CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-610

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

MCNeil

JUN 2 2 2000

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-610/ BZ,

Trade Name: Colazal® Capsules

Stamp Date: 5/2/00

Active Ingredient: Balsalzide Disodium

Sponsor: Salix Pharmaceuticals

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Phase IV Commitments & labeling Amendments

Background

NDA 20-610 for Balsalazide disodium (——) capsules was submitted to the Agency on June 23, 1997 for the treatment of mildly to moderately active ulcerative colitis. The recommended dose is three 750 mg capsules three times daily for a total dose of 6.75 gm/day. Balsalazide (BSZ) is a prodrug designed to deliver mesalamine (5-ASA) to the colon, where it is cleaved by bacteria azoreductases to release the active moiety (5-ASA) and the inactive carrier, 4-amino benzoyl-β-alanine (4-ABA). The application was found to be approvable by the Agency on July 15, 1998, pending satisfactory resolution of several deficiencies outlined in a letter dated June, 15, 1998. It should be noted that the trade name for NDA 20-610 recently changed from —— to Colazal®.

The Firm's response is outlined as follows:

1. Regarding the Food-Effect study requested by the Agency, the sponsor commits to conducting a study in healthy subjects to assess the effect of food on the absorption of balsalazide.
2. Regarding requested *in vitro* plasma binding information on balsalazide, the sponsor has already conducted an *in vitro* plasma binding study covering the proposed relevant balsalazide plasma concentration —— . In the event that balsalazide plasma levels higher than —— are observed during the course of the multiple-dose PK study, the sponsor commits to conducting an additional *in vitro* plasma
   binding study to cover the observed concentration range.
3. Regarding requested *in vitro* drug interaction studies, the sponsor has committed to conducting *in vitro* drug interaction studies to evaluate the potential for commonly co-administered drugs to interact with balsalazide.
4. With respect to requested *in vivo* drug interaction studies, based on the results of the *in vitro* drug interaction studies, the sponsor agrees to conduct *in vivo* drug interaction studies in appropriate animal species and evaluate the PK (as deemed necessary). Based on the outcome of these studies, the sponsor will discuss with the Agency the need for any additional studies.

5. Regarding the requested renal impairment study, the sponsor agrees to compare the PK data from the multiple-dose PK study to that obtained from literature on patients with varying degrees of renal impairment that are receiving mesalamine or related prodrugs. Based on the outcome of the analysis of the multiple-dose PK study, it will be decided whether an additional study is needed to assess PK of balsalazide in patients with varying degrees of renal impairment.

6. Regarding the hepatic impairment study, the sponsor suggested that the hepatic impairment study should be secondary to the renal impairment study. Hence. the sponsor proposes evaluating the PK of balsalazide in hepatically-impaired patients only if clinically-relevant results are obtained in the renal impairment study.

7. Regarding the studies requested by the Agency to support the use of balsalazide in pediatric patients, the sponsor suggests that the diagnosis of ulcerative colitis in infants (1 month-2 years) is usually rare and uncommon. Hence, the sponsor requests a pediatric waiver for both the neonate (birth-1 month) and infant (1 months-2 years) age groups. Additionally, the sponsor proposes conducting a study in the combined pediatric population of children and adolescents (2-18 years) to characterize PK of balsalazide in this age group.

8. Regarding the Agency's request that the sponsor reanalyze the data from study GLY01/93 to examine the effect of gender on the disposition of balsalazide. the sponsor agrees to reanalyze the data.

The sponsor committed to submitting the study protocols prior to study initiation. Furthermore, the final protocols to [redacted] for studies identified in items 1, 2, 3 and 7 will be submitted within one year of receiving the approval letter for NDA 20-610.

Labeling

The following paragraph has been revised from,

"**Absorption:** [redacted]

To,

"**Absorption:** In healthy individuals, the sSystemic absorption of intact balsalazide was very low and variable. The mean C_{max} [redacted] occurs at approximately 1-2 hours after single oral doses of 1.5 grams or 2.25 grams. The absolute bioavailability of this compound was not determined. In a study of ulcerative colitis patients in remission receiving long-term therapy with balsalazide, 1.5 grams twice daily, for over one year, systemic drug exposure, based on mean AUC values, was [redacted] up to 60 times greater after equivalent multiple doses

of 1.5 g twice daily when compared to healthy subjects [redacted]. There was a large intersubject variability in the plasma concentration of balsalazide versus time profiles in all studies, thus its half-life could not be determined. The effect of food intake on the absorption of this compound was not studied."

Recommendations:

The current submission was submitted on May 2, 2000 by Salix Pharmaceuticals Company to address Agency comments dated Jun 15, 1998 regarding NDA 20-610. In the submission, the Firm commits to conducting several post-approval studies, including a food-effect study, drug-drug interaction studies and studies to evaluate PK in special populations such as pediatrics, and hepatic and renal impairment patients. The submission has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II), and from the view point of OCPB, the Firm's response is found to be acceptable.

In addition, the **CLINICAL PHARMACOLOGY** section in the proposed Colazal® (balsalazide sodium) labeling has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II) and is found to be acceptable, provided the Firm makes the appropriate corrections.

/S/ 6/22/00

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Suresh Doddapaneni, Ph.D., Team leade /S/ 6/22/00

cc: HFD-180: NDA 20-610 (1x); DIV FILE (1x); MMCNEIL (1x); SDODDAPANENI (1x); SALFAYOUMI (1x); HFD-870: SHUANG (1x); CDR: ATTN ZOM ZADENG

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Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-610/AZ

Trade Name —— Capsules

Stamp Date: 9/24/1999

Active Ingredient: Balsalazide Disodium

Sponsor: Salix Pharmaceuticals

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Response to FDA Letters Dated 6/15/98, 1/9/98 and 3/16/99

What is the nature of the application?

NDA 20-610 for Balsalazide disodium ——) capsules was submitted to the Agency on 6/23/97 for the treatment of mildly to moderately active ulcerative colitis. The recommended dose is three 750 mg capsules three times daily for a total dose of 6.75 gm/day. Balsalazide (BSZ) is a prodrug designed to deliver mesalamine (5-ASA) to the colon. Balsalazide is cleaved by bacteria azoreductases in the colon to release the active moiety (5-ASA) and the inactive carrier, 4-amino benzoyl-β-alanine (4-ABA). The application was found to be approvable by the Agency on 6/15/98, pending satisfactory resolution of several deficiencies.

What is the nature of the issues ?

What is the Firm's response to Agency comments ?

The deficiencies cited by the Agency include:

1. Insufficient data was provided to assess the systemic exposure of the parent drug and its metabolites for the To-Be-Marketed (TBM) formulation as recommended for use in the proposed labeling. The Agency recommended that the Firm conduct a multiple-dose pharmacokinetic study in the target population using the TBM formulation from a representative production size batch of drug (See letter dated 1/15/98).

Subsequently, the Firm committed to conducting the study as a Phase IV Commitment using a pharmacokinetic protocol agreed upon with the Agency, and will submit a final study report by the fourth quarter of 2000 or sooner.

2. The Agency noted that the formulation of Asacol (Mesalamine) used as the active comparator in both pivotal studies in the NDA submission was unapproved for marketing in the US. This called into question the validity of the results of both pivotal studies. Hence, the Firm was required by the Agency to provide data to adequately demonstrate comparability between the unapproved and approved Asacol formulations (See letter dated Mar 16, 1999).

In the current submission, the Firm submitted data in an attempt to show that the Asacol formulation employed in the pivotal studies (UK-93 formulation) and that approved in the US (US-93 formulation) are both chemically and clinically equivalent. The Firm provided the following points in support of their claim:

- A side-by-side qualitative comparison of UK-93 and US-93 formulations indicates that both formulations are identical except for the presence or absence of colloidal silicon dioxide, which is deemed by the Firm to be a minor formulation difference (Table 1).

- A multi-point comparative dissolution study was conducted by the Firm in accordance with the drug release procedure in SUPAC-MR. The method was the same as that used in the original NDA.

Mean dissolution data was subsequently applied to calculate the similarity factor. Based on mean dissolution data (Table 2), the Firm concluded that the absence of dissolution during the acid stage indicated that the enteric coatings between UK-93 and US-93 formulations were "functionally equivalent". The Firm also pointed out that once tablet dissolution was initiated, the dissolution profiles of UK-93 and US-93 formulations appeared similar.

- Symptom improvement data from 3 and 6 week assessments in the Norwich Eaton C.14 study (appears to be US-89 formulation) were compared to the 2 and 4 week assessments from the Salix study CP099301 (UK-93 formulation). The Firm concluded based on the comparison that UK-93 and US-93 formulations yield comparable improvements in patient symptoms, which supports their claim of equivalency between the two formulations.

Table 1. Side-by-side comparison of Asacol formulations

Ingredient	1993 UK-Asacol	1993 US-Asacol	1997 UK-Asacol
Mesalamine	400 mg	400 mg	400 mg
Colloidal silicon dioxide	---	√	---
Dibutyl phthalate	√	√	√
Edible black ink	---	√	---
Iron oxide red	√	√	√
Iron oxide yellow	√	√	√
Lactose	√	√	√
Magnesium stearate	V	√	√
Methacrylic copolymer B (Eudragit S)	√	√	√
Polyethylene glycol	√	√	√
Povidone	√	√	√
Sodium starch glycollate	√	√	√
talc	√	√	√

Table 2. Mean dissolution results for US-93 and UK-93 formulations

	UK-93 formulation	US-93 formulation
Acid stage		
120 min	0.0	0.0
Buffer stage		
30 min	26.6 ± 22.7	2.2 ± 4.3
60 min	73.3 ± 7.3	35.2 ± 30.6
90 min	83.7 ± 8.6	93.3 ± 9.5
120 min	98.1 ± 5.4	98.6 ± 3.9

Table 3. Comparison of f_2 values

Formulation 1	Formulation 2	f_2 value
UK-93	UK-97	35.9
US-93	US-99	59
UK-93	US-99	35.3
UK-93	US-93	31.8
UK-97	US-99	72.2
UK-97	US-93	52.1

Is adequate data provided to support the Firm's point of view?

The Firm's claim of equivalency between UK-93 and US-93 formulations is unfounded as per the following points:

- *With respect to the claim of similarity in composition between the two formulations, the firm bases this claim on qualitative information extracted from package inserts and patient information leaflets. This type of information does not specify the amount of each ingredient; neither does it specify the manufacturing processes involved, such as the manufacturing equipment or procedure. Hence, this sort of comparison is not a valid one.*
- *The f_2 value for US-93 and UK-93 formulations indicates that both formulations are markedly different, with the average dissolution profile difference exceeding — whereas the cutoff limit for an acceptable difference is 10%. The Firm did, however, dispute the results of the f_2 test based on the high variability observed at some of the early dissolution time points in the buffer stage (Table 2).*

Overall, Asacol formulations did not appear to be associated with high variability as all formulations other than UK-93 passed the f_2 test (Table 3). Since UK-97 and US-93 appeared to be equivalent based on the f_2 test, the Firm concluded that UK-93 and US-93 must also be equivalent. However, this is an invalid conclusion since UK-93 and UK-97 were inequivalent based on the f_2 test. It is a likely possibility that changes were introduced to the Asacol formulation between 1993 and 1997.

It should be noted that the dissolution testing guidance states that only one measurement should be considered after 85% dissolution of the test products, as this would lead to positive bias in the similarity assessment. However, both 90 and 120 min dissolution time points were included in the dissolution profiles of UK-93 and US-93 even though the dissolution had virtually reached or exceeded —

In Addition, the Firm suggests that the age of the UK-93 tablets might have affected its dissolution. However, US-93 tablets were equivalent to US-99 and UK-97 formulations despite being of similar age and storage conditions as UK-93 formulation.

- *The Firm claims that both US-93 and UK-93 were equivalent based on symptom improvement data. However, the Firm was making the comparison between two independent clinical studies. One other important point to note is the marked differences observed between the enrolled patient populations in both studies, particularly, with respect to the symptom severity at entry. The reviewing medical officer was requested to*

undertake a thorough evaluation of this data.

It can be concluded that the overall dissolution profiles of UK-93 and US-93 are different. Hence, UK-93 and US-93 are deemed inequivalent.

What is the regulatory action recommended?

