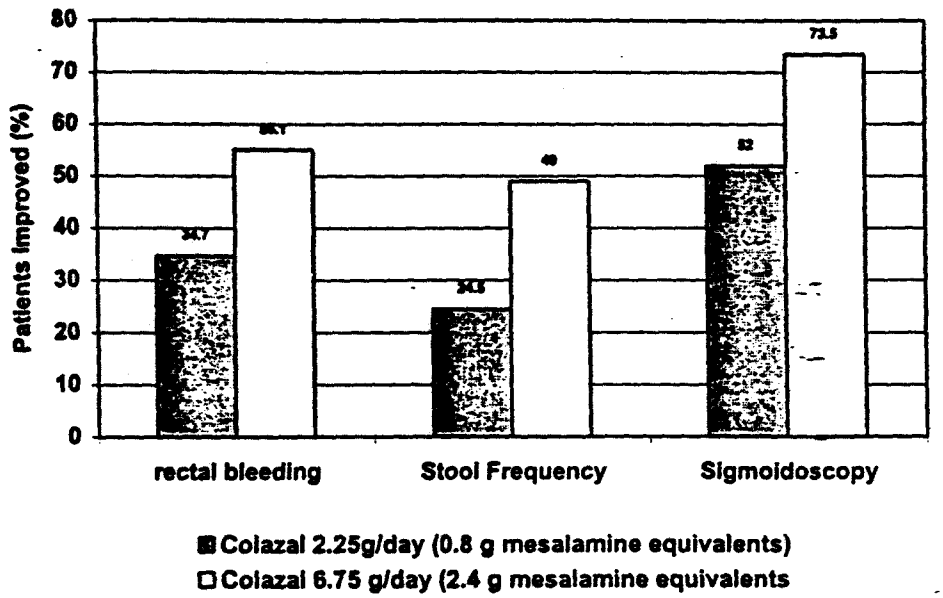
/S/ /S/ 6/19/00

Yi-Tsong, Statistical Reviewer, HFD-705 Thomas Permutt, Team Leader, HFD-170

archival: NDA 20-610
cc:
HFD-715/Nevius, Welch
HFD-160/McNeil, Prizont, Gallo Torres, Talarico
HFD-170/Permutt
HFD-705/Tsong
HFD-180/HFD-705/HFD-715/Division file

APPEARS THIS WAY
ON ORIGINAL

Figure 1: Percentage of Patients Improved at 8 Weeks



APPEARS THIS WAY
ON ORIGINAL

relapsed patients with mild to moderate ulcerative colitis. Patents were excluded from entry based on two criteria: safety related or usage of concomitant medications which might mask the evaluation of efficacy.

The primary and secondary endpoints of the phase III clinical trials proposed by the sponsor are summarized in the following table

Table I.2 Sponsor proposed primary and secondary endpoints in the 3 phase III clinical trials

	CP099301	57-3001	CP069101
Primary Endpoint	At 8 weeks: improvement in rectal bleeding and at least one other symptom*	At 12 weeks: remission= symptom normal or mild and sigmoidoscopic grade normal or mild	At 4 weeks: improvement in rectal bleeding and at least one other symptom*
Secondary Endpoint	At 8 weeks: remission = rectal bleeding - normal stool; frequency - normal sigmoidoscopic grade - normal or mild physician global - quiescent	1. Time to complete remission 2. Complete remission at clinic visits 3. Symptomatic remission at clinic visits 4. Sigmoidoscopic remission	At 4 weeks: No. of patients achieving histologically verified remission

*included: Stool frequency, patient functional assessment, abdominal pain, sigmoidoscopic grade, and physician's global assessment.

It is to be noted that, as stated in the protocol, Study 57-3001 was originally planned as a 2-phased maintenance study: an acute phase and a chronic phase with the primary focus on the chronic/maintenance phase. The original primary endpoint was defined as the percentage of tolerance. The current primary efficacy endpoint was the criterion used for patient randomized to the chronic phase and was retrospectively selected following the sponsor's decision to submit the study as a pivotal efficacy study in this NDA.

