CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205613Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM to OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 205613	Supporting document: 0050 Applicant's letter Date: 08/26/2014
Submission Type; Code	505 (b)(2); Standard Review
Brand Name	Uceris Rectal Foam
Generic Name	Budesonide rectal foam
Reviewers	Dilara Jappar, Ph.D., Doanh Tran, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Sponsor	Salix Pharmaceuticals, Inc
Formulation; Strength(s)	Rectal Foam, 2 mg
Proposed Indication	Induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge
Proposed Dosing Regimen	2 mg BID for 2 weeks followed by 2 mg QD for 4 weeks

Background:
The sponsor originally submitted NDA 205613 (Uceris Rectal Foam) as a 505(b)(1) application. However, in some nonclinical and clinical pharmacology sections of the proposed label for Uceris Rectal Foam, the sponsor has relied on information in the Entocort label and Uceris tablet label. In addition, the sponsor has not conducted any relative bioavailability (BA) study comparing the exposure of Uceris 2 mg rectal foam to that of oral Entocort or Uceris tablet. On August 15, 2014, at the request of FDA, the sponsor amended NDA 205613 from a 505(b)(1) to 505(b)(2) application in order to reference Entocort® Capsule and Uceris® tablet labels and published literature. Note that the application for Uceris oral tablets (NDA 203634) is a 505(b)(2) submission referencing Entocort Capsules (NDA 21324).

On August 26, 2014 the sponsor submitted their scientific justification for this 505(b)(2) application to utilize the findings in Entocort capsules, Uceris tablets, and available published literature.

Summary and Evaluation:

Sponsor's justification: The sponsor claims that the data referenced in support of the Uceris Rectal foam application are scientifically relevant due to the comparable or greater systemic exposures in studies cited to describe clinical pharmacology section of the Entocort or Uceris tablet label as compared to doses and exposures for Uceris Rectal foam.

The sponsor compared the exposure of Uceris Rectal foam to that of Entocort and Uceris tablet. According to the Entocort PI, Cmax of Entocort EC in healthy volunteers is approximately 5 nmol/L (1.78 ng/ml) with an exposure (AUC) of approximately 30 nmol.hr/L (10.7 ng.hr/L). According to Uceris tablet label, Cmax of Uceris tablet was 1.35 ng/mL and AUC was16.43 ng.hr/mL in healthy subjects. Based on population PK analysis from phase 3 data, mean budesonide AUC0-12h in the target patient population following administration of Uceris Rectal foam 2 mg BID was estimated to be 4.31 ng*hr/mL. (b) (4)

Reviewer's comments: The above comparisons of systemic exposure are cross-study comparisons and there are no studies to compare head-to-head the bioavailability between Uceris rectal foam and either Entocort or Uceris oral tablets. As such, we disagree with the sponsor that (b) (4) However, the data showed that the systemic exposure for these dosage forms are most likely to be in the same order of magnitude and the information in the proposed label for Uceris rectal foam that relies on Entocort label such as metabolism, distribution, excretion, use in specific populations and drug-drug interaction is appropriate. Note that this review pertains only to the clinical pharmacology information referenced from Entocort or Uceris tablet labels. The justification for nonclinical information is reviewed by the Pharmaoclogy/Toxicology reviewer of DGIEP.

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/s/

DILARA JAPPAR
09/08/2014

SUE CHIH H LEE
09/08/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205613	**Reviewer:** Kelly M. Kitchens, Ph.D.	
Submission Date:	November 15, 2013		
Division:	Division of Gastroenterology and Inborn Errors Products	**Team Leader:** Tapash Ghosh, Ph.D.	
Applicant:	Salix Pharmaceuticals, Inc.	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	Budesonide	**Date Assigned:**	November 20, 2014
Established Name:	TBD	**Date of Review:**	July 29, 2014
Indication:	Induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.	**Type of Submission:** NDA 505(b)(1)	
Formulation/ strengths	Foam/2 mg		
Route of Administration	Rectal		
Type of Review:	In Vitro Release Test Method and Acceptance Criteria		

SUMMARY:

Background: On November 15, 2013, Salix Pharmaceuticals, Inc. submitted NDA 205613 for Budesonide Rectal Foam. Budesonide is a high potency corticosteroid that exhibits a high ratio of topical to systemic activity. Budesonide was developed to minimize the systemic adverse consequences of first generation corticosteroids (e.g. hydrocortisone). The rectal foam formulation was specifically designed to improve both the patient's ability to retain the drug in the rectum following administration as well as distribution of the active drug to the rectum and sigmoid colon. Rectally administered budesonide foam is designed to address the potential limitations of oral budesonide formulations (i.e., the ability to deliver drug adequately to the rectum and sigmoid colon); and other topical steroid enema treatments (i.e., the ability of patients to retain the liquid). Budesonide foam is approved in Europe for the treatment of distal ulcerative colitis.

There was no Biopharmaceutics-related information included in original submission of this NDA. However, the following recommendation was submitted to the Applicant on January 17, 2014 via e-mail as an Information Request (IR):

We suggest that you propose an in vitro release acceptance criterion (range) based on a developed in vitro release test (IVRT) methodology for your product at release and during stability as a quality control parameter. Your proposed acceptance criterion should

be based on generated data on the final to be marketed batches.