The Firm's response to Agency comments has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II), and from the view point of OCPB, the Firm's proposal regarding the pharmacokinetic study is acceptable. However, the Firm's justification with respect to equivalence of the TBM and clinical trial formulations is inadequate.

/S/ 2/25/00

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Initialed by Suresh Doddapaneni, Ph.D., Team lea /S/ 2/25/00

cc: HFD-180: NDA 20-610 (1x); DIV FILE (1x); MMCNEIL (1x); SDODDAPANENI (1x); SALFAYOUMI (1x); SHUANG (1x); CDR: ATTN ZOM ZADENG

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Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-610/ BC

Trade Name: —— Capsules

Stamp Date: 10/25/1999

Active Ingredient: Balsalzide Disodium

Sponsor: Salix Pharmaceuticals

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: CMC Amendment - Capsule Change and Process Scale-up

Background

NDA 20-610 for Balsalazide disodium —— capsules was submitted to the Agency on June 23, 1997 for the treatment of mildly to moderately active ulcerative colitis. The recommended dose is three 750 mg capsules three times daily for a total dose of 6.75 gm/day. Balsalazide (BSZ) is a prodrug designed to deliver mesalamine (5-ASA) to the colon, where it is cleaved by bacteria azoreductases to release the active moiety (5-ASA) and the inactive carrier, 4-amino benzoyl-β-alanine (4-ABA). The application was found to be approvable by the Agency on July 15, 1998, pending satisfactory resolution of several deficiencies outlined in the letter.

The current submission addresses changes proposed by the Firm to the capsule composition, as well as manufacturing process scale-up.

What is the nature of the proposed CMC changes?

The original US capsule contains FD&C Red Number 3, which is not approved in Europe. Hence, in order to harmonize the capsule to the European capsule, the Firm proposes to change the red and maroon hard gelatin capsules to the beige capsule currently available in Europe (See Table 1).

Table 1. Comparison of hard gelatin capsule composition

Component	% Total Capsule Weight (Capsule in original NDA)	% Total Capsule Weight (Proposed US Capsule)
——	——	——
Gelatin-NF	——	——

In addition to capsule composition changes, the Firm proposes the use of an —— which would allow the scale-up of the commercial process from —— apsules in the NDA pilot batch to —— capsules. Both the original and proposed alternative blenders have similar operation principles ——

Is adequate data provided to support the proposed changes?

Reviewer's Comments: According to the guidance on Scale-Up and Post-Approval Changes, changes in ingredients intended to affect the color of the drug product would constitute level 1 changes, which are defined as a change that are unlikely to have any detectable impact on formulation quality and performance.
As for the proposed changes in the manufacturing equipment, in accordance with the guidance on Scale-Up and Post-Approval Changes, a change in the batch size up to a factor of 10 times the size of the pilot/biobatch is deemed a level 1 change.

Dissolution Testing

To support the comparability of pre- and post- change batches, the Firm conducted a multi-point dissolution study using the approved dissolution method specifications (See signed review dated May 19, 1998).
The dissolution specifications were met when —— of the label amount of the drug substance dissolved within 30 min using the USP apparatus 1 (baskets) at 100 rpm in a volume of 900 ml of deionized water at 37°C. The medium was sampled at 10. 20, 30 and 40 min through filters. The samples were analyzed for basalazide content by _ against a reference standard.
Upon subjecting the data to the f2 similarity test, an f2 value of 54.5 was calculated.

Reviewer's Comments: For dissolution curves to be considered similar, f2 values should be greater than 50. Hence, both pre- and post-change formulations are deemed to be similar.

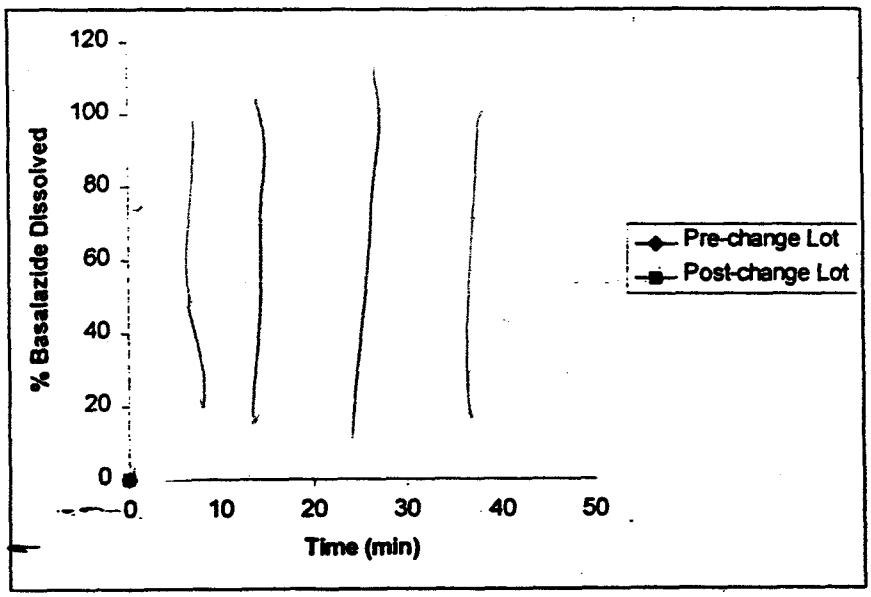

Fig. 1. Comparison of mean dissolution of pre- and post-change lots

Recommendations:

The current report was submitted on Oct 25, 1999 by Salix Pharmaceuticals company in support of proposed changes to the formulation and manufacturing process for NDA 20-610. The submission has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II), and from the view point of OCPB, the changes proposed by the Firm are found to be acceptable.

/S/ 2/1/2000

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Initialed by Suresh Doddapaneni, Ph.D., Team leader /S/ 2/1/00

cc: HFD-180: NDA 20-610 (1x); DIV FILE (1x); MMCNEIL (1x); SDODDAPANENI (1x); SALFAYOUMI (1x); HFD-870 JHUNT (1x); SHUANG (1x); CDR: ATTN Barbara Murphy

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MAY 10 1999

Clinical Pharmacology and Biopharmaceutics Review

NDA: **20-610**

Trade Name: —— Capsules

Active Ingredient: Balsalazide Disodium

Sponsor: Salix Pharmaceuticals, Inc.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Protocol for Pharmacokinetic Clinical Study

Submission Date: November 20, 1998

Stamp Date: November 23, 1998

Review Date: May 10, 1999

Synopsis:

NDA 20-610 for Basalazide disodium —— capsules was submitted to the agency on June 23, 1997 for the treatment of mildly to moderately active ulcerative colitis. The recommended dose is three 750 mg capsules three times daily for a total dose of 6.75 gm/day. Balsalazide (BSZ) is a prodrug designed to deliver mesalamine (5-ASA) to the colon, where it is cleaved by bacteria azoreductases to release the active moiety (5-ASA) and the inactive carrier, 4-amino benzoyl-β-alanine (4-ABA). The application was found to be approvable by the agency on July 15, 1998, pending (among other things) a multiple-dose pharmacokinetic study in the target population using the drug formulation that is proposed for clinical trials (see attachment).
The applicant submitted a study protocol (CP 109801) entitled, "A Multiple-Dose Pharmacokinetic Study of Balsalazide disodium in Patients with Active, Mild to Moderate Ulcerative Colitis".

Objective

Evaluation of the multiple dose pharmacokinetics of Balsalazide and its metabolites in adult patients with active, mild to moderate ulcerative colitis.

Study Design:

Open label, non-randomized, multi-center treatments with multiple oral doses

Subjects	25 patients with active, mild to moderate ulcerative colitis (dropouts are not replaced).
Inclusion Criteria	Active, mild to moderate ulcerative colitis with at least 12 cm of disease (sigmoidoscopically verified). Rectal bleeding and a Patient Functional Assessment score of moderate or severe within the last 48 hrs.
Exclusion Criteria	Severe ulcerative colitis.

Hypersensitivity to ASA or other salicylates.
History of Crohn's disease.
Clinically significant hepatic or renal disease.

Dosing	Balsalazide with meals (3 × 750-mg capsules) t.i.d. (total daily dose of 6.75 gm) for a period of 8 weeks. Dosing will be conducted on days 14 and 56-59 for pharmacokinetic profile assessment (see attached scheme).
Sampling	Blood samples will be collected over the 8-week treatment period for the pharmacokinetic evaluation of Balsalazide and its major metabolites.
Sampling Times	**On days 13, 14, 28, 55 and 56**: Pre-dose. **On days 14 and 56**: At 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18 and 20 hrs post-dose. **On days 15, 57, 58 and 59**: Following the morning dose.
PK Analysis	T_{max}, C_{max}, AUC_{0-24}, AUC_{last} (AUC from 0 to last time point above BQL), C_{ave}, C_{min}, C_{max}/C_{min}, C_{max}/C_{ave} and % Fluctuation will be calculated for Balsalazide and its major metabolites using Microsoft Excel 4.0.
Efficacy	The time to symptomatic remission as well as, the proportion of patients with symptomatic remission, will be assessed based on Patient Functional Assessment ratings.
Safety	Patients will be closely monitored for incidence of adverse events, which will be assessed for severity and relationship to Balsalazide.

Recommendations:

The protocol submitted on November 23, 1998 by Salix Pharmaceuticals company to NDA 20-610 for a multiple-dose pharmacokinetic study in patients with active mild to moderate ulcerative colitis has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II) and is found to be acceptable provided the comments below are considered.

Comments To Be Sent To The Firm

1. Previously, the agency requested the sponsor use the to be marketed formulation in a multiple dosing study (see attached). It is not clear from the submitted protocol whether the sponsor will use the to be marketed formulation. Please clarify.

2. A complete assay description and validation i.e. specificity, linearity, sensitivity, stability of the samples, accuracy and precision for the drug and metabolites, should be included in the study report.

3. Since Balsalazide will be administered as three daily divided doses, please comment on whether AUC_{0-t}, where t is the time within each divided dosing interval (e.g., AUC 5 to 10 hrs after the morning dose, i.e. AUC_{0-5}), may be a more relevant pharamacokinetic parameter compared to AUC_{0-24}. Also, regarding t_{max} and C_{max}, on days 14 and 56, there will be 3 t_{max} and 3 C_{max} values. Please further elaborate or define what is meant by t_{max} and C_{max} (section 11.2 of the protocol). Likewise, there will be 3 C_{min} values. Please comment on the proposed C_{min} calculation as stated in the protocol.

4. In a teleconference held on July 28, 1998 between the Firm and the agency, the agency recommended the effect of food and fasting on Balsalazide pharmacokinetics be assessed in a planned study over a period of eight weeks (see attached meeting minutes). What is the Firm's comment on this matter? In addition, please provide information regarding the composition of the meals used in the pharmacokinetic study, and specify how the product is given in relation to meals (e.g. fasting, before, after, or with meals, etc).