Summary of Sponsor's Efficacy Analyses Results

There were 154 patients randomized to receive study treatment in Study CP099301. Of the 50 patients randomized to receive Colazide 2.25g/day, 33 completed 8 weeks of treatment; of the 53 patients randomized to receive Colazide 6.75g/day treatment. 37 completed 8 weeks of treatment; and of the 51 patients randomized to receive Asacol 4.2g/day treatment, 36 completed 8 weeks of treatment (see Table III.1, page 5 of this review). Compared to Asacol, sponsor's analysis results failed to show any significant increase in improvement rate in either of the Colazide treated groups (6.75g/day or 2.25g/day) at week 8 for the primary endpoint stool bleeding (64.7% vs. 52.8%, p=0.275 for patients who completed the study, and 55.1% vs. 44.9%, p=0.315 for intent-to-treat analysis for the Colazide 6.75 vs. Asacol comparison). Similar results were obtained for six other primary endpoints (See Table I.2). However, a dose response relationship was suggested in the comparison of the two Colazide treatment groups. In the analyses of patients who completed the trial. this study showed a significant increase in improvement rate in Colazide 6.75g/day group as compared to Colazide 2.25g/day group for stool blood (64.7% vs. 32.4%, p=0.006) and for stool frequency (58.8% vs. 29.4%, p=0.006). These observed differences remained significant even after adjustment for multiple comparisons by the Tukey, Heyes and Ciminera method for the six endpoints. For the intent-to-treat (ITT)

Colazide 2.25 g/day for up to 6 weeks in patients who completed the double-blind phase of the study. Since this NDA submission is in support of the acute treatment and not the maintenance indication, this review includes only the results of the double-blind phase.

The primary endpoints of the study are the cumulative proportion of patients with improved symptoms or signs of acute ulcerative colitis by eight weeks. Efficacy was defined as 1) significant improvement in rectal bleeding plus: 2) significant improvement in at least one of six other symptoms or signs of the primary measurements (score of stool frequency, rectal bleeding, abdominal pain, physician global assessment, overall symptom assessment and flexible sigmoidoscopy) recorded in 24 hours preceding baseline and at the last visit.

The secondary endpoints are the cumulative proportion of patients achieving remission of disease activity, improvement of patient's quality of life (Inflammatory Bowel Disease Questionnaire) and the incidence of treatment-related adverse events.

Overall study plan -
The overall study plan is given in the following figure

Figure III.1* Overall Study Plan, Study CP099301

	Clinic Visit				
	Screening	Baseline	2 Week	4 Week	8 Week
	-7 to 0 day	96 hrs Initial	48h | 48 h Interim 1	48h | 48h Interim 2	96h | Final
			Daily Assessment		
Clinical History	x				
Sigmoidoscopy	x		x		x
Biopsy	x		x		x
Stool culture	x				
Symptoms	x	x	x		x
IBDQ	x	x	x		x
Laboratory	x		x		x
Adverse events	x	x	x		x

* From NDA

Patient population and sample size -
The study was originally planned to enroll 165 patients (with adjustment to accommodate a 10% loss of patients due to attrition). The projected number of patients completing the study was 150. This sample size was calculated based on the assumption that improvement rate of overall symptom assessment and rectal bleeding for Asacol at week 8 was 55%; and was sufficiently large enough to detect a greater response rate (of improvement of rectal bleeding and overall symptom assessment at week 8) of 82% (i.e. one and a half times of that of the Asacol

group) for the Colazide 6.75 g/day group with more than 80% power.

Of the one hundred sixty three patients recruited and screened in 13 centers, 154 were enrolled and randomized to receive blinded study treatment. To assure balance, among treatment groups, a block of six patients was used to randomize patients to Colazide 6.75 g/day, Colazide 2.25 g/day or to Asacol 2.4 g/day. Fifty three patients received Colazide 6.75 g/day, 50 received Colazide 2.25 g/day and 51 received Asacol 4.2 g/day.

Disposition of Patients - The disposition of patients is given in the following flow chart.

Table III.1* Disposition of Patients, Study CP099301

	Colazide 2.25 g/day	Colazide 6.75 g/day	Asacol 4.2 g/day
Enrolled/Randomized	50	53	51
Sponsor claimed ineligible	1	4	2
ITT analysis	50	53	51
Withdrew prior to week 2	2	2	5
Completed week 2	48	51	46
Discontinued after week 2	8	3	4
Withdrew prior to week 4	1	1	2
Completed week 4	39	47	40
Discontinued after week 4	5	6	3
Withdrew prior to week 8	1	4	1
Completed week 8	33	37	36

From NDA.