Submission: On February 14, 2014, the Applicant submitted the following response to the IR:

Salix agrees to develop and validate an in vitro release rate testing procedure for Budesonide 2 mg Rectal Foam with anticipated completion of that activity in June 2014. Salix will use the validated procedure to test three process validation batches currently scheduled for production immediately after approval of the marketing application. Those batches represent the first to be marketed batches. As those data will not be available until after approval of the NDA and since they represent a limited population of drug product batches, Salix proposes to submit acceptance criterion for the new in vitro release test approximately two months after the first anniversary of the approval of the NDA. At that time, Salix will have collected release data from drug product manufactured during the first twelve months of commercial production along with approximately 12 months of stability data for the first three commercial batches of drug product. Those data will better represent batch-to-batch variability of drug product manufactured with the validated manufacturing process while also providing information on drug release performance during storage of the drug product under long-term storage conditions, data that does not currently exist at this time.

On May 12, 2014, the following additional IR was submitted to the Applicant:

We acknowledge your agreement to develop and validate an in vitro release test (IVRT) procedure, with an anticipated completion date of June 2014. We also acknowledge your proposal to develop acceptance criterion based on IVRT data generated for the final to-be-marketed batches post-approval of the NDA. The IVRT method development report and validation reports should be submitted to the Agency for review.

The IVRT method development report should contain (but is not limited to) justification for the selection of the following methodology components:

a. (b) (4)
b.
c.
d.
e.

The IVRT method validation report should contain (but is not limited to) the following validation components:

a. (b) (4)
b.
c.
d.
e.
f.
g.

h. (b) (4)

On July 8, 2014, the Applicant submitted the following response to the IR:

An in vitro release rate testing (IVRT) procedure for Budesonide 2 mg Rectal Foam has been developed and fully validated. Salix document METH-VALRPT-184 describes the activities surrounding the development of the procedure and the results of the validation of the method. The method presented therein will be implemented at (b) (4) *and used for the testing of drug product process validation and future commercial batches of drug product. This method will also be added to ongoing and future stability studies for the drug product. Salix will submit acceptance criterion for the new in vitro release test approximately two months after the anniversary of the approval of the NDA. At that time, Salix will have collected release data from drug product manufactured during the first twelve months of commercial production along with approximately 12 months of stability data for the first three commercial batches of drug product. Those data will better represent batch-to-batch variability of drug product manufactured with the validated manufacturing process while also providing information on drug release performance during storage of the drug product under long-term storage conditions, data that does not currently exist at this time.*

Review: The Biopharmaceutics review is focused on the evaluation of the proposed IVRT method. However, the review of the proposed IVRT method and acceptance criteria is ongoing.

RECOMMENDATION:
There are no approvability issues for NDA 205613 from a Biopharmaceutics perspective.

Signature
Kelly M. Kitchens, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. RLostritto.

BIOPHARMACEUTICS ASSESSMENT

Drug Product:

- Budesonide 2 mg Rectal Foam is an aerosol foam delivered by a disposable, (b) (4) dose metering, multi-dose canister. The drug product formulation is a (b) (4) emulsion. The emulsion is filled into a 54-mL, white, aluminum (b) (4) canister (b) (4)
- Each canister is fitted with a 1-inch metered-valve system consisting of a (b) (4) valve body and stem. A propellant consisting of propane, isobutane, and butane is added to the (b) (4) can before a 1.35-mL dispenser head and a (b) (4) foam shield are installed.
- Each multi-dose canister delivers fourteen 1.35-mL doses of foam product (equivalent to 2 mg budesonide per dose) and will be provided with 14 single-use, disposable, white, polyvinyl chloride rectal applicators. Each applicator is pre-coated with paraffin lubricant and stored in a protective, white, (b) (4) tray (7 applicators per tray). Plastic bags are included in the secondary packaging for safe and hygienic disposal of the used applicators.
- The drug composition is described in the following table:

Table 1: Components and Composition of Budesonide 2 mg Rectal Foam in Metered-dose Canisters

Ingredient	Quality Standard	Function	Quantity per Dose (mg)	Quantity per Can (mg)[a]	Concentration (% w/w)
Drug Product Emulsion					
Budesonide	USP	Active Ingredient	2.0	(b) (4)	
Propylene Glycol	USP	(b) (4)			
Cetyl Alcohol	NF				
Emulsifying Wax	NF				
Polyoxyl (10) Stearyl Ether	NF				
Purified Water	USP				
Edetate Disodium	USP				
Citric Acid Monohydrate	USP				
(b) (4)					
Total Emulsion Weight:	---				
Drug Product Propellant[b]					
Propane	NF	Propellant		(b) (4)	(b) (4)
Isobutane	NF	Propellant			
Butane	NF	Propellant			
Total Theoretical Weight:	---	---			100.0%

Abbreviations: Can = Canister, NA = not applicable, NF = (United States) National Formulary, USP = United States Pharmacopeia

[a] The canister delivers 14 doses (2 mg of budesonide per dose) but is filled with an overfill to ensure the accuracy of each delivered dose.

[b] The drug product propellant, (b) (4) is a mixture of butane, NF, isobutane, NF and propane, NF combined at a molar ratio of (b) (4) respectively. Each of the components meets its respective NF quality standard.

In Vitro Release Testing (IVRT) Method Development and Validation:

IVRT Method Development:

(b) (4)

(b) (4)

(b) (4)

Reviewer's comments on IVRT method development and validation:

- On August 6, 2014, the following Information Request (IR) was submitted to the Applicant:
  We are concerned with (b) (4)

  Please revise your IVRT method with one of the suggested revisions to the sample preparation. You may submit your revised IVRT method for review before embarking on the new method.

  Provide us with a timeline to complete the new IVRT method and submission of your results.