/S/ 5/10/99

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by David lee, Ph.D., Team leader 4/30/99

FT initialed by David lee, Ph.D., Team leader /S/ 5/10/99

cc: HFD-160: NDA 20,955 (1x); DIV FILE (1x); MMCNEIL (1x); DLEE (1x); HFD-870 JHUNT (1x); MCHEN (1x); HFD-850 SHUANG (1x); CDR: ATTN Barbara Murphy

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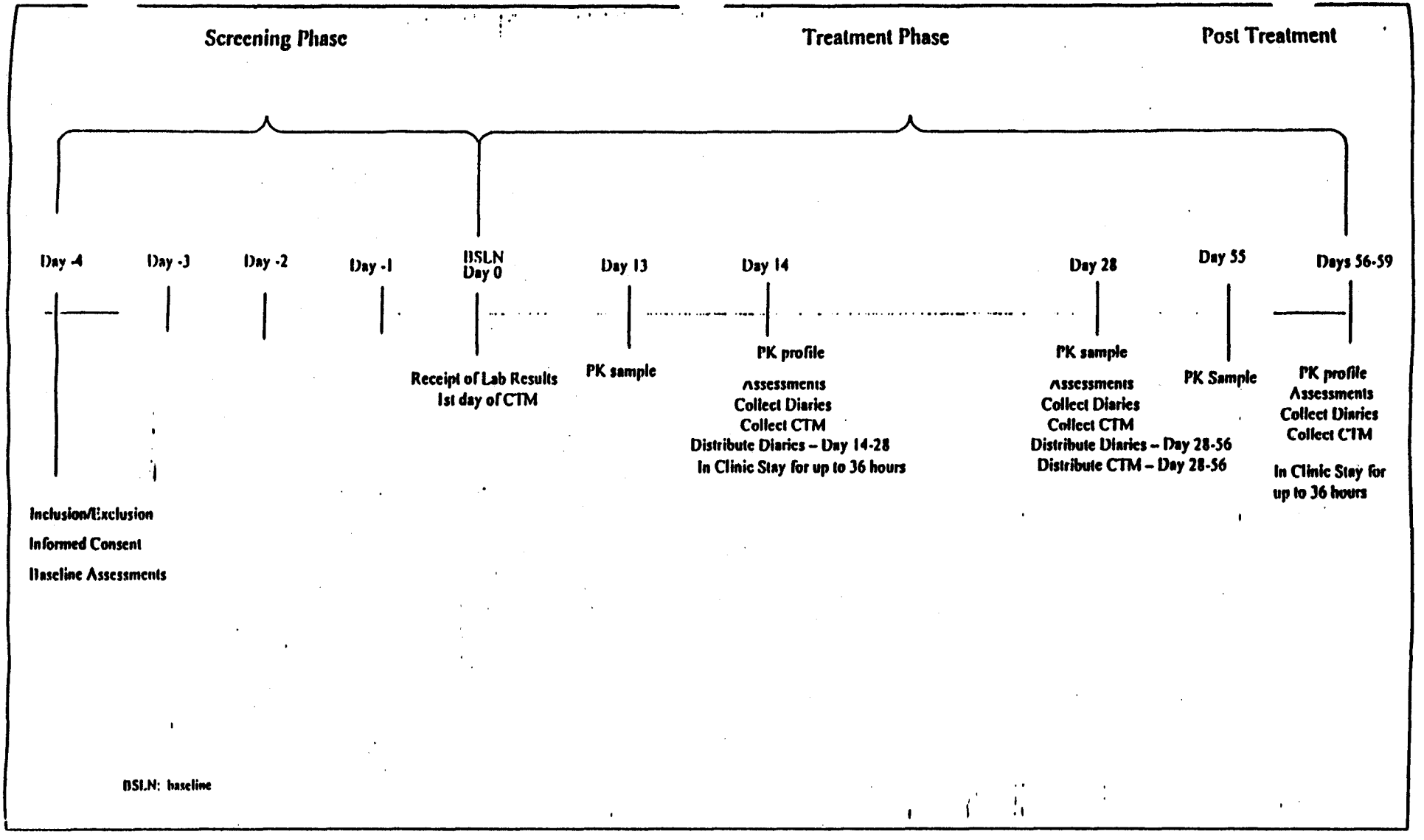

Figure 1. Timeline of Events

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Table 1. Schedule of Time and Events

Assessments Performed	Study Phase								
	Screening	Treatment						Post Treatment	
	Day -4 to Day -1	Day 0	Day 13	Day 14	Day 28	Day 55	Day 56	Days 57-58	Day 59 Or Early Term
Informed Consent	X								
Inclusion and Exclusion Criteria	X								
Medical/Ulcerative Colitis History	X								
Tobacco and Nicotine Product Use	X			X	X				X
Body Weight and Vital Signs	X			X	X				X
Physical Examination	X								X
Distribution of Patient Diaries[a]	X	X		X	X				
Collection of Patient Diaries		X[b]		X	X		X		
Distribution of CTM		X		X	X				
First day of CTM Administration		X							
Collection of CTM Supplies				X	X		X		
Baseline Symptom Assessment	X								
Sigmoidoscopy	X[c]								
PK Blood Sample			X[d]	X[e]	X[d]	X[d]	X[e]	X[f]	X[f]
Confinement up to 36 hours[e]				X			X		
Laboratory Assessments	X			X	X				X
Adverse Event Evaluation				X	X		X	X	X
Concomitant Medications	X			X	X		X	X	X

[a]Patient diary entries will include information on daily bowel events, rectal bleeding, Patient Functional Assessment, and tenesmus.

[b]Evaluation of rectal bleeding and Patient Functional Assessment for determination of eligibility

[c]During sigmoidoscopic evaluation the patient's extent of disease will be determined. (Patients must have at least 12 cm of disease and may not have a diagnosis of ulcerative proctitis.)

[d]Pre-dose morning blood sample only

[e]Blood samples at pre-dose and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18 , 20 and 24 hours following morning dose. Patients will come in the night prior to the morning sample and remain until the 24 hour sample has been drawn.

[f]Morning blood sample only

MEMORANDUM OF TELECON

DATE: July 28, 1998

APPLICATION NUMBER: NDA 20-610; balsalazide disodium Capsules

BETWEEN:

Name: Dr. David Boyle, Executive Vice-President

Dr. Ping Hsu, Data Management
Dr. Don Jung, Pharmacokinetics
Ms. Debra Hathaway, Regulatory Affairs
Phone: (650) 849-5908
Representing: Salix Pharmaceuticals, Inc.

AND

Name: Ms. Melodi McNeil, Regulatory Health Project Manager
Dr. Lilia Talarico, Division Director
Dr. Hugo Gallo-Torres, Medical Team Leader
Dr. Robert Prizont, Medical Reviewer
Dr. Carol Cronenberger, Biopharmaceutics Reviewer
Mr. John Hunt, Biopharmaceutics Team Leader
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Discussion of Pharmacokinetics Study, Requested in June 15, 1998-Approvable Letter

BACKGROUND: NDA 20-610 was submitted June 23, 1997 by Salix Pharmaceuticals, Inc. to market balsalazide disodium 750 mg Capsules, at a dose of 2.25 gm tid, for the treatment of mildly to moderately active ulcerative colitis. The application was approvable, pending (among other things) a multiple-dose pharmacokinetic study in the target patient population using the formulation of the drug that is proposed for marketing.

In a June 26, 1998 submission, the firm requested a teleconference with the Division to clarify the type of pharmacokinetic study that is required for approval. The request included a list of questions which are reproduced below. (Note: The firm's questions are in regular print: the Agency's responses are in bold print).

TODAY'S PHONE CALL:

1. Confirm that the proposed pharmacokinetic study will be conducted with one drug product lot at one dose level, balsalazide disodium 6.75 g (3 x 750 mg capsules to be taken three times a day).

The firm was informed that this proposal is acceptable, however, Agency representatives reiterated that the study should be carried out in the target patient population (patients with acute [active] ulcerative colitis) and that, in general, the drug should be administered in the same manner it is expected to be given in clinical practice (e.g., three times daily, instead of every eight hours around the clock; to patients of both genders and of a wide age range; etc.). Although not required for approval, the Agency suggested that the effect of fasting vs. fed state on balsalazide pharmacokinetics be assessed, since balsalazide is likely to be administered with meals in clinical practice.

2. Clarify whether the purpose of the multiple-dose pharmacokinetic study is to evaluate the plasma pharmacokinetics and metabolites of balsalazide disodium at steady-state, or the potential accumulation and elimination.

   Agency representatives said the purpose of the study is to evaluate the pharmacokinetics, accumulation, and elimination of balsalazide disodium (the parent compound) and each of its three metabolites and added that there should be sufficient numbers of patients to ensure an accurate assessment of these characteristics. Also, since ulcerative colitis can affect absorption from the gastrointestinal tract, the firm was advised to assess whether there is a relationship between balsalazide pharmacokinetics and patients' disease state.

3. Clarify the length of treatment to be followed in the multiple-dose pharmacokinetic study.

   Agency representatives said the study duration should be eight weeks, to ensure that the pharmacokinetics of balsalazide are accurately characterized.

4. Salix would like to discuss use of a smaller batch size for the proposed study. Since the product is not commercialized in the US, the drug product manufacturer's batch size is approximately [redacted] of the proposed commercial scale ([redacted]).

   The firm was informed that the use of a smaller batch size is acceptable, provided its size is greater than or equal to 10% of a full scale batch.

In addition, the Agency requested that the firm evaluate patient symptoms during the study, and other endpoints such as endoscopy scores or flexible sigmoidoscopy findings. In response to a question, the Agency said that patients could be enrolled from multiple sites, provided that plasma levels are analyzed using a standard, accurate assay at a single location. Agency representatives also said that there was no need to have a washout period for patients who are taking other medications prior to their enrollment in this study. The firm was requested to submit the protocol for the pharmacokinetic study to the Agency for review and comment, prior to its execution.

The firm was asked to verify that the formulation of Asacol used in the pivotal clinical trials (as an active comparator) is the same formulation as what is approved in the US. The firm agreed to provide the requested information. Agency representatives commented that if a non-US formulation of Asacol was used in the clinical trials, all references to "Asacol" will have to be deleted from the labeling. The call was then concluded.

/S/ 9/8/98

Melodi McNeil
Regulatory Health Project Manager

/S/ MD 9-8-98

cc: Original NDA 20-610
HFD-180/Div. File
HFD-180/Melodi McNeil
HFD-180/Prizont
HFD-180/Gallo-Torres
HFD-870/Hunt
HFD-870/Cronenberger
HFD-870/Chen

RD Init: CCronenberger 8/28/98
HGallo-Torres 9/1/98
RPrizont 9/1/98
LTalarico 9/2/98
Final 09/08/98

TELECON

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ON ORIGINAL

Protocol Summary

In the June 15, 1998 Approvable Letter issued by the Division to Salix Pharmaceuticals, Inc. the following was stated under Item 2:

2. Biopharmaceutics

Insufficient data was provided to assess the systemic exposure of the parent drug and its metabolites for the to-be-marketed formulation as recommended for use in the proposed labeling. Please conduct a multiple-dose pharmacokinetic study in the target patient population using the to-be-marketed formulation from a representative production size batch of drug. The drug should be administered as recommended in the proposed package insert. All moieties should be analyzed using a precise and accurate validated assay.

On July 28, 1998, a teleconference was held between the Division and Salix Pharmaceuticals, Inc. to clarify issues relating to the design of the requested study. Copies of the teleconference minutes submitted by Salix Pharmaceuticals, Inc., refer to Attachment 1, and those prepared by the Division, refer to Attachment 2, are provided for your convenience. During the teleconference, it was agreed with the Division that the proposed study protocol would be submitted for review and comment prior to its initiation. Also provided are sample Case Report Forms.

The proposed study is designed to assess the systemic exposure of the drug substance, balsalazide, and its metabolites, 5-aminosalicylic acid (ASA), 4-aminobenzoyl-β-alanine (ABA), N-acetyl-5-aminosalicylic acid (NASA), and N-acetyl-4-aminobenzoyl-β-alanine (NABA), in the targeted population of patients using the recommended dosing regimen. Patients with active, mild to moderate ulcerative colitis will be enrolled and treated for eight weeks at a total daily dose of 6.75 grams of balsalazide per day (three capsules, 750 mg balsalazide per capsule, taken three times per day). Plasma samples will be obtained in order to assess the steady state, accumulation and elimination plasma pharmacokinetics of the parent drug and metabolites. Data for assessing symptomatic remission, i.e., Patient Functional Assessment and stool blood, will also be obtained. The clinical supply material will be obtained from a batch size that is at least 10% of the proposed commercial scale.

Salix Pharmaceuticals, Inc., has tentatively identified two or three sites where this protocol will be conducted. Note, per the Division recommendation, a single analytical laboratory will be used for the analysis of the plasma samples. At this time, initial site visits are in progress. Based on the outcome of these visits, Salix Pharmaceuticals, Inc., would like to initiate this protocol in January 1999. Thus, Salix Pharmaceuticals, Inc., would like to request a teleconference with the Division to resolve any issues concerning the proposed protocol. Salix Pharmaceuticals, Inc. would like to hold this teleconference by December 23, 1998.

MAY 19 1998

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-610
SUBMISSION DATE: June 23, 1997

Balsalazide Disodium
750 mg oral capsules
Colazide®
Salix Pharmaceuticals, Inc.