Demographics and patients characteristics

Patients demographic and baseline characteristics are given in Appendices F.1.1, F.1.2 and F1.3, Table 6 and Table 7. in NDA vol. 1.085 and vol. 1.1086. The sponsor reported that there was no statistically significant difference in baseline and demographic characteristics among the three treatment groups in mean age, sex distribution, and in smoking history, disease duration, disease status, extent of disease and duration of current relapses at baseline.

Clinical Efficacy

Primary efficacy endpoint:

Rectal Bleeding -

Among patients who completed treatment at week 2, week 4 and final visit. those receiving Colazide 6.75 g/day experienced the largest proportion of improvement. The difference between Colazide 6.75 and 2.25 g/day were statistically significant at the final visit, 64.7% vs. 38.6%, p=0.006 by the Cochran-Mantel-Haenszel (CMH) test (Table III.3). However, the rate of improvement in Colazide 6.75 g/day was not statistically significantly different from that of

Asacol 4.2 g/day (64.7% vs. 52.8%, p=0.275 CMH). These findings were also supported by measurement of changes from baseline in stool blood score and stool blood loss. At week 8, patients in Colazide 6.75 g/day had numerically bigger reduction than both Colazide 2.25 patients and Asacol patients. The difference was significant when compared with Colazide 2.25 g/day patient group (p= 0.036 and 0.010 for blood score and blood loss respectively using ANOVA). The difference between Colazide 6.75 g/day and Asacol were, however not statistically significant (p=0.506 and 0.967 for blood score and blood loss respectively using ANOVA). There was no significant site effect or treatment-by-site interaction effect (see Table III.3, page 7 of this *review).*

Intent-to-treat analyses were carried out by the sponsor with two approaches:
In intent-to-treat analysis 1 (partial intent-to-treat), the last observation carried forward principle was applied as shown in Table III.2.

Table III.2* Last Observation Carried Forward (LOCF) Application in ITT1, Study CP099301

Data Category	Baseline	2 week	4 week	8 week	LOCF status
Complete data	X	X	X	X	NA
Early Termination due to:					
• Treatment failure	X	LOCF	LOCF	LOCF	LOCF
• Withdrawal due to AE associated with worsening of symptom	X	X	LOCF	LOCF	
• Withdrawal due to patient's request due to worsening of symptom	X	X	X	LOCF	
Early termination due to other reasons	X	X	ND*	ND	No LOCF
No baseline	ND	X	ND	ND	No LOCF
No data	ND	ND	ND	ND	No LOCF

* From NDA. x: observed , #: No data

If the patient withdrew due to reasons related to treatment failure or worsening of symptom, the last observation was carried forward in order to determine whether there was improvement from baseline. However, if a patient withdrew from study due to reasons other than the ones stated as related to either failure of treatment or worsening of symptom, the patient's data was deleted from the ITT1 analysis. For this ITT analysis, the improvement rate in Colazide 6.75 g/day were significantly higher than Colazide 2.25 g/day (p=0.02 CMH) and supported by changes from baseline in blood loss score (p=0.014 ANOVA). However, for the reduction in changes in blood score, no significant difference were observed. In particular, Colazide 6.25 g/day was not differentiated from Colazide 2.25 g/day. Also, the difference between Colazide 6.75 g/day and Asacol 4.2 g/day was not significant (Table III.3, page 7 of this review).

In intent-to-treat analysis 2 (full intent-to treat analysis), the last observation carried forward principle was applied not only to the patients who withdrew from study due to reasons related to treatment failure and worsening of symptom, but also to any patients who withdrew for other reasons. Any patient with measurements at baseline were included in this ITT2 analysis. In this traditional ITT analysis, the only statistically significant difference was the improvement rate in

stool blood when comparing Colazide 6.75 g/day with Colazide 2.25 g/day (55.1% vs. 35.7% with p=0.04 CMH) [see Table III.3 of this review].