- The Applicant provided the following response on August 8, 2014:
  Salix will identify and validate a new IVRT sample preparation technique with the intent of (b) (4) *Salix will then update the IVRT method with the optimal*

technique and provide it and supporting method validation information to FDA by December 15, 2014. The updated method will be implemented at (b) (4) *after Salix is notified of FDA's concurrence and will be used to test all available validation and distributed commercial batches of the drug product as well as all future commercial batches. This method will also be added to ongoing and future stability studies for the drug product. Salix continues to commit to submitting an acceptance criterion for the new in vitro release test approximately two months after the anniversary of the NDA approval.*

- The Applicant's proposal to revise their sample preparation procedures for the IVRT method is acceptable.

In Vitro Release Acceptance Criteria

- The Applicant indicated they would submit acceptance criteria approximately 2 months after the anniversary of the approval of the NDA. This is to provide release data from drug product manufactured during the first 12 months of commercial production, along with approximately 12 months of stability data for the first three commercial batches of drug product, since information on the drug product batch-to-batch variability and drug release performance during storage does not currently exist at this time.
- The Applicant's proposal for establishing acceptance criteria is acceptable, and the acceptability of the proposed IVRT method and acceptance criteria will be evaluated post-approval.

Recommendation:

There are no approvability issues for NDA 205613 from a Biopharmaceutics perspective.

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/s/

KELLY M KITCHENS
08/19/2014

TAPASH K GHOSH
08/19/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 205613	Submission Date(s): 11/15/2013, 02/05/2014, 02/27/2014, 07/18/2014, 07/22/2014, 07/28/2014
Submission Type; Code	505 (b)(2); Standard Review
Brand Name	Uceris Rectal Foam
Generic Name	Budesonide rectal foam
Reviewers	Dilara Jappar, Ph.D., Doanh Tran, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
PM Reviewer:	Justin Earp, Ph.D.
PM Team Leader:	Nitin Mehrotra, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Sponsor	Salix Pharmaceuticals, Inc
Formulation; Strength(s)	Rectal Foam, 2 mg
Proposed Indication	induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge
Proposed Dosing Regimen	2 mg BID for 2 weeks followed by 2 mg QD for 4 weeks
PDUFA Goal Date:	09/15/2014

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1 Executive Summary

Budesonide rectal foam is a new dosage form of budesonide with the proposed indication of induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge. Currently, there are various approved budesonide formulations available on the market for other indications including inhalation, nasal, and oral capsule and tablet formulations. Hereinafter, Uceris rectal foam may be referred to as budesonide rectal foam.

In support of this application, the sponsor has submitted two Phase 1 studies, one Phase 2 and five Phase 3 studies. In addition, the sponsor had also evaluated budesonide rectal foam's potential to suppress HPA axis in the two pivotal phase 3 studies (Studies BUCF 3001 and BUCF 3002) by evaluating the morning cortisol levels and conducting ACTH stimulation tests.

The sponsor relies on Entocort label for most of its nonclinical and clinical pharmacology sections of their proposed label, making this NDA application a 505(b)(2) application. However, the sponsor did not conduct any relative bioavailability (BA) study comparing the exposure of budesonide 2 mg rectal foam to that of oral Entocort. Nonetheless, these two products can be bridged scientifically without a direct relative BA study for the following reasons:

- These products have different routes of administration, they will not be interchangeable.
- Most of the information in the proposed label for Uceris rectal foam that relies on Entocort label such as metabolism, distribution, and excretion is drug substance specific and independent of budesonide exposure.
- Safety and efficacy of budesonide rectal foam was established based on two pivotal phase III studies (Studies BUCF 3001 and BUCF 3002) and one long term safety trial.

1.1 Recommendation

The application is acceptable from a clinical pharmacology perspective provided that a mutual agreement between the FDA and the sponsor can be reached on the labeling languages.

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Dose Selection Rationale:
The proposed dosing regimen is 2 mg BID for 2 weeks followed by 2 mg QD for 4 weeks.
The sponsor had conducted a phase 2b dose finding study (BUF-5/UCA) where 2 mg BID dosing regimen of budesonide rectal foam yielded more favorable treatment effect compared to that of placebo and 2 mg QD dosing (4 mg/day (BID)> 2 mg/day(QD) > placebo) . Supportive phase 3 studies (BUF-9/UCA and BUF-6/UCA) have shown that majority of subjects experienced maximum treatment response after the first 2 weeks of treatment. Thus, the sponsor considers it reasonable to have a dosing regimen of 2 mg BID for the first 2 weeks followed by a reduced dose of 2 mg QD for 4 weeks. This dosing regimen was tested in the pivotal Phase 3 trials and found to be safe and efficacious.

Single-Dose and Multiple Dose PK:
Both single dose and multiple doses PK of budesonide 2 mg rectal foam were evaluated in healthy subjects in this application (study BUF-7/BIO). However, since the stability of budesonide in the serum PK samples under the storage conditions was not properly established in

this study, it is difficult to interpret the result of this PK study. Therefore, the PK parameters from this study will not be reflected in the label.

Population PK Analysis:
The sponsor had collected sparse PK samples in two phase 3 studies (study BUCF 3001 and 3002) and conducted population PK analysis. Following administration of budesonide rectal foam 2 mg BID, mean budesonide $AUC_{0\text{-}12h}$ in the target patient population was estimated to be 4.31 ng*hr/mL with a CV of 64%.

Hypothalamic pituitary adrenal (HPA) axis suppression
Adrenocorticotropic hormone (ACTH) stimulation test was performed in two Phase 3 trials where budesonide rectal foam was administered for 6 weeks. For the combined data from the two trials, 83.5% of subjects in the budesonide foam group had a normal response to the ACTH challenge at baseline and at Week 6, 68.5% of subjects had a normal response to the ACTH challenge for a difference of 15.0%; in the placebo group, these values were 85.6% and 76.6%, respectively, for a difference of 9.0%. If one takes into account subjects who were discontinued prior to week 6 due to reasons related to HPA axis suppression, the baseline vs. week 6 rates were 83.5% and 62.7% for budesonide and 85.6% and 75.9% for placebo; A larger difference was seen (a decrease of 20.8% for budesonide vs a decrease of 9.7% for placebo).