REVIEWER: Carol Cronenberger, MS, PhD
TYPE OF SUBMISSION: Original NME (1S)

SYNOPSIS:
NDA 20-610 for Colazide capsules was submitted to the Agency on June 23, 1997 for the treatment of mildly to moderately active ulcerative colitis. The recommended dose is three 750 mg capsules three times daily for a total dose of 6.75 gm/day. Balsalazide disodium is a prodrug which consists of 5-aminosalicylic acid, the active moiety, connected by an azo-bond to 4-aminobenzoyl-β-alanine, the "carrier" portion. The prodrug is designed to pass with very little systemic absorption into the colon, where bacterial azoreductases then cleave the compound and release the 5-aminosalicylic acid to exert its effect locally. The carrier portion of the prodrug is subsequently eliminated primarily in the feces. Unlike typical immediate-release drug products, which usually rely on systemic exposure to exert their effects in body systems often removed from the gastrointestinal tract, the pathophysiology of ulcerative colitis itself has the potential to directly impact the absorption, and possibly the metabolism, of this compound. For these reasons, and because of Colazide's dosage form, some unique pharmacokinetic behavior is expected.

The sponsor has submitted three pharmacokinetic(PK)/bioavailability(BA) studies which examined single (Study #20060) and multiple (Study #20061) doses of Colazide in healthy male subjects. Study #20061 examined the disposition of Colazide at the dose recommended in the labeling, however, the data may be of limited value since the PK/BA of this compound appears to be different in patients with ulcerative colitis that is in remission. Multiple doses of Colazide were also examined in patients with ulcerative colitis that was in remission (Study #GLY01/93), but not as recommended in the package insert.

Preliminary data are available in subjects with mild renal impairment, and a limited gender analysis was performed. However, Colazide was not studied in hepatically impaired subjects nor are there data available for pediatric or geriatric subjects. No food effect or drug interaction

studies were performed and protein-binding determinations were not made. The formulations used in the pharmacokinetic and clinical studies were sufficiently similar; the to-be-marketed formulation was used in the clinical studies and in PK/BA Study #GLY01/93. An acceptable dissolution method and specification has been provided.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed Section 6 of NDA 20-610 for balsalazide disodium (Colazide). Although the sponsor has submitted studies in compliance with the Agency's regulations as covered under 21 CFR 320, the submitted studies give less than ideal information to accurately assess the systemic exposure of the parent drug and its metabolites for the to-be-marketed product as it is intended to be administered in the target population (i.e., given to patients with mildly to moderately **active** ulcerative colitis, as three 750 mg capsules (2.25 gm) three times daily with food, for a total daily dose of 6.75 gm/day for 8 weeks).

More specifically, from the three provided pharmacokinetic/bioavailability studies, there are several concerns as related to the usefulness of the provided information and data to accurately characterize how this product performs in the intended population according to the proposed dosing recommendations. These concerns are summarized as follows:

1. Studies #20060 and #20061 examined the single and multiple dose pharmacokinetics of Colazide in healthy male subjects. Based upon the findings in Study #GLY01/93, which examined long-term administration of Colazide to patients with ulcerative colitis **in remission**, the systemic exposure ranged from approximately 60 times or 2-15 times greater for BSZ and most of the metabolites, respectively, in the patients as compared to healthy individuals when given as the same dosing regimen. Therefore, the relevance of the data obtained in the healthy subjects is of limited value.

2. The to-be-marketed formulation was not used in Studies #20060 and #20061. However, the differences in formulation components were minor; i.e., no difference in balsalazide disodium and $\leq$0.1% change in silicon dioxide and magnesium stearate. These changes would be defined as Level 1 changes according to SUPAC for Immediate Release Solid Oral Dosage Forms (CDER, November 1995), which indicates that further testing need not be documented beyond application/compendial dissolution requirements.

3. The ulcerative colitis "patients" in Study #GLY01/93 were taking Colazide as 1.5 gm, 2.25 gm, or 3.0 gm **bid**. The following issues are of concern: i) the patients were in **remission** and not experiencing "mildly to moderately" active disease, ii) the patients had been exposed to drug for at least one year prior to entering the study, as opposed to the recommended exposure of 8 weeks, iii) the proposed dosing regimen of 2.25 gm **tid** was not employed , and iv) the sponsor cannot specify how the product was given in relation to meals, even though the proposed package insert recommends that "Colazide should be taken with food."

4. For all of the studies there are concerns about the accuracy and precision of drug/metabolite levels, primarily at the lower concentrations in plasma, urine, and feces.

Therefore, it is recommended that prior to approval, a study be conducted to obtain information for Colazide as it is intended to be administered in the target population (as outlined in #1 below). In addition, the other requested information (#2-8 below) should also be obtained in the study outlined in #1, or in additional studies as appropriate, or from the literature if available.

1. A multiple-dose pharmacokinetic study in the target population using the to-be-marketed formulation from a representative production size batch of Colazide. The drug should be administered as recommended in the package insert. All moieties of Colazide should be analyzed using a precise and accurate validated assay.

2. Since Colazide is recommended to be given with food, but there is some question as to whether this was done in the pivotal clinical studies, an assessment of the effect of food on the absorption of Colazide is needed. (This can be incorporated into the multiple-dose PK study outlined above, if desired.)

3. In vitro plasma protein-binding information for Colazide, covering the relevant concentration range. (Data regarding protein binding may be obtained from the multiple-dose pharmacokinetic study above.)

4. In vitro metabolism/Colazide drug interaction studies. The sponsor is encouraged to consult the "Guidance for Industry; Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies in vitro" when designing these experiments.

5. In vivo drug interaction studies with antibiotics and other drugs that are likely to be routinely coadministered with Colazide.

6. In the NDA submission, only limited systemic exposure/PK data was provided for Colazide in patients with a modest degree of renal impairment. Therefore, once the study identified in Item #1 above has been completed and analyzed, an assessment of the systemic exposure/PK information should be compared to similar information that is available in the literature for subjects with different degrees of kidney disease who have received ASA itself or as other prodrugs; i.e., sulfasalazine and olsalazine. PK comparative analyses and simulations, if appropriate, should be carried out to assess what might occur in patients receiving Colazide with all degrees of renal disease. Depending on these data analyses, a Colazide PK study in patients with different degrees of renal impairment may or may not be necessary. If so, a well-designed and well-controlled study examining the disposition of Colazide in patients with mild, moderate, and severe renal impairment would be indicated and the sponsor encouraged to consult the "Guidance for Industry; PK in Patients with Impaired Renal Function", FDA, CDER, May, 1998.

7. A study examining Colazide disposition in hepatically impaired subjects.

8. Studies examining the disposition of Colazide in the geriatric and pediatric populations.

9. Lastly, a reanalysis of the data from Study #GLY01/93 to examine the effect of gender on the disposition of Colazide taking into account the influence of body weight.

If it is felt by HFD-180 that obtaining the information outlined above prior to NDA approval is not critical to have from a safety and efficacy perspective, as well as for providing additional information for the product's package insert, then the requested information could be obtained post-NDA approval within an agreed specified time. Before initiating any studies, the sponsor should submit each study protocol for review by OCPB staff.

The following dissolution method and specification are acceptable:

[redacted]

The above Recommendation section, as well as the labeling comments found on pages 25-27 of this review, should be sent to the sponsor as appropriate.

Carol Cronenberger, Ph.D. /S/ 5/19/98
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by John Hunt, Interim Team Leader J. Hunt
FT initialed by John Hunt, Interim Team Leader /S/ 5/19/98
Division of Pharmaceutical Evaluation II

cc: NDA 20-610, HFD-180, HFD-850 (Lesko), HFD-870 (Chen, Hunt), Central Document Room (Barbara Murphy).

TABLE OF CONTENTS:

Abbreviations:

BSZ	Balsalazide disodium, Colazide®
ASA	5-aminosalicylic acid
NASA	N-acetyl-5-aminosalicylic acid
ABA	4-aminobenzoyl-β-alanine
NABA	N-acetyl-4-aminobenzoyl-β-alanine
SSZ	Sulfasalazine
SP	Sulfapyridine
NASP	N-acetyl-sulfapyridine
MSZ	Mesalazine
UC	Ulcerative colitis
PK	Pharmacokinetic
Cl_R	Renal Clearance
Cl_{CR}	Creatinine clearance
BE	Bioequivalence
SD	Standard Deviation

BACKGROUND:

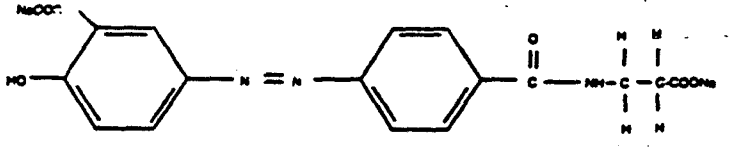
Colazide® (balsalazide disodium) is an anti-inflammatory agent intended for the treatment of mildly to moderately active ulcerative colitis. The proposed dose included in the labeling is three 750 mg capsules (2.25 gm) three times a day, for a total daily dose of 6.75 gm, for a duration of 8 weeks. BSZ was conceived as a prodrug to deliver ASA to the colon, utilizing the innocuous ABA as a carrier moiety. ABA and ASA are connected via an azo-bond. The prodrug passes nearly unabsorbed through the small intestine, and becomes activated upon reaching the colonic microflora where bacterial azoreductases release the therapeutically active ASA. The colon is the primary site in the body with sufficient azoreductase activity to release ASA from BSZ. The use of ABA as a carrier, which has low potential for causing adverse events, is expected to result in improved tolerance and efficacy over SSZ, a standard of therapy in the treatment of UC. SSZ is a prodrug which is also designed to deliver ASA to the colon, however, it contains SP as the carrier, which is thought to cause numerous adverse side effects. BSZ is not marketed anywhere in the world.

The sponsor has submitted six PK studies in support of the clinical pharmacology and biopharmaceutics issues related to NDA 20-610. Three of these studies were not reviewed as they used a formulation and dosage form different from that intended to-be-marketed, and are not relevant to the current submission. The only documented interaction between the sponsor and the Agency regarding the contents of NDA 20-610 prior to its submission was a pre-NDA meeting, which was held between members of Salix Pharmaceuticals, Inc. and the FDA on October 9, 1996. At that time, Lydia Kaus, Ph.D. (former Biopharm team leader) informed the sponsor that only qualitative conclusions could reliably be drawn from the presented data due to the high degree of intersubject variability. As a result, there were no PK data provided regarding half-life, total clearance, or volume of distribution for either BSZ or its metabolites.

Chemistry

The structure of BSZ is displayed below:

Balsalazide Disodium



Molecular formula: $C_{17}H_{13}N_3O_6Na_2 \cdot 2H_2O$
Molecular weight of balsalazide disodium: 401.32 (437.32 for the dihydrate)
Molecular weight of the corresponding di-acid: 357.32
Chirality: There are no asymmetric carbons in the molecule.

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS/ PHARMACODYNAMICS:

I. BIOAVAILABILITY/BIOEQUIVALENCE:

A. Absolute Bioavailability:

This parameter was not determined in the current NDA submission.

B. Relative Bioavailability:

The bioavailability of ASA from BSZ was compared to that of standard approved treatments for UC, namely SSZ (Salazopyrin®) and MSZ (Asacol®). SSZ is an azo-bonded drug, which contains ASA as the active moiety and utilizes SP as the "carrier" portion of the compound. SP is believed to be responsible for many of the toxic side effects observed with SSZ administration. MSZ is an enteric-coated preparation of ASA.

Results from Study #20060 (see Appendix I), which was designed to administer equimolar doses of ASA from the three products, indicate that mean ASA Cmax values were higher after BSZ administration when compared to SSZ (392±282 vs 286±221 ng/ml), but lower for BSZ when compared to MSZ (528±276 vs 981±930 ng/ml). These differences did not achieve statistical significance. However, AUC_{last} for ASA was significantly greater in the BSZ-treated individuals vs SSZ-treated subjects (2593±2278 vs 1175±1110 ng*hr/ml; p=0.040). Subjects who received BSZ had lower AUC_{last} values than their MSZ-treated counterparts, but this did not reach statistical significance (3661±1962 vs 4797±3032 ng*hr/ml). The only significant difference seen in Tmax was a lower value for ASA in the MSZ-treated subjects compared to those who received BSZ (7.2±4.4 vs 9.3±1.3 hours; p=0.039). On the other hand, plasma concentrations of ABA were two to three orders of magnitude lower in the BSZ-treated individuals than were SP plasma levels in SSZ-treated subjects (Cmax =13.7±16.8 **ng/ml** vs 10.2±1.9 **μg/ml** and AUC_{last}=81±154 **ng*hr/ml** vs 183 **μg*hr/ml**, in BSZ-treated and SSZ-treated subjects, respectively).