Table III.3* Improvement in Rectal Bleeding, Analysis of Patients Completed Final Visit, ITT1 and ITT2 (96 hr data), Study CP099301

Stool Bleeding Change	Treatment			p-value	
	Colazide 2.25 g/day	Colazide 6.75 g/day	Asacol 4.2 g/day	Colazide 6.75 g/day vs. 2.25 g/day	Colazide 6.75 g/day vs. Asacol
Analysis based on Completed patients					
Improvement at week 2	17/44 (38.6%)	22/44 (50.0%)	18/42 (42.9%)		
Improvement at week 4	16/41 (39.0%)	24/40 (64.7%)	24/39 (52.8%)		
Improvement at final visit	11/34 (32.4%)	22/34 (64.7%)	19/36 (52.8%)	0.006 CMH	0.275 CMH
Blood Score change Mean (SE)	-0.42 (0.12)	-0.69 (0.12)	-0.59 (0.15)	0.036 ANOVA	0.516 ANOVA
Blood Loss Score Change Mean (SE)	-0.96 (0.78)	-3.79 (0.76)	-4.22 (1.06)	0.010 ANOVA	0.967 ANOVA
Intent-to-treat Analysis 1					
Improvement at week 2	17/44 (38.6%)	22/45 (48.9%)	18/43 (41.9%)		
Improvement at week 4	16/42 (38.1%)	25/43 (58.1%)	26/41 (63.4%)		
Improvement at final visit	13/39 (33.3%)	22/36 (61.1%)	20/40 (50.0%)	0.020 CMH	0.356 CMH
Blood Score change Mean (SE)	-0.41 (0.11)	-0.64 (0.12)	-0.55 (0.14)	0.086 ANOVA	0.674 ANOVA
Blood Loss Score Change Mean (SE)	-1.19 (0.69)	-3.53 (0.75)	-3.84 (0.97)	0.014 ANOVA	0.971 ANOVA
Intent-to-treat Analysis 2 (Improvement at final visit)*	17/49 (34.7%)	27/49 (55.1%)	22/49 (44.9%)	0.004 CMH	0.315 CMH

* From NDA

Other Primary efficacy endpoints-

Among patients who completed treatment of eight weeks, Colazide 6.75 had higher improvement rate than both Colazide 2.25 g/day group and Asacol 4.2 g/day group for stool frequency, patient functional assessment, sigmoidoscopy, physician's global assessment and overall symptom assessment (Table III.4). Based on the observed p-values, the improvement rates were statistically significantly higher than Colazide 2.25 g/day in improved stool frequency (p= 0.006, by Cochran-Mantel-Haenszel test), in improved sigmoidoscopy score (p=0.015 CMH test), and in physician global assessment (p=0.030 CMH test). Results based on multiple endpoint adjustments are given in page 11 of this review.

Appendix A

Table A.1 Other Primary Endpoints, Study CP069101

Efficacy Endpoint	Colazide 6.75g/day	Placebo	Colazide 4.25g/day	p-value 6.75 vs. Placebo	p-value 4.26 vs. Placebo
Physician's Global Assessment					
Week 2					
Improved	18 (26.5%)	17 (50%)	26 (36.6%)	0.020 CMH	0.209 CMH
Not improved	50 (73.%)	17 (50%)	45 (63.4%)		
Total assessed	68	34	71		
Week 4					
Improved	26 (37.7%)	16 (48.5%)	32 (46.4%)	0.303 CMH	0.811 CMH
Not improved	43 (62.3)	17 (51.5%)	37 (53.6%)		
Total assessed	69	33	69		
Improved Stool Frequency (24 Hour Data)					
At week 2					
Improved	27 (40.9%)	8 (25.0%)	32 (50.8%)	0.123CMH	0.015 CMH
Not improved	39 (59.1%)	24 (75.0%)	31 (49.2%)		
Missing	2	2	8		
Total assessed	66	32	63		
At week 4					
Improved	19 (50.2%)	9 (30.0%)	31 (49.2%)	0.952 CMH	0.074 CMH
Not improved	44 (69.8%)	21 (70.0%)	32 (50.8%)		
Missing	6	3	6		
Total assessed	63	30	63		
Improved Stool Frequency (96 Hour Data)					
At week 2					
Improved	21 (30.9%)	14 (42.4%)	29 (44.6%)	0.285CMH	0.882 CMH
Not improved	47 (69.1%)	19 (57.6%)	36 (55.4%)		
Missing	0	0	0		
Total assessed	68	33	65		
At week 4					
Improved	25 (39.7%)	10 (30.3%)	25 (39.1%)	0.424 CMH	0.500 CMH
Not improved	38 (60.3%)	23 (69.7%)	39 (60.9%)		
Missing	0	0	0		
Total assessed	63	33	64		