Assessment of drug interaction potential: In vitro evaluation of Cytochrome P450 and transporters

The sponsor has conducted several in vitro studies to assess the drug interaction potential for budesonide rectal foam. Aside from the known interaction with CYP3A inhibitors, the new data did not reveal any potential for significant metabolism or transporter-mediated drug-drug interactions in vivo.

Based on in vitro results showing IC50 >1130 ng/mL, budesonide rectal foam at therapeutic concentration is not expected to inhibit CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 in vivo. No data is available for CYP2C8 and CYP2C19. Based on in vitro results showing little or no effect of budesonide concentration up to 9000 nM (3875 ng/mL) on the activity or messenger RNA (mRNA) expression of CYP1A2, CYP2B6, CYP2C9, and CYP3A4, budesonide rectal foam at therapeutic concentration is not expected to induce CYP enzymes in vivo.
In vitro studies showed that budesonide is not a substrate of BCRP and a weak substrate of P-gp. Budesonide was a weak inhibitor of P-glycoprotein (IC_{50} 9.78 µM or 4.21 µg/mL) and BCRP (IC_{50} 43.1 µM or 18.6 µg/mL). Based on these IC50 values, budesonide foam is not expected to inhibit these transporters in clinical use.
In vitro studies showed that budesonide is not a substrate of OATP1B3. The results were inconclusive for OATP1B1 and suggested that budesonide is either not a substrate of OATP1B1 or a weak substrate of OATP1B1. Budesonide at concentrations up to 300 nM did not inhibit OATP1B1 or OATP1B3. Budesonide foam is not expected to inhibit these transporters in clinical use.

Pediatric Studies:
The sponsor has sought a waiver for pediatric population 0 to <5 years of age and a deferral for 5-(b)(4) years of age. However, PREA does not appear to apply to this indication so the sponsor may not be required to conduct pediatric studies. There will be further discussions on this matter.

2 Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA

Type of Study	Study Identifier	Objective(s) of the Study	Study Design/Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Healthy Subjects or Diagnosis of Patients
PK/PD	BUF-7/BIO (Dr Falk)	Evaluation of the single- and multiple-dose pharmacokinetics and pharmacodynamics of budesonide 2 mg rectal foam (Budenofalk foam)	Prospective, open-label, single-center, phase 1, PK, and PD study with 5 days treatment	Budesonide 2 mg rectal foam once daily	18 Healthy adults
PK	BUF-4/BIO (Dr Falk)	Evaluation of the spread, retention, pharmacokinetics, acceptance, safety, and tolerability of ^{99m}Tc-labeled budesonide rectal foam (Budenofalk foam)	Prospective, single dose, open-label, single-center, phase 1, PK study	Single dose of ^{99m}Tc-labeled budesonide 2 mg rectal foam	12 Mild to moderate active ulcerative colitis
Combined PK/PD	Population pharmaco-kinetics report (Salix)	Development of a population pharmacokinetic model for budesonide 2 mg rectal foam	Pharmacokinetic and pharmacodynamic modeling of budesonide was performed using data from studies BUF-7/BIO, BUF-4/BIO, BUCF3001, and BUCF3002 with up to 6 weeks of treatment	Budesonide 2mg rectal foam or was administered as described for studies BUF-7/BIO, BUF-4/BIO, BUCF3001, and BUCF3002	145 Mild to moderate active ulcerative colitis (12 subjects); mild to moderate active ulcerative proctitis or proctosigmoiditis (115 subjects); healthy adults (18 subjects)
Drug interac-tions	BUDM0102 (Salix)	In vitro evaluation of budesonide as an inhibitor of CYP enzymes	In vitro assays of CYP enzymes/ positive and negative control inhibitors with 5 minutes of incubation time	Budesonide dissolved in DMSO	Human microsomes isolated from 16 individuals
Drug interac-tions	BUDM0103 (Salix)	In vitro evaluation of budesonide as an inducer of CYP enzymes	In vitro assays of CYP enzymes/ positive and negative control inducers with 3 days of incubation time	Budesonide dissolved in DMSO and then diluted further in hepatocyte growth media	Human hepatocytes isolated from 3 individuals

Drug interac-tions	BUDM0104 (Salix)	In vitro evaluation of budesonide as an inhibitor and substrate of transporter proteins	In vitro assays of substrate transport/ positive and negative control inhibitors or substrates of transporter proteins with 120 minutes of incubation	Budesonide dissolved in DMSO and then diluted further in cell growth media	Caco-2 cells (human colon carcinoma cells), MDCKII-BCRP cells (canine kidney cells), and HEK293 cells

In addition to the above clinical pharmacology studies, the sponsor had also conducted 1 phase II study (BUF-5/UCA with Dr. Falk formulation), two Phase III studies with Dr. Falk formulation (studies BU-6/UCA and BUF-9/UCA) and three phase III clinical studies with Salix formulation (studies BUCF 3001, BUCF 3002 and BUPS3073) in mild to moderate active ulcerative proctitis or proctosigmoiditis patient population.