Urinary excretion data indicated that very little, if any, ASA was recovered in the urine, regardless of the compound administered. However, while virtually no ABA could be recovered in the urine of BSZ-treated subjects, approximately 9% of a dose of SSZ was recovered as the toxic SP.

The plasma data indicate that there may have been less ASA retained in the colon in BSZ-treated subjects as compared with those who received SSZ, which could impact therapeutic efficacy. This could not be confirmed, however, as fecal samples were not collected from the subjects who were administered SSZ. On the other hand, systemic levels of the "carrier" portion of BSZ (ABA) were much lower than the concentrations observed for SP, therefore, an improved safety profile is possible for patients taking

C. Bioequivalence:

The drug substance used in PK Studies #20060/#20061 and #GLY01/93 was produced by different manufacturers (——— , respectively). Furthermore, one of the pivotal clinical trials (#CP099301) administered BSZ made by yet another manufacturer (——. The second pivotal clinical study (#57-3001A) used drug substance manufactured by —— It is not known at this time whether the manufacturing processes are sufficiently similar; this information is pending according to the Chemistry Reviewer.

The sponsor has not performed BE testing on any of these drug batches, although the formulations were almost identical (see Section VIII, Formulation for details). The BSZ batches used in the clinical trials were at least 10% of a representative production-scale batch size, however, PK Studies #20060 and #20061 used pilot-scale batches. PK Study #GLY01/93 used BSZ from 5 different batches which varied from pilot-scale to >10% production-scale. (see Section VIII, Formulation for details). A complete list of the BSZ manufacturers, batch sizes, lot numbers, formulations, and the studies in which they were used can be located in Appendix II, "Formulation/Manufacturing Information."

D. Food Effect:

No food effect studies were included in this submission, although the labeling recommends that BSZ be taken with food. BSZ was administered 30 minutes to 2 hours after a meal in PK Studies #20060 and #20061 (menus included), however, there is no information available as to how BSZ was administered in relation to food intake in PK Study #GLY01/93. BSZ was given in the fasting state in the clinical trials according to the Medical Officer (Dr. Prizont), although the sponsor claims that this information was not specified (see "Response to FDA Inquiry Dated 8/8/97," pg 14).

II. PHARMACOKINETICS:

Single dose studies:

BSZ was administered as a single dose to healthy volunteers in Studies #20060 and #20061 (2.25 gm and 1.5 gm, respectively). Details regarding study design and results can be located in Appendix I, "Studies I and II". Table 1 summarizes the plasma PK data obtained, which is normalized to a dose of 1.5 gm. Results are presented as means±SD. All values which were below the assay LOQs were reported as zero and included in the calculations.

Table 1. Dose-normalized Plasma PK data from Studies #20060 and #20061.

	C_{max} (ng/ml)		$AUC_{0\text{-last}}$[a] (ng*hr/ml)		T_{max} (hr)	
	1.5 gm[b]	2.25 gm[c]	1.5 gm	2.25 gm	1.5 gm	2.25 gm
BSZ	7.9±4.9	12.6±5.9	5.7±5.7	25.1±28.8	1.1±0.8	1.6±1.1
ASA	292±156	307±188	1581±1182	2084±1433	7.2±2.6	9.3±1.8
NASA	900±278	765±267	10708±1977	13075±3719	8.7±1.0	10.1±1.7
ABA	11.9±14.2	9.1±11.2	29.7±45.6	54±103	3.8±4.4	4.7±5.3
NABA	49.4±14.4	39.5±14.5	892±562	948±495	13.5±11.7	15.6±10.3

[a]$AUC_{0\text{-last}}$ determined over 72 hours for the 1.5 gm dose and for 96 hours for the 2.25 gm dose.
[b]Study 20061; N=12 for all values obtained with the 1.5 gm dose.
[c]Study 20060; N=24 for all values obtained with the 2.25 gm dose.

In some subjects BSZ was quickly absorbed after single doses. The Tmax indicates that the drug was most likely absorbed in the upper gastrointestinal tract, as BSZ could not reasonably be expected to reach the colon and absorbed within 1 or 2 hours after dosing. However, over 80% of the subjects in both single-dose studies had only 1 or 2 quantifiable levels of BSZ, or concentrations which were below the assay LOQ. In the subjects who had greater than 2 detectable levels of BSZ, the plasma concentrations were near the assay LOQ, therefore, half-lives could not be determined. Furthermore, dose-proportionality of BSZ could not be assessed because the AUCs were poorly characterized.

Likewise, >50% of the subjects in both studies had no detectable levels of ABA in plasma. Only 1 or 2 concentrations were obtained in each of the remaining subjects and these were all near the assay LOQ. Again, as the ABA plasma concentration vs time profiles were incomplete in almost every subject, no half-life for this carrier portion of BSZ could be determined.

There were readily quantifiable plasma concentrations of ASA, NASA, and NABA observed after single doses of BSZ in all of the subjects. However, the majority of the plasma concentration vs time curves exhibited erratic profiles. Therefore, comparisons of AUC values are not reliable. Although not determined in the current studies, literature estimates of half-lives for ASA[1] are 0.6 and 1.4 hours after 250 and 500 mg oral ASA, respectively. After administration of NASA[2] to healthy subjects, the half-life was observed to be from 6-9 hours.

Of interest was the appearance in >50% of the subjects of the N-acetylated metabolites (NASA and NABA) prior to that of the "parent" metabolite (ASA and ABA, respectively) in the systemic circulation. Furthermore, some subjects had readily quantifiable concentrations of NASA or NABA when no ASA nor ABA could be detected. One possible explanation for this phenomenon is that ASA and ABA were either absorbed in quantities too low to be detected or were absorbed more slowly than their acetylated metabolites.

Overall, plasma concentration vs time profiles for BSZ and its metabolites in healthy subjects indicated inconsistent and erratic absorption into the systemic circulation following single doses of BSZ. Although AUCs were determined for a time span which was 24 hours longer in Study

#20060 (the 2.5 gm dose), there were no detectable plasma levels for any compound, except NASA, after 72 hours in any of the subjects.

Table 2. Urinary and fecal recovery data from Studies #20060 and #20061.

	Fecal recovery[a] (%)		Urinary recovery[b] (%)		Cl_R[b,c] (L/hr)	
	1.5 gm	2.25 gm	1.5 gm	2.25 gm	1.5 gm	2.25 gm
BSZ	0	0.04±0.1	0.1±0.1	0.1±0.1	150±85	63.7
ASA	3.7	7.1±4.1	0	0	0	0
NASA	6.0	17.2±11.1	17.4±8.9	20.5±8.2	16.1±6.1	11.2
ABA	2.1	36.6±26.6	0	0	0	0
NABA	1.6	2.6±1.6	2.2±1.5	3±1.7	52± 33.5	26.9

[a]N=1for the 1.5 gm dose and N=10 for the 2.25 gm dose.
[b]N=12 for the 1.5 gm dose and N=24 for the 2.25 gm dose.
[c]Values were determined for a 4-hour period for the 1.5 gm dose and a 96-hour period for the 2.25 gm dose.

The fecal recovery data for the single 1.5 gm dose of BSZ was virtually meaningless, as sample collection was incomplete and N=1. This was apparent as the total recovery of BSZ and metabolites in this study (including urine) was only about 33% of the total dose.

The fecal recovery of BSZ as the parent compound was <1% after a single 2.25 gm dose. ASA and NABA were also recovered in feces in relatively small quantities, however, NASA and ABA contributed to >50% of the recovery of the BSZ dose. These data were obtained from only 10 subjects.

Urinary recovery of BSZ and its metabolites was consistent in both studies. Again, <1% of a dose of BSZ was recovered as the parent compound. Virtually no ASA or ABA was excreted into the urine. While relatively small quantities of a BSZ dose were recovered as NABA, between 15 and 20% of the dose was eliminated into the urine in the form of NASA.

Overall, approximately 90% of a single 2.25 gm dose of BSZ was recovered in urine and feces as parent compound and metabolites. Less than 1% of a BSZ dose was recovered in either biological matrix as parent compound, indicating that the prodrug was efficiently cleaved in the colon by bacterial azoreductases. Likewise, ABA was recovered exclusively in the feces, confirming the low systemic exposure observed with the plasma concentration data. ASA appeared to be eliminated primarily as its N-acetylated metabolite into both the urine and feces. Finally, relatively small quantities of NABA were recovered in either the urine or the feces.

Renal clearance values for BSZ were apparently very high, however, these were probably a reflection of incomplete characterization of the plasma concentration vs time profiles, resulting in errors in AUC, and subsequently, Cl_R determinations (Cl_R = amount of drug excreted in the urine/plasma AUC over the collection interval). Both NASA and NABA had Cl_R values which exceeded normal creatinine clearance values (~7 L/hr), which may indicate active tubular secretion for these metabolites. Indeed, Rasmussen[3] and coworkers observed renal clearances for

NASA that were 2 times greater than the corresponding creatinine clearances following oral ingestion of 1.5 gm ASA/day in healthy subjects. In the case of NABA and NASA, erratic plasma concentrations vs time curves made it difficult to compare AUCs, and therefore, Cl_R values between the two doses. In addition, Cl_R was examined over vastly different time intervals in the two studies (4 hr vs 96 hr).

Pharmacokinetic Summary - Single Doses

It should be remembered that single-dose studies of BSZ were examined in healthy male subjects only, therefore, the relevance of the data to the target population is unknown.

Overall, there was limited systemic exposure to BSZ and ABA with inconsistent absorption of all compounds from the gastrointestinal tract. Half-life values were not determined for any of the compounds secondary to the incomplete plasma concentration vs time curves (BSZ and ABA) or erratic plasma profiles (ASA, NASA, and NABA) in the majority of the subjects.

Very little BSZ was recovered as parent compound in either the urine or feces, indicating efficient breakdown of the prodrug in the colon. Virtually all of the ABA released from BSZ was either recovered in the feces intact or acetylated to NABA. Small quantities of ASA were recovered in the feces, however, the majority was recovered in the form of NASA in both urine and feces.

Dose-proportionality of BSZ was difficult to assess due to the erratic plasma concentration vs time profiles. This caused error to be introduced into the AUC calculations, therefore, they could not be compared with any degree of confidence. Furthermore, the two single doses of BSZ were administered in different studies to different individuals.

Multiple-dose studies

The PK results from multiple-dose studies in both healthy volunteers (#20061) and in patients with UC (#GLY01/93) are presented in the following tables for BSZ and its metabolites. Results are presented as means±SD. All values which were below the assay LOQs were reported as zero and included in the calculations.

Table 3. Steady State PK parameters for BSZ after multiple dosing in Studies #GLY01/93 and #20061.

	C_{min} (ng/ml)	C_{max} (ng/ml)	AUC_{last}[a] (ng*hr/ml)	T_{max} (hr)	Urinary recovery	Cl_R[g] (L/hr)
Study #GLY01/93[b] *(1.5 gm BSZ bid)*	12.1±14.1	131±52.6	481±227	1.2±0.5	0.2±0.2	5.2±3.2
Study #20061[c] *(1.5 gm BSZ bid)*	0	7.2±5.5	7.5±9.6	1.0±0.9	0.1±0.1	143±73
Study #GLY01/93[d] *(2.25 gm BSZ bid)*	23.8±15.8	224±124	825±374	1.2±0.4	0.2±0.1	3.8±1.4
Study #20061[e] *(2.25 gm BSZ tid)*	0	11.9±7.6	13.9±10.4	3.9±10.1	0.2±0.1	182±212
Study #GLY01/93[f] *(3.0 gm BSZ bid)*	15±5.3	142±35	713±236	1.6±0.9	0.1±0.1	4.5±1.3

[a] AUC_{last}=$AUC_{0\text{-}12hr}$ for all doses except the 2.25 mg dose in Study 20061, where AUC_{last} = $AUC_{0\text{-}8hr}$.
[b] N=30-38, [c] N=12, [d] N=6, [e] N=11, [f] N=9
[g] Cl_R determined over 12 hours in Study GLY01/93 and 4 hours in Study #20061.