Improved Patient Factional Assessment (24 Hour Data)					
At week 2					
Improved	25 (38.5%)	16 (48.4%)	30 (48.4%)	0.271CMH	0.826 CMH
Not improved	40 (61.5%)	15 (48.4%)	32 (51.6%)		
Missing	3	3	9		
Total assessed	65	31	62		
At week 4					
Improved	25 (39.7%)	13 (44.8%)	33 (54.1%)	0.663 CMH	0.401 CMH
Not improved	38 (60.3%)	16 (55.2%)	28 (45.9%)		
Missing	6	4	8		
Total assessed	63	29	61		
Improved Patient Factional Assessment (96 Hour Data)					
At week 2					
Improved	25 (36.8%)	11 (33.3%)	24 (37.5%)	0.786CMH	0.668 CMH
Not improved	43 (63.2%)	22 (66.7%)	40 (62.5%)		
Missing	0	0	1		
Total assessed	68	33	64		
At week 4					
Improved	28 (44.4%)	9 (27.3%)	23 (37.7%)	0.126 CMH	0.312 CMH
Not improved	35 (55.6%)	24 (72.7%)	38 (62.3%)		
Missing	0	0	3		
Total assessed	68	33	61		
Improved Abdominal Pain (24 Hour Data)					
At week 2					
Improved	19 (28.8%)	10 (33.3%)	31 (50.0%)	0.706CMH	0.100 CMH
Not improved	47 (71.2%)	20 (66.7%)	31 (50.0%)		
Missing	2	4	9		
Total assessed	66	30	62		

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At week 4					
Improved	18 (28.6%)	14 (50.0%)	30 (49.2%)	0.061 CMH	0.941 CMH
Not improved	45 (71.4%)	14 (50.0%)	31 (50.8%)		
Missing	6	5	8		
Total assessed	63	28	61		
Improved Abdominal Pain (96 Hour Data)					
At week 2					
Improved	17 (25.4%)	10 (30.3%)	18 (27.7%)	0.541CMH	0.880 CMH
Not improved	50 (74.6%)	23 (69.7%)	47 (72.3%)		
Missing	1	0	0		
Total assessed	67	33	65		
At week 4					
Improved	14 (22.6%)	10 (30.3%)	20 (32.3%)	0.557 CMH	0.585 CMH
Not improved	48 (77.4%)	23 (69.7%)	42 (67.7%)		
Missing	1	0	2		
Total assessed	62	33	62		
Improved Sigmoidoscopy					
At week 2					
Improved	29 (43.3%)	10 (29.4%)	28 (41.2%)	0.195CMH	0.266 CMH
Not improved	38 (56.7%)	24 (70.6%)	40 (58.8%)		
Missing	1	0	3		
Total assessed	67	34	68		
At week 4					
Improved	31 (47.0%)	15 (45.5%)	27 (40.9%)	0.907 CMH	0.658 CMH
Not improved	35 (53.0%)	18 (54.5%)	39 (59.1%)		
Missing	3	0	3		
Total assessed	66	33	66		
Improved Overall Symptom Assessment					
At week 2					
Improved	14 (21.2%)	11 (33.3%)	19 (30.2%)	0.209CMH	0.808 CMH
Not improved	52 (78.8%)	22 (66.7%)	44 (69.8%)		
Missing	2	1	8		
Total assessed	66	33	63		

At week 4					
Improved	19 (30.2%)	12 (38.7%)	28 (44.4%)	0.424 CMH	0.597 CMH
Not improved	44 (69.8%)	19 (61.3%)	35 (55.6%)		
Missing	6	2	6		
Total assessed	63	31	63		

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