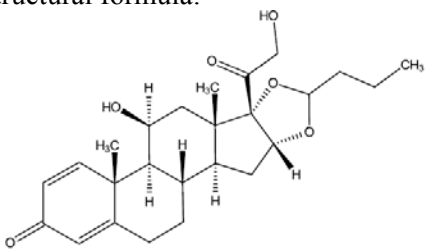
Plasma levels of budesonide were measured in two phase 3 studies (BUCF 3001 and BUCF 3002) via sparse PK sampling. A new population PK analysis was conducted by the sponsor after the original NDA submission because data from the two Phase 1 studies are not interpretable. The new population PK analysis just based on the phase 3 sparse PK samples provided the PK information that will be reflected in the label.

2.2 General Attributes

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug products?

Drug Substance:

- Name: Budesonide
- Chemical formula: $C_{25}H_{34}O_6$
- Molecular Weight: 430.5 g/mol
- Structural formula:



Formulation:

Budesonide 2 mg Rectal Foam is an aerosol foam delivered by a disposable, [redacted] (b) (4) dose metering, multi-dose canister. The drug product formulation is an emulsion which is filled into an aluminum canister with aerosol propellant. Each multi-dose canister delivers fourteen 1.35-mL doses of foam product (equivalent to 2 mg budesonide per dose).

Budesonide 2 mg rectal foam was initially developed by Dr. Falk Pharma and received marketing approval in Europe in 2006 (referred as Dr Falk formulation or also referred to as Budenofalk rectal foam in the submission). After [redacted] (b) (4) was removed from Dr. Falk Pharma formulation

and replaced by [redacted], the new formulation was transferred to [redacted] in USA to produce the drug product for Salix-sponsored Phase 3 studies, BUCF3001 and BUCF3002. The new formulation is referred as Salix formulation in this submission.

Table 1. Components and Composition of Budesonide 2 mg Rectal Foam in Metered-dose Canisters

Ingredient	Quality Standard	Function	Quantity per Dose (mg)	Quantity per Can (mg)[a]	Concentration (% w/w)
Drug Product Emulsion					
Budesonide	USP	Active Ingredient	[redacted]	[redacted]	[redacted]
Propylene Glycol	USP	[redacted]			
Cetyl Alcohol	NF				
Emulsifying Wax	NF				
Polyoxyl (10) Stearyl Ether	NF				
Purified Water	USP				
Edetate Disodium	USP				
Citric Acid Monohydrate	USP				
[redacted]	[redacted]				
Total Emulsion Weight:	---	---			
Drug Product Propellant[b]					
Propane	NF	Propellant			
Isobutane	NF	Propellant			
Butane	NF	Propellant			
Total Theoretical Weight:	---	---		[redacted]	100.0%

Abbreviations: Can = Canister, NA = not applicable, NF = (United States) National Formulary, USP = United States Pharmacopeia

[a] The canister delivers 14 doses (2 mg of budesonide per dose) but is filled with an overfill to ensure the accuracy of each delivered dose.

[b] The drug product propellant, [redacted] is a mixture of butane, NF, isobutane, NF and propane, NF combined at a molar ratio of [redacted] and [redacted] respectively. Each of the components meets its respective NF quality standard.

2.2.2 What is the proposed indication?

The proposed indication for budesonide rectal foam is induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.

2.2.3 What are the proposed mechanisms of actions?

The proposed mechanism of action of budesonide is that it has a glucocorticoid effect.

2.2.4 What are the proposed dosage and route of administration?

The proposed dosage is 1 metered dose (2 mg/ metered dose) administered rectally twice daily for 2 weeks followed by 1 metered dose administered once daily for 4 weeks.

2.2.5 What is the regulatory background?

Entocort EC is capsule oral formulation of budesonide for treatment of mild to moderate Crohns' disease. Oral Uceris 9 mg tablet was approved on 2013 for ulcerative colitis via 505(b)(2) pathway referencing Entocort EC capsule. In that submission for oral Uceris, in addition to two phase III studies to demonstrate the safety and efficacy, the sponsor had also conducted relative

BA study comparing oral Uceris 9 mg exposure to that of Entocort EC capsule to bridge these two products.

Budesonide 2 mg rectal foam (also referred to as Budenofalk rectal foam in the submission) was developed by Dr. Falk Pharma and received marketing approval in Europe in 2006. After (b) (4) was removed from Dr. Falk Pharma formulation and replaced (b) (4) the new formulation (also referred as Salix formulation) was transferred to (b) (4) in USA to produce the drug product for Salix-sponsored Phase 3 studies, BUCF3001 and BUCF3002.

This NDA application was originally submitted as 505(b)(1) application, and sponsor had conducted two phase 3 studies to demonstrate safety and efficacy of Uceris rectal foam. However, since the applicant had relied on Entocort oral label for nonclinical and clinical pharmacology sections of their proposed label for Uceris rectal foam, the sponsor was requested to change the submission type from 505(b)(1) to 505(b)(2).

However, the sponsor did not conduct a relative bioavailability (BA) study comparing the exposure of budesonide 2 mg rectal foam to that of oral Entocort. This issue was discussed with DCP3 management and it was determined that these two products can be bridged scientifically without a direct relative BA study.

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The budesonide rectal foam clinical development program is consisted of 5 clinical studies with Dr. Falk formulation (two Phase I studies, one Phase II studies, and two phase III studies) and three Phase III studies (including two adequate and well-controlled studies) with Salix formulation with sparse PK samples. In addition, the sponsor had conducted one population PK analysis.