The subjects from Study #GLY01/93 were patients with UC, however, the disease was in remission. They had received BSZ continuously at doses of either 1.5 gm, 2.25 gm, or 3.0 gm bid for at least one year prior to entry into the study. Subjects in Study #20061 were healthy, male volunteers who received BSZ for 9 days as 1.5 gm bid, followed by a 5-day washout period. After the washout, subjects were administered 2.25 gm BSZ tid, but only received a total of 4 doses.

Clearly plasma levels of BSZ were much higher in the patients (as per Cmin, Cmax, and AUC). Indeed, some of the healthy subjects had no quantifiable plasma concentrations of BSZ, and those that did had BSZ levels which were all near the assay LOQ. Overall, there were very few plasma samples in Study #20061 with any BSZ detected. Conversely, all of the UC patients had readily measurable quantities of plasma BSZ.

BSZ was quickly absorbed with Tmax values of 1-2 hours in most subjects, most likely indicating absorption of drug in the upper gastrointestinal tract. The relatively high Tmax for the 2.25 gm dose in Study #20061 is misleading, in that 8/9 subjects with quantifiable levels of BSZ had Tmax values of 1 or 2 hours. The Cmax within the patient study was significantly greater for the 2.25 gm dose as compared to the 1.5 gm and 3.0 gm doses (p=0.008, ANOVA). However, the small number of subjects (N=6) in this group probably confounded the results.

The BSZ plasma concentration vs time curves were incompletely defined from Study #20061 due to the sparse data, and because all of the BSZ concentrations were near the assay LOQ. In addition, the profiles from Study #GLY01/93 were erratic in the majority of patients, most likely implying irregular absorption of BSZ from the gastrointestinal tract. For these reasons, half-lives for the different treatments could not be determined with any degree of confidence. Likewise, comparison of the AUC values could not be achieved in a reliable manner. However, there did not appear to be any obvious relationship between the AUCs which would indicate dose-proportionality, especially in the patient study.

It was assumed that BSZ levels had reached steady state in Study #20061, as all of the trough concentrations for the two dosing regimens were below the assay LOQ and there was no apparent drug accumulation. The patients in Study #GLY01/93 were obviously at steady state as they had taken BSZ for over a year, however, drug accumulation with multiple dosing was not assessed.

There are several possible explanations for the differences in BSZ levels between the two populations. It is conceivable that patients with UC had different absorption profiles for this compound than would be observed in healthy individuals. For example, patients with quiescent disease often exhibit longer gastrointestinal transit times compared with normal subjects.[4] This could allow more time for absorption of intact BSZ prior to its arrival in the colon where it is cleaved by the bacterial microflora. In addition, as UC most likely alters the colonic microflora, BSZ could be less efficiently cleaved, allowing for more absorption of intact drug. Increased gastrointestinal permeability may also facilitate greater absorption of compounds in UC patients. Alternatively, it is possible that accumulation of BSZ does occur with long-term administration, and that this effect was not evident during the relatively short-term studies performed in healthy volunteers.

The design of Study #GLY01/93 also contributed to a limited extent to the large differences observed between BSZ exposure in the two studies. AUC values for BSZ and all of the metabolites were reported for a 12-hour dosing interval, however, blood was sampled for only 8 hours. The pre-dose (trough) concentrations were incorporated into the AUC calculations as the 12-hour drug concentration, and this was oftentimes greater than the actual 8-hour concentration obtained via sampling. This procedure overestimates AUC and probably contributed to the differences observed between healthy volunteers and UC patients. In addition, inadequate assay validation at the upper LOQ ——— ı) in Study #GLY01/93 most likely introduced some error into the plasma BSZ concentrations that were obtained.

The urinary data was consistent between the studies; <1% of a BSZ dose was recovered as the parent compound in urine. This confirmed the results from the single-dose studies. The Cl_R values for BSZ appear to be unreasonably high in healthy subjects, and is most likely a reflection of the inadequate definition of the plasma concentration profiles, resulting in questionable AUC values. On the other hand, the overestimation of AUCs in Study #GLY01/93 may have underestimated the Cl_R values (Cl_R determined as amount of drug recovered in urine/AUC over the collection interval) obtained in that study. Furthermore, Cl_R was calculated for different time intervals in the two studies.

Approximately 8% of the BSZ dose was recovered in feces as parent drug after the tid dosing regimen in Study #20061. No feces were collected from the UC patients.

Table 4. PK parameters for ASA from multiple dosing in Studies #GLY01/93 and #20061.

	C_{min} (ng/ml)	C_{max} (ng/ml)	AUC_{last}[a] (ng*hr/ml)	T_{max} (hr)	Urinary recovery	Cl_R[g] (L/hr)
Study #GLY01/93[b] *(1.5 gm BSZ bid)*	340±236	676±405	6010±3481	5.1±3	2.3±2.9	1.4±1.7
Study #20061[c] *(1.5 gm BSZ bid)*	182±107	377±178	2590±1329	9±1.8	0.6±1.6	1.3±2.6
Study #GLY01/93[d] *(2.25 gm BSZ bid)*	755±320	1025±412	10864±4609	5.3±2.7	3.7±2.4	2.4±1.8
Study #20061[e] *(2.25 gm BSZ tid)*	205±137	413±220	1408±813	12.4±7.9	0.8±2.2	1.1±1.3
Study #GLY01/93[f] *(3.0 gm BSZ bid)*	548±270	889±476	8316±4164	4.5±3.1	3.8±3.1	4.6±5.4

[a] $AUC_{last}=AUC_{0\text{-}12hr}$ for all doses except the 2.25 mg dose in Study 20061, where $AUC_{last}=AUC_{0\text{-}8hr}$.
[b] N=33-38, [c] N=12, [d] N=6, [e] N=11, [f] N=8-10
[g] Cl_R determined over 12 hours in Study GLY01/93 and 4 hours in Study #20061.

There were readily quantifiable plasma levels of ASA in all of the subjects. As for BSZ, there was greater systemic exposure to ASA in UC patients compared to healthy subjects. Cmax also occurred earlier in the ulcerative colitis patients, with a mean tmax of 4-5 hours.

The plasma concentration vs time profiles were either erratic (#22061) or at a plateau (#GLY01/93), therefore, no half-life values were determined. Although dose-proportionality was difficult to assess from the AUC data provided in healthy subjects due to the irregular plasma profiles, examination of the AUC values determined in UC patients revealed no clear dose-proportional relationship between the three dosing regimens. Based on Cmin plasma concentrations (trough levels), ASA achieved steady state in healthy subjects in 7-13 days with the bid dosing regimen and by the third dose in the tid dosing regimen. However, ASA accumulated during the tid multiple dosing regimen in healthy subjects, with almost all individuals exhibiting greater Cmax and AUC values after each successive dose (4 total doses).

Again, it is possible that the pathophysiology of the UC disease process somehow facilitates increased systemic absorption for this active moiety of BSZ. This phenomenon could be of clinical significance, in that there may be decreased amounts of ASA at the therapeutic site of action (colonic mucosa) resulting in decreased efficacy for this population. However, a systemic role for ASA in the efficacy of UC has not be ruled out. It should also be remembered that the UC patients in this study had taken BSZ for at least a year, whereas the labeling for this compound recommends administration for a duration of only 8 weeks, therefore, it would be difficult to predict the extent of absorption over a much shorter time period. In addition, the patients in Study #GLY01/93 were in remission from their disease and BSZ is intended to be used in people with active UC. It is likely that differences in the severity of the disease process would result in perturbation of absorption patterns for ASA, as well as the other metabolites.

Less than 5% of a dose of BSZ was recovered as ASA in the urine of both healthy subjects and UC patients. About 21% of the BSZ dose was recovered as ASA in the feces of healthy subjects

after the 2.25 gm dose.

Renal clearance values were fairly consistent, however, became larger with increasing doses in the UC patients, up to rates approaching normal creatinine clearances at the highest dose. These differences were statistically significant (p=0.014, ANOVA), however, the relatively small number of subjects in the group of patients who received the 2.25 gm and 3.0 gm bid doses of BSZ may have confounded the results.

Table 5. PK parameters for ABA from multiple dosing in Studies #GLY01/93 and #20061.

	C_{min} (ng/ml)	C_{max} (ng/ml)	AUC_{last}[a] (ng*hr/ml)	T_{max} (hr)	Urinary recovery	Cl_R[g] (L/hr)
Study #GLY01/93[b] *(1.5 gm BSZ bid)*	6.5±12.4	20.5±36	133±232	1.7±2.7	0.03±0.2	0
Study #20061[c] *(1.5 gm BSZ bid)*	8.1±12.6	24.7±14.2	130±153	8.5±7.9	0	0
Study #GLY01/93[d] *(2.25 gm BSZ bid)*	0	10.8±16.9	59±93	2±3.1	0 -	0
Study #20061[e] *(2.25 gm BSZ tid)*	14.7±13.2	31.7±18.2	103±115	11±8.1	0	0
Study #GLY01/93[f] *(3.0 gm BSZ bid)*	0	25±38.1	74±143	1.3±2.2	0	0

[a] $AUC_{last}=AUC_{0-12hr}$ for all doses except the 2.25 mg dose in Study 20061, where $AUC_{last}=AUC_{0-8hr}$.
[b] N=33-38, [c] N=12, [d] N=6, [e] N=11, [f] N=8-10
[g] Cl_R determined over 12 hours in Study GLY01/93 and 4 hours in Study #20061.

The large differences in exposure between patients and healthy volunteers noted for BSZ and ASA were not present with ABA. Overall, the majority of the plasma concentrations from both studies were near the assay LOQ. In addition, there were many individuals with blood samples that contained no detectable ABA. As for ASA, Tmax values were much shorter for UC patients, which may be a reflection of increased gastrointestinal permeability in this population. No reliable estimates of half-life nor comparisons of AUCs could be undertaken due to the incomplete and/or erratic ABA plasma concentration vs time profiles.

There was virtually no ABA recovered in the urine of healthy individuals or UC patients, indicating limited systemic exposure to this "carrier" portion of BSZ. Approximately 43% of the 2.25 gm dose of BSZ was recovered in the feces of healthy subjects in the form of ABA.

Table 6. PK parameters for NASA from multiple dosing in Studies #GLY01/93 and #20061.

	C_{min} (ng/ml)	C_{max} (ng/ml)	AUC_{last}[a] (ng*hr/ml)	T_{max} (hr)	Urinary recovery	Cl_R[g] (L/hr)
Study #GLY01/93[b] *(1.5 gm BSZ bid)*	710±344	1065±433	10535±4459	5.0±2.7	15.3±9.0	10±3.7
Study #20061[c] *(1.5 gm BSZ bid)*	551±245	852±301	7429±3230	8.3±2.6	12.8±6.6	0.01±0.01
Study #GLY01/93[d] *(2.25 gm BSZ bid)*	1242±309	1507±360	16847±3887	4.5±3.2	14.5±4.9	8.8±2.2
Study #20061[e] *(2.25 gm BSZ tid)*	618±196	951±287	4751±1628	12.5±7.9	4.4±1.8	12.5±6.3
Study #GLY01/93[f] *(3.0 gm BSZ bid)*	1031±371	1427±468	14234±4519	3.1±3.1	12±4.9	12.8±9.4

[a] AUC_{last}=$AUC_{0\text{-}12hr}$ for all doses except the 2.25 mg dose in Study 20061, where AUC_{last}=$AUC_{0\text{-}8hr}$.
[b] N=33-38, [c] N=12, [d] N=6, [e] N=11, [f] N=9-10
[g] Cl_R determined over 12 hours in Study GLY01/93 and 4 hours in Study #20061.

All individuals had readily quantifiable plasma concentrations of NASA. Again, higher plasma concentrations of NASA were observed in subjects with UC compared to healthy volunteers. It is unlikely that alterations in the biotransformation of ASA to NASA contributed to this observation, as [redacted] was unable to demonstrate any significant differences in acetylation of ASA in UC vs normal subjects. As with ABA and ASA, Cmax was observed at earlier times in the UC patients and probably indicates altered absorption in this population.

NASA plasma concentration vs time profiles tended to be erratic in healthy subjects and at a plateau in patients, therefore, half-lives were not calculated. Due to suboptimal characterization of the plasma curves, comparison of AUC values between treatments in healthy subjects was tenuous at best. As for ASA, AUC values failed to reveal dose-proportionality between the three treatments regimens in UC patients. NASA achieved steady state within 7-13 days and by the third dose, in the bid and tid dosing regimens, respectively, in healthy subjects. However, both mean and individual Cmax and AUC values increased with dosing frequency over the tid dosing regimen, indicating accumulation with multiple dosing.

In general, urinary recovery of NASA ranged from 12-15%, although was somewhat lower in healthy subjects. About 8% of the 2.25 gm dose of BSZ was recovered in the feces of healthy volunteers. Renal clearances for NASA exceeded normal creatinine clearance values (~7 L/hr) in both populations, indicating contribution of active tubular secretion to the elimination process. No ready explanation exists for the low Cl_R value observed in the 1.5 gm bid group (Study #20061).

Table 7. PK parameters for NABA from multiple dosing in Studies #GLY01/93 and #20061.

	C_{min} (ng/ml)	C_{max} (ng/ml)	AUC_{last}[a] (ng*hr/ml)	T_{max} (hr)	Urinary recovery	Cl_R[g] (L/hr)
Study #GLY01/93[b] *(1.5 gm BSZ bid)*	163±173	296±263	2502±2448	4.2±3	6.7±8.6	17.6±10.5
Study #20061[c] *(1.5 gm BSZ bid)*	54.9±21.7	72.6±23.5	643±261	9.4±6.2	2.2±2.1	31.4±43.7
Study #GLY01/93[d] *(2.25 gm BSZ bid)*	418±256	774±426	6691±3814	2.4±2.6	11.1±5.2	22.8±10.3
Study #20061[e] *(2.25 gm BSZ tid)*	59.5±32.1	85.3±37	451±235	13.6±6.7	0.8±0.7	34.4±20.4
Study #GLY01/93[f] *(3.0 gm BSZ bid)*	273±220	717±726	5825±5650	1.9±2.1	11.8±10.1	48.1±51.6

[a] $AUC_{last}=AUC_{0\text{-}12hr}$ for all doses except the 2.25 mg dose in Study 20061, where $AUC_{last}=AUC_{0\text{-}8hr}$.
[b] N=30-38, [c] N=12, [d] N=5-6, [e] N=11, [f] N=7-10
[g] Cl_R determined over 12 hours in Study GLY01/93 and 4 hours in Study #20061.

All individuals had readily detectable plasma levels of NABA; again, exposure was substantially greater and at earlier times in UC patients as compared to healthy volunteers. Erratic or plateau plasma concentration vs time profiles were observed for the majority of subjects, so half-lives were not determined. NABA appeared to achieve steady state in 7-13 days with multiple bid dosing in healthy subjects. However, trough concentrations continued to increase during tid dosing with each of four successive doses, indicating failure to achieve steady state with the regimen employed.

Less than 3% and from 6-12% of a BSZ dose was recovered in the urine of healthy and UC patients, respectively. Only around 7% of the 2.25 gm BSZ dose was recovered as NABA in the feces. As for NASA, Cl_R values for NABA exceeded normal creatinine clearance values. There was also a statistically significant difference for renal clearances between the treatments in the UC patient study, with greater values observed after higher doses ($p=0.01$). The small number of subjects in the intermediate and high dose groups may have affected the analysis results, however.

Pharmacokinetic Summary - Multiple Doses

In general, patients who were in remission from UC had much greater plasma concentrations of BSZ and most of its metabolites as compared to the healthy volunteers. Low systemic exposure to ABA was observed in both populations, however. Erratic (healthy subjects) and plateau (UC patients) plasma concentration vs time profiles prevented reliable determination of mean half-life data for BSZ or any of its metabolites. As in the single-dose studies, dose-proportionality was difficult to assess.

Less than 1% of a BSZ dose was recovered in the urine as either the parent compound or the "carrier" metabolite, ABA, in both healthy subjects and in patients with UC. Significant amounts of ASA were observed in the plasma, but little was recovered in the urine (<5%), presumably due to N-acetylation. NASA and NABA were also prevalent in the plasma;

approximately 5-15% of a BSZ dose was recovered as these two N-acetylated metabolites in the urine of healthy subjects, while 20-25% was recovered in the urine of UC patients.

Fecal recovery data were only available for healthy subjects. Small quantities of parent BSZ were recovered, indicating efficient reduction of the compound by bacterial reductases in the colon. The bulk of a BSZ dose was recovered in the feces as metabolites and totaled ~80%. Approximately 90-95% of a 2.25 gm single dose of BSZ was recovered in the urine and feces of healthy individuals. It is possible that there are additional minor pathways for BSZ metabolism that would account for unrecovered drug, however, they were not examined in this NDA submission.

Renal clearance for BSZ in patients with UC approached normal creatinine clearance values (~7 L/hr). Again, the inordinately large values observed in Study #20061 are probably a reflection of inadequate characterization of plasma concentration vs time profiles. ASA appeared to have limited clearance via the kidneys, nor was there any excretion apparent by this pathway for ABA. The Cl_R of both NASA and NABA exceeded normal creatinine clearance values, indicating significant renal tubular secretion of these two metaboites.[3]

In conclusion, it appears that there were obvious differences in the systemic exposure to BSZ and its metabolites (with the exception of ABA) in Studies #20061 and #GLY01/93, with UC patients exhibiting greater and faster absorption when compared to healthy subjects. Therefore, the relevance of BSZ PK data in healthy subjects is questionable. Furthermore, in Study #20061 the recommended dose was examined for too short a duration of time to allow for an accurate assessment of the accumulation of BSZ metabolites in healthy volunteers. On the other hand, it is difficult to draw conclusions from the data which was provided in the patient study (#GLY01/93), as these individuals had received BSZ for >1 year and were in remission from UC. Unfortunately, the recommended dosing regimen for BSZ (2.25 gm tid for 8 weeks) was not examined in the target population (mildly to moderately active UC).

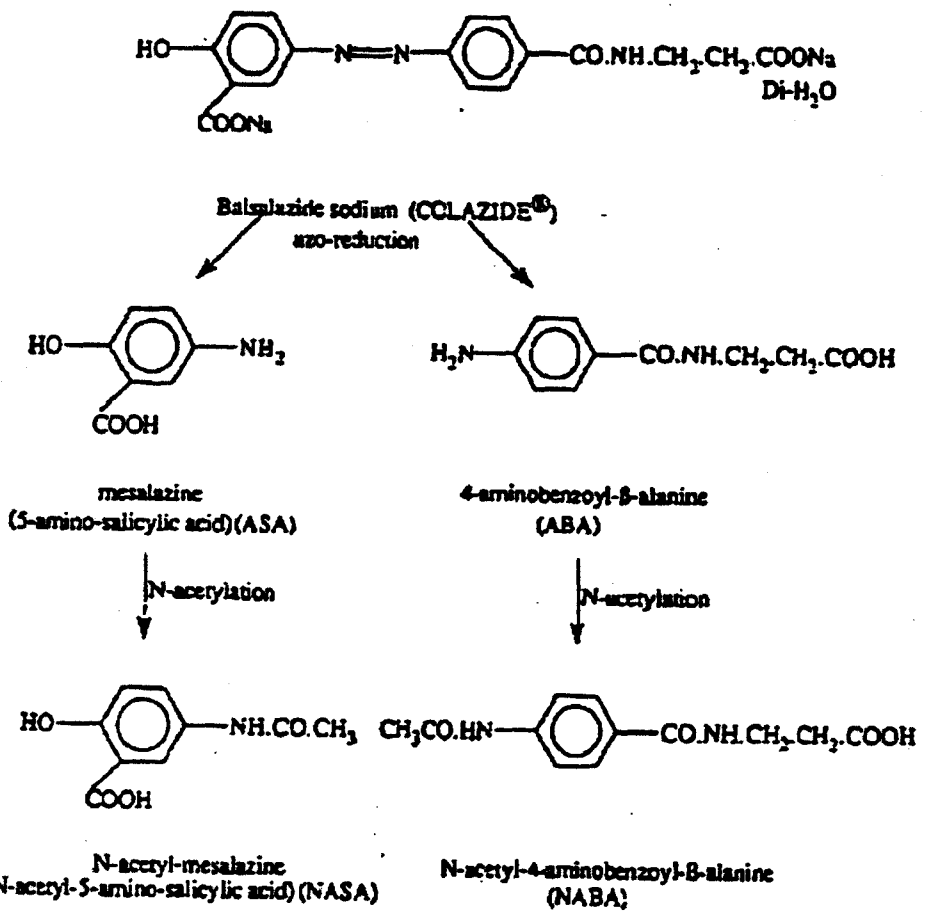
Protein-binding.

No studies examining the binding of BSZ to serum proteins were included in this NDA submission.

III. METABOLISM:

The metabolic pathway of BSZ is displayed below:

Figure 1: Metabolism of balsalazide



ASA serves as the "active" moiety and is believed to exert its anti-inflammatory effect locally in the colon, while ABA serves as the "carrier" metabolite. Both ASA and ABA are N-acetylated. Presystemic acetylation of ASA takes place in the liver, but is believed to be primarily mediated by colonic mucosal enzymes and bacterial processes.[6,7,8] ASA acetylation has been shown to be independent of polymorphic acetylator status by numerous investigators.[3,5,9,10] In addition, the sponsor has provided sufficient data to support their claim that the acetylation of ABA is not genetically controlled (see "Response to FDA Inquiry" dated 8/8/97, pgs. 25-28).

IV. DOSE AND DOSAGE FORM PROPORTIONALITY:

No formal dose-proportionality studies were included in this NDA submission and it is difficult to draw conclusions from the data provided. Although two multiple dosing regimens (1.5 gm bid and 2.25 gm tid) were employed in healthy subjects (Study #20061), AUC values could not be compared in a reliable manner, as the majority of the plasma concentration vs time profiles for BSZ and its metabolites were either erratic or incompletely defined secondary to sparse data and plasma concentrations which were near the respective assay LOQs. Patients in Study #GLY01/93 were not randomized to treatments (1.5, 2.25, and 3.0 gm BSZ bid), nor were the groups balanced for number of subjects. In addition, BSZ was not administered to this population as recommended in the package insert.

V. SPECIAL POPULATIONS:

Limited renal impairment and gender effects were studied. However, BSZ was not studied in pediatric or elderly subjects, nor hepatically impaired patients. There are no labeling claims made for any special populations.

A. Renal Impairment:

Data analysis was performed for patients with mildly impaired (Cl_{CR}=43-78ml/min, N=18) and normal (Cl_{CR}=80-163ml/min, N=29) renal function in Study #GLY01/93. The "Guidance for Industry, PKs in Patients with Impaired Renal Function" (CDER, draft 2/98), recommends that normal subjects be classified as having Cl_{CR} values >80 ml/min. Mild renal impairment is defined as Cl_{CR} values of 50-80 ml/min.

Subjects from all three dosing regimens were included and the results were normalized to a BSZ dose of 1.5 gm. It should be noted that the two groups were not balanced for gender, age, or weight. None of the PK parameters (Cmin, Cmax, Tmax, AUC_{0-12}, % recovered in urine, and Cl_R) displayed statistically significant differences at a p value of 0.05. The only exception was the Cmin for ABA, with mildly impaired subjects exhibiting greater mean values than normal subjects (10.4±13 ng/ml vs 1.7±8.7 ng/ml; p=0.014).

B. Gender

PK parameters for BSZ and its metabolites were analyzed for gender effect in Study #GLY01/93. It should be noted that the number of males and females in each group were not balanced nor were the groups randomized for age or renal impairment. There was a statistically significant gender effect for Cmax and AUC_{0-12} for BSZ, ASA, and NASA and in Cmin for BSZ, with females exhibiting greater values than males. However, the data could not be analyzed for body weight because individual body weights were unavailable. In general, plasma PK parameters were greater for all analytes in females, even though some of these values did not achieve statistical significance. There were essentially no gender effects present in urinary recoveries or renal clearance values. Detailed results of this analysis can be located in Appendix I, Study III.

VI. DRUG INTERACTIONS:

No drug-drug interaction studies were provided in this NDA submission.

VII. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

No PK/PD relationships were described in this NDA submission. These would be difficult to characterize as the action of ASA is thought to be localized primarily to the intestinal mucosa.