Studies with Dr Falk Formulation:

Phase I studies:

- Study BUF-7/BIO was a prospective, open-label, single-center, phase-1 PK/PD study in 18 healthy subject to evaluate single and multiple dose (5 days dosing) PK of budesonide 2 mg rectal foam with Dr Falk formulation

- Study BUF-4/BIO was a prospective, open-label, single-center, phase 1 PK study in 12 mild to moderate active ulcerative colitis patient to evaluate the spread, retention, pharmacokinetic, acceptance, safety and tolerability of ^{99m}Tc-labeled budesonide 2 mg rectal foam with Dr Falk formulation

Phase II studies:

- BUF-5/UCA was randomized, double-blind, placebo-controlled, multicenter, phase 2b, dose finding study in 223 mild to moderate active ulcerative proctitis or proctosigmoiditis patients

to evaluate the efficacy and safety of 2 doses (QD vs. BID) of budesonide 2 mg rectal foam (Budenofalk foam) compared to placebo foam over 6 weeks of treatment

Phase III studies:

- BUF-6/UCA was randomized, active-controlled, open-label, parallel group, multicenter, phase 3 studie in 251 mild to moderate active ulcerative proctitis or proctosigmoiditis patients to evaluate the comparative efficacy and safety of budesonide 2 mg rectal foam (Budenofalk foam) QD and hydrocortisone 100 mg rectal foam (Colifoam) QD over 8 weeks of treatment

- BUD-9/UCA was randomized, double-blinded, double-dummy, active-controlled, parallel group, multicenter, phase 3 study in 541 mild to moderate active ulcerative proctitis or proctosigmoiditis patients to evaluate the comparative efficacy and safety of budesonide 2 mg rectal foam (Budenofalk foam) QD and budesonide 2 mg enema (Entocort) QD over 4 weeks of treatment

Studies with Salix Formulation:

- BUCF 3001 and BUCF 3002 (identical in study design) were randomized, double-blind, placebo-controlled, parallel group, multicenter, phase 3 studies in 265-281 mild to moderate active ulcerative proctitis or proctosigmoiditis patients to evaluate the efficacy and safety of budesonide 2 mg rectal foam compared to placebo foam where patients were treated with budesonide 2 mg rectal foam or placebo foam twice daily for 2 weeks followed by once daily for 4 weeks (total of 6 weeks of treatment).

- BFPS3073 was open-label, long-term multicenter phase 3, extension safety study in 108 mild to moderate active ulcerative proctitis or proctosigmoiditis patients to evaluate the long-term safety and tolerability of budesonide 2 mg rectal foam in subjected who completed BUCF3002 or BUCF 3002 and had active ulcerative proctitis or proctosigmoiditis

2.3.2 What was the clinical endpoint in the Phase 3 trials?

The primary endpoint in the BUCF3001 and BUCF3002 was the proportion of subjects who achieved remission with budesonide foam, as compared to an equivalent volume/regimen of placebo foam administered over 6 weeks (2 mg BID for 2 weeks followed by 2 mg QD for 4 weeks) in subjects with a diagnosis of active mild to moderate UP or UPS. Remission was defined as an endoscopy score of ≤ 1, a rectal bleeding score of 0, and an improvement or no change from baseline in stool frequency subscales of the Modified Mayo Disease Activity Index (MMDAI) at the end of 6 weeks of treatment.

2.3.3 What were the results of phase 3 trials?

The sponsor claims that in each study and in pooled analyses of these studies, budesonide was statistically superior to placebo for the primary endpoint. Larger proportions of subjects treated with budesonide 2 mg foam, compared with subjects treated with placebo foam, achieved remission at the end of 6 weeks of treatment in each study independently and in pooled data. The treatment differences were statistically significant in favor of budesonide foam treatment in BUCF3001 (38% vs. 26%, $\Delta = 12\%$, $p = 0.0322$), BUCF3002 (44% vs. 22%, $\Delta = 22\%$, $p < 0.0001$), and in the pooled data (41% vs. 24%, $\Delta = 17\%$, $p < 0.0001$) for the Intent-to-Treat (ITT) population. Medical Reviewers, Drs. Zana Marks and Anil Rajpal (team leader) agreed with the above statement.

2.3.4 What is sponsor's dose selection rationale?

- The sponsor had conducted a supportive phase 2b dose finding study (BUF-5/UCA) where BID dosing of budesonide rectal foam was compared with QD dosing and placebo. Under more stringent definition of clinical remission (eg, primary endpoint CAI $\leq$ 1, DAI $\leq$ 1 at week 6), budesonide 2 mg rectal foam BID group had statistically significant favorable result compared to placebo. BID dosing regimen also yields more favorable treatment effect compared to that of QD dosing where a statistically significant dose response trend between study groups (4 mg/day > 2 mg/day > placebo) was shown with Cochran- Armitage trend test applied to the supplemental efficacy variable

- The exploratory scintigraphy data from the BUF-4/BIO budesonide foam study suggested that the foam reaches its maximum spread by 6 hours after administration, with less than 50% present in the rectum by 6 hours after administration of a single dose. These data suggest that at least twice-daily administration would be appropriate to maintain continuous residence of budesonide foam in contact with rectal tissue.

- In the phase 3 study BUF-9/UCA, a CAI assessment taken at 2 weeks confirmed that the majority of subjects experienced an early treatment response, with the greatest change from baseline observed after the first 2 weeks of treatment. While a 2-week CAI or DAI assessment was not measured in BUF-6/UCA (ie, first assessment at 4 weeks), subject diary information was collected in both studies, with mean weekly scores of stool number and rectal bleeding. These data also demonstrate the rapid onset of drug effect, with the greatest percent reduction in bowel frequency and blood in stools occurring after the first 2 weeks of treatment.

- A pilot study (BUF-3/UCA) with a slightly different foam formulation used a 2 mg budesonide BID dosing regimen for 2 weeks followed by 2 weeks of 2 mg budesonide foam QD, as compared to 5 mg/100 mL betamethasone enema. The greatest response with budesonide treatment occurred during the 2-week BID treatment period, with a 5.5-point decrease in the mean CAI endpoint observed at 2 weeks (N = 22) and a 6.7-point decrease at 4 weeks (N = 19).

- A clinical study comparing budesonide Entocort® enema versus prednisolone enema over 8 weeks of treatment (18) demonstrated that the majority (70%) of the patients receiving budesonide experienced a statistically significant change from baseline in their endoscopy scores within the first 2 weeks of treatment.

The sponsor's dose selection rationale appears to be reasonable.

2.3.5 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters?

The bioanalytical methods used in PK studies with extensive sampling in study BUF-7/BIO (HPLC/MS) and BUF-4/BIO (HPLC-MS/MS) were not properly validated in terms of stability of serum budesonide PK samples.
However, the sparse PK plasma samples collected in phase 3 studies (BUCF 3001 and BUCF 3002) were analyzed with validated LC-MS/MS bioanalytical method.
Please see section 2.7.1 for detail.

2.3.6 What is the rate of hypothalamic pituitary adrenal (HPA) axis suppression in subjects administered budesonide rectal foam?

Overall, treatment with budesonide rectal foam for 6 weeks led to a net HPA axis suppression rate increase of 20.8%. This was higher compared to placebo although the suppression rate appears to be lower than that of oral budesonide as noted in oral Uceris label.

HPA axis suppression was evaluated in two identical placebo controlled Phase 3 safety and efficacy trials 3001 and 3002 in a total of 546 subjects with active mild to moderate ulcerative proctitis or proctosigmoiditis. Subjects were required to have a 30 minute post adrenocorticotropic hormone (ACTH) challenge cortisol level >18 μg/dL to be enrolled into the trial. Subjects were randomized to study treatment in a 1:1 ratio to receive either 2 mg/25 mL budesonide foam BID for 2 weeks followed by 2 mg/25 mL QD for 4 weeks, or placebo foam BID for 2 weeks followed by placebo foam QD for 4 weeks.

Morning serum cortisol level were measured in all subjects at baseline, week 1, week 2, week 4, and week 6. If morning cortisol level in any subject were <5 μg/dL, they were administered and unscheduled ACTH challenge test after stopping the treatment for at least 24 hours. If a subject fail the unscheduled ACTH challenge test (i.e., having the 30 minute post ACTH challenge cortisol level <18 μg/dL), that subject would be discontinued from the trial.

A final ACTH challenge test was administered to all subjects still in the trial at week 6. ACTH challenge were administered as 250 mcg dose given intramuscularly in the morning between 8 and 10 am. Serum cortisol was assessed pre- and 30 minutes post-challenge.

HPA axis function was assessed based on the following 3 criteria. The primary endpoint of normal response is defined as meeting all 3 criteria.

1. Morning cortisol >138 nmol/L (5 μg/dL)
2. Change in serum cortisol following ACTH challenge ≥193 nmol/L (7 μg/dL) above baseline
3. Cortisol following ACTH challenge >500 nmol/L (18 μg/dL)

The results were generally similar across the 2 trials. There were initial decreases in morning serum cortisol levels at Weeks 1 and 2 that gradually returned toward baseline levels by Week 6 in the budesonide group (Figures 1 and 2). It should be noted that 20* subjects from the budesonide arm that had failed an unscheduled ACTH challenge test prior to weeks 6 were discontinued from the trial and could partly contributed to the apparent return to baseline cortisol level in the budesonide treatment arm (only 2 subject in the placebo arm were discontinued for the same reason). (*Reviewer's note: * One of these 20 subjects was discontinued after low morning cortisol levels at weeks 1 and 2 but ACTH challenge test were either not performed or not reported).*

From the combined data from both trials, serum cortisol levels > 5 μg/dL (138 nmol/L) were maintained in at least 84.0% of subjects in the budesonide and placebo treatment groups at Weeks 1, 2, 4, and 6 (Table 2). The proportion of subjects who maintained serum cortisol levels > 5 μg/dL was lower in the budesonide group than in the placebo group at Weeks 1 and 2 (BID treatment phase): 85.2% budesonide versus 98.1% placebo at Week 1 and 84.0% versus 98.9%, respectively, at Week 2. During the QD treatment phase (Weeks 3 through 6) this difference between treatments was attenuated and the percentages of budesonide-treated and placebo-treated subjects had serum cortisol levels > 5 μg/dL by Week 6 were 94.2% and 97.1%, respectively. As noted above, 22 subjects (mainly from the budesonide arm) who had failed the unscheduled

ACTH challenge test were discontinued from the trial prior to week 6 and may partly contributed to this apparent attenuation in the budesonide arm.

Regarding the primary HPA axis suppression assessment, at baseline, 83.5% of subjects in the budesonide foam group had a normal response to the ACTH challenge and at Week 6, 68.5% of subjects had a normal response to the ACTH challenge for a difference of 15.0%; in the placebo group, these values were 85.6% and 76.6%, respectively, for a difference of 9.0%. If one take into account subjects who were discontinued prior to week 6 due to failure of the unscheduled ACTH challenge test, the baseline vs. week 6 rates were 83.5% and 62.7% for budesonide and 85.6% and 75.9% for placebo; A larger difference was seen (a decrease of 20.8% for budesonide vs a decrease of 9.7% for placebo). Applying the single criterion of cortisol level following ACTH challenge >18 µg/dL, a similar magnitude of change in rate was seen for budesonide (a decrease of 19.9%) while the placebo group only decreased by 3.5%. Regardless of which criteria is used, budesonide rectal foam led to higher rate of HPA axis suppression compared to placebo although the suppression rate appears to be lower than that of oral budesonide as noted in oral Uceris label.