VIII. FORMULATION:

The formulations used in the PK and clinical studies are provided in the following table.

Ingredient	Formulation A	Formulation B
Balsalazide disodium	750 mg	750 mg
Colloidal silicon dioxide	15 mg	14 mg
Magnesium stearate	7.5 mg	8 mg
PK or Clinical Study	20060, 20061	GLY 01/93, CP099301, 57-3001

Formulations A and B were used in the PK studies (#20060, #20061, and #GLY 01/93), while only Formulation B was used in the pivotal clinical trials (#CP099301 and #57-3001) and is the to-be-marketed formulation. The differences are not expected to be clinically significant as quantities of the active ingredient (BSZ) were identical, and the silicon dioxide and magnesium stearate changed by ≤0.1%. According to SUPAC for Immediate Release Solid Oral Dosage Forms (CDER, November 1995), the differences in components constitute a Level 1 change, and indicates that further testing need not be documented beyond application/compendial dissolution requirements. It should be noted that no dissolution data are available for BSZ used in PK Studies #20060 and #20061 (Formulation A).

Representative production-scale batches of BSZ contain ——— None of the PK or clinical studies used BSZ from batches which were production scale. However, as per SUPAC IR guidelines, if batch sizes are at least 10% the quantity of production-scale batches, no additional information need be provided beyond application/compendial dissolution requirements. The clinical studies used BSZ batches which were >10% production scale. BSZ for PK Study #GLY 01/93 was supplied as 5 batches; two batches were >10% production scale, while the remaining three were <10% production scale. Pilot scale batches of BSZ were used in PK Studies #20060 and #20061. The lot numbers, batch sizes, manufacturers, and formulations of BSZ, and the PK and clinical studies in which they were used, are included in Appendix II, "Formulation/Manufacturing Information."

IX. DISSOLUTION:

A development study was conducted to determine the dissolution characteristics of BSZ under the following media conditions:

The drug substance used in this study was manufactured by ~~~ and was not used in any of the PK nor clinical studies. The results revealed that BZS was essentially insoluble in HCl ~~~) but readily soluble in the phosphate buffers and water (about ~~~). Although pepsin was not included in the HCl (sometimes included to control for pellicle formation within the capsules), this is not likely to be clinically relevant, as in vivo systemic concentrations of BSZ are reported to be very low. Results of this testing can be located in Appendix II, "Results of Dissolution Testing."

Based on the results of the above study, the following has been proposed as the dissolution method and specification:

Apparatus: USP I (basket)

Analytical Method: A validated method with UV absorption at ~~~ against a reference standard was used (NDA 20-610, Vol. 4, pgs. 97-120).

Water is an acceptable medium in that the dissolution characteristics of BSZ were similar in water and in buffer. Furthermore, the addition of one 750 mg capsule of BSZ to 900 ml deionized water did not change the pH of the water with dissolution (pH=7.5 before and after addition of BSZ). It should be noted that stability and release testing are also both performed using water as the dissolution medium.

The results of dissolution testing for the different lots of BSZ used in the two pivotal clinical trials and in PK Study #GLY 01/93 are included in Appendix II, "Results of Dissolution Testing". No dissolution data are available for PK Studies #20060 nor #20061, as the lots used in these studies were manufactured prior to the implementation of the dissolution test. The individual data from Clinical Study #57-3001 and from PK Study #GLY01/93 met the criteria of no single unit less than Q+5%. However, the individual data from one batch of BSZ used in Clinical Study #CP099301 did not meet the specification, as 2/6 capsules revealed —— dissolution.

X. ASSAY:

The sponsor has provided the following analytical studies:

Validation Study	PK Study	Analyte	Biological Matrix
#1067/35 (8/25/92-12/13/93)	20060 20061 GLY01/93	BSZ and metabolites BSZ and metabolites Metabolites only	Plasma and urine Plasma and urine Plasma and urine
#1067/36 (11/11/92-12/17/93)	20060	SSZ, SP, and NASP	Plasma and urine
#1067/47 (7/9/93-1/14/94)	20060 20061	BSZ and metabolites BSZ and metabolites	Feces Feces
#1067/50 (11/10/93-9/23/94)	GLY01/93	BSZ	Plasma
#1067/52 (5/12/94-9/16/94)	GLY01/93	BSZ	Urine

These validation studies were all performed by [redacted] An [redacted] for BSZ, ABA, and NABA and fluorescence detection for ASA and NASA. In addition, an [redacted] was used for the determination of SSZ, SP, and NASP in plasma and urine.

Several pitfalls were apparent in the methods and results of these studies. One of the primary points for concern was the exclusion of an internal standard from the workup procedure, particularly in Study #1067/35. The resulting validation parameters were applied to PK Studies #20060 and #20061. The sponsor attempts a lengthy justification for not including an internal standard, and claims that its use may actually be detrimental to the precision and accuracy of the assay. [redacted]

a[redacted]

There were numerous other concerns with regards to each of the five validation studies and the primary ones are outlined below.

Study #1067/35 -

Plasma:

1. Poor precision at LOQs for BSZ, ASA, and NASA.
2. Chromatographic issues of concern included analyte peaks which eluted off adjacent peaks, peaks which were poorly formed at assay LOQs, or unstable baselines.

Urine:

1. No stability testing performed at LOQ.
2. Poor recoveries of metabolites at 100 µg/ml.

Study #1067/36 -

Result of this study were generally acceptable.

Study #1067/47 -

1. Poor accuracy and precision at BSZ assay LOQ.
2. No recovery, freeze/thaw, or stability data at BSZ assay LOQ.
3. Numerous problems with accuracy, precision, recovery, and stability for all metabolites.
4. Interfering peak in blank chromatogram at BSZ elution time.
5. NABA peak had adjacent interfering peak.

Study #1067/50 -

1. Poor precision at assay LOQ.
2. Poor accuracy for some calibration curve samples.
3. Low recoveries for QC standards.
4. No stability data

Study #1067/52 -

1. Poor precision at assay LOQ.
2. No stability data.

The analytical assay validation package as submitted in the NDA was consulted to [redacted] His report includes detailed results for each analyte in each assay and can be located in Appendix III, "Assay Validation Consult." Overall, it appears that BSZ cannot be accurately quantitated in plasma below concentrations of 20 ng/ml. This is the most likely explanation for the high variability observed in the plasma data and the inability to adequately characterize the plasma concentration vs time profiles in PK Studies #20060 and #20061. The results of PK studies where compounds are observed in low concentrations, and for which the corresponding assay has poor precision and accuracy at the LOQs, should be viewed with caution. Quantitative results will be tenuous, therefore, the data may be best described and interpreted in a qualitative manner.

GENERAL COMMENTS (need not be sent to the firm):

[redacted]

Number of Pages Redacted 4

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Draft Labeling
(not releasable

APPENDIX I

Study I: #20060 - Single-dose study in healthy subjects.

Study II: #20061 - Multiple-dose study in healthy subjects.

Study III: #GLY01/93 - Multiple-dose study in UC patients.

TITLE: A Comparative Tolerability and Pharmacokinetic Study of Balsalazide Sodium (Colazide®), Sulfasalazine (Salazopyrin®), and Mesalazine (Asacol®) following a single oral dose.

Study Number: 20060

Investigator and Site: Dr. J. Riddell, Harris Laboratories, Ltd.

Study Dates: September 2-22, 1992.

Abbreviations used: BSZ = Balsalazide
ASA = 5-aminosalicylic acid
NASA = N-acetyl-5-aminosalicylic acid
ABA = 4-aminobenzoyl-β-alanine
NABA = N-acetyl-4-aminobenzoyl-β-alanine
SSZ = sulfasalazine
SP = sulfapyridine
NASP = N-acetylsulfapyridine
MSZ = mesalazine
PK = pharmacokinetics
Cl_R = renal clearance

OBJECTIVES:
1. To evaluate the absorption, disposition, and elimination of single doses of BSZ.
2. To compare the disposition of BSZ with that of established treatments for ulcerative colitis (SSZ and MSZ).

METHODS:
Study Design:
This study was composed of two arms; the first compared BSZ and SSZ and the second compared BSZ with MSZ. Each arm was an open, randomized, two-way crossover study with a one week washout period.

Study Population:
Twenty-four healthy, adult, male volunteers.

Treatment and Administration:
The 24 subjects were divided into two groups, Group A (Sub. 1-12) and Group B (Sub. 13-24). The following treatments were determined by a balanced, randomized design:

Group A: Six of the subjects received a single dose of BSZ followed by a single dose of SSZ. The two doses were separated by a 13-day washout period. The other six subjects underwent the

same treatment except that they received the single dose of SSZ prior to the single dose of BSZ.

Group B: Six of the subjects received a single dose of BSZ followed by a single dose of MSZ.

The two doses were separated by a 13-day washout period. The other six subjects underwent the same treatment except that they received the single dose of MSZ prior to the single dose of BSZ.

Of the 24 subjects, all 24 received BSZ, 12 received SSZ, and 12 received MSZ.
The molar dose of ASA (the therapeutic active moiety) from each study drug was intended to be as close as possible to that contained in the proposed clinical dose for BSZ (3 x 750 mg capsules). The study drugs were taken 30 minutes after a standardized breakfast as follows:

BSZ - 3 x 750 mg capsules (5.14 mmole ASA)
SSZ - 4 x 500 mg tablets (5.02 mmole ASA)
MSZ - 2 x 400 mg tablets (5.22 mmole ASA)

Administration of a single dose of the study drug took place at 8:00 AM on Day 1. Blood, urine, and fecal samples were collected over the next four days for PK analyses. Standard meals and drinks were provided from the eve of Day 1 until the end of Day 4 at predesignated times. Subjects were not permitted to consume any alcohol or caffeine-containing beverages for 24 hours prior to nor throughout the study duration. A detailed Study Plan can be found in the Appendix.

Study Drug Supplies:

Generic name	Balsalazide disodium (BSZ)	Sulfasalazine (SSZ)	Mesalazine (MSZ)
Trade name	Colazide®	Salazopyrin®	Asacol®
Dosage form	750 mg capsule	500 mg tablet	400 mg tablet
Lot number	2814	SE44345	245/507
Expiry date	August 1995	May 1997	September 1997
Manufacturer	Biorex Lab., Limited	Kabi Pharmacia, Limited	Smith, Kline, and French Lab.

Biological Sampling:
1. Blood - samples were collected immediately before and at 1, 2, 4, 6, 8, 10, 12, 14, 24, 30, 36, 48, 72, and 96 hours after drug administration.
2. Urine - samples were collected over the following intervals: 0-4 hr, 4-8 hr, 8-12 hr, 12-16 hr, 16-24 hr, 24-36 hr, 36-48 hr, 48-72 hr, and 72-96 hr.
3. Feces - collections were made of all feces voided between the eve of study drug administration and 96 hours post-dose.

Pharmacokinetic Analysis:
As the elimination profiles for most of the analytes was erratic, the PK analyses were limited to the following parameters for BSZ and it metabolites (ASA, NASA, ABA, and NABA), SSZ and

its metabolites (ASA, NASA, SP, and NASP), and MSZ (ASA and NASA):
1. Cmax - maximum observed plasma concentration
2. tmax - time to Cmax
3. AUC_{last} - area under the plasma concentration time curve from time 0 to the time of the last quantifiable concentration
4. %Dose excreted in the urine - 100*amount excreted in the urine/dose corrected for the molecular weight of the compound
5. %Dose excreted in the feces - 100*amount excreted in the feces/dose corrected for the molecular weight of the compound
6. Cl_R - renal clearance computed as amount of drug excreted in the urine/plasma AUC over the collection interval.

Statistical Analysis:
Summary statistics were presented for demographic data and adverse events. The incidence of adverse events was compared using Fisher's exact test.

Plasma, urine and fecal concentrations and computed parameters were listed and summarized by dose (mean, SD, minimum, and maximum). Mean and individual plasma concentrations versus time curves were plotted for each dose.

Statistical analyses were performed using the SAS procedure, PROC GLM. Analysis of the computed kinetic parameters for ASA and NASA (common to all three treatments) was carried out with an ANOVA model appropriate for a crossover design. The model included terms for treatment, sequence, period, and subject within sequence. The analyses were performed for Groups A and B independently of one another. A p value of ≤ 0.05 was considered to be statistically significant.

Analytical Methods:

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