It should be noted that the primary assessment was not conducted during period of more frequent BID dosing (i.e., weeks 1 and 2). Based on the higher rate of low morning cortisol during weeks 1 and 2 compared to later weeks, the rate of HPA axis suppression based on ACTH testing may be higher during period of BID dosing compared to period of QD dosing.

Figure 1: Mean ± SD cortisol values by visit and treatment group from trial 3001 (safety population)

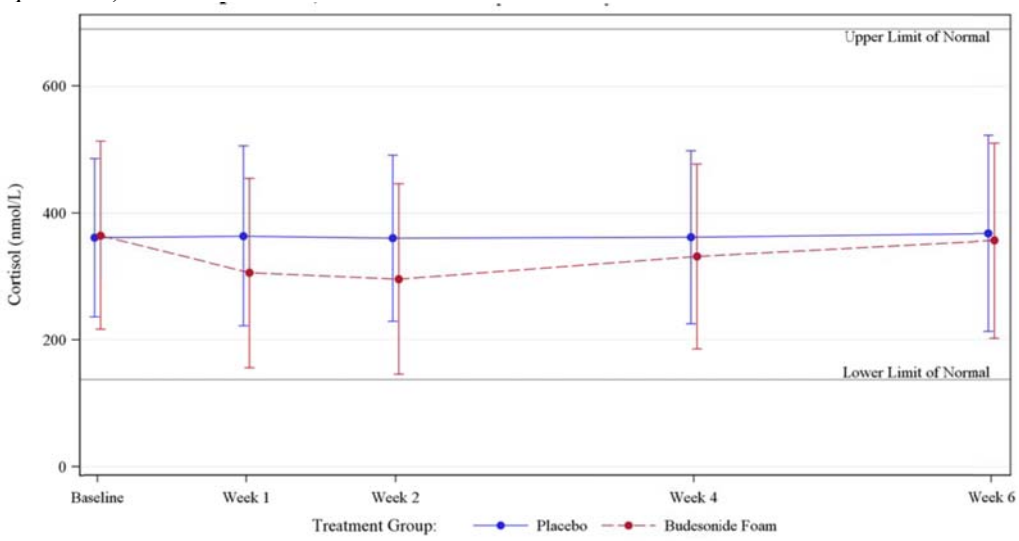


Figure 2: Mean ± SD cortisol values by visit and treatment group from trial 3002 (safety population)

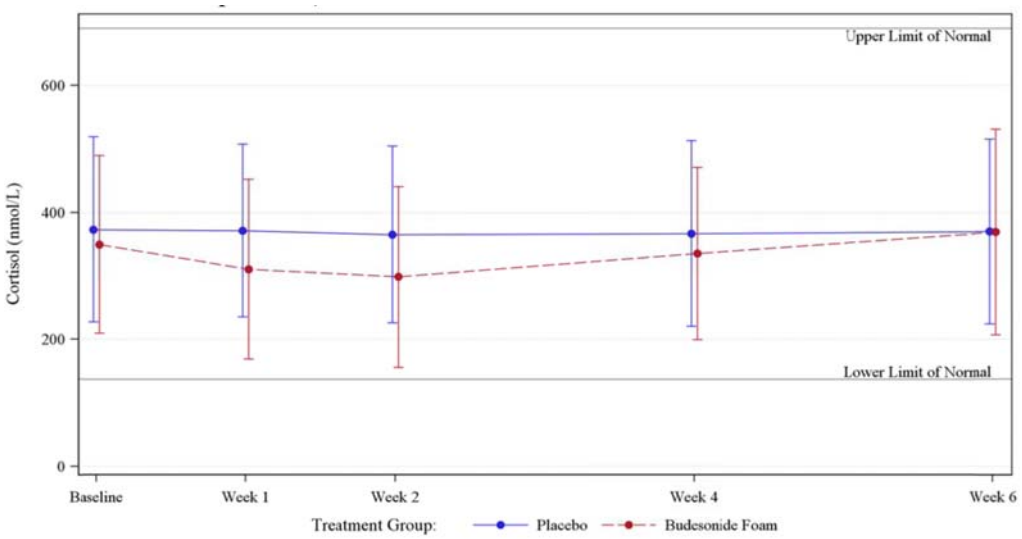


Table 2: Proportion of Subjects with Normal Endogenous Cortisol Levels (> 5 µg/dL) During the Study and Proportion of Subjects with Normal Response to ACTH Challenge from both trials 3001 and 3002 combined.

Cortisol Parameter	Budesonide Foam 2 mg/25 mL N = 268 n (%)	Placebo N = 278 n (%)
Total cortisol > 5 µg/dL (lower limit of normal range)		
Baseline	259/268 (96.6)	275/278 (98.9)
Week 1	224/263 (85.2)	264/269 (98.1)
Week 2	216/257 (84.0)	263/266 (98.9)
Week 4	218/235 (92.8)	243/249 (97.6)
Week 6	211/224 (94.2)	234/241 (97.1)
Normal response to ACTH challenge[a]		
Baseline	222/266 (83.5)	238/278 (85.6)
Week 6	148/216 (68.5)	180/235 (76.6)
Week 6 (including subjects discontinued)[b]	148/236 (62.7)	180/237 (75.9)
Cortisol Following ACTH Challenge > 18 µg/dL		
Baseline	261/266 (98.1)	275/278 (98.9)
Week 6	186/216 (86.1)	226/235 (96.2)
Week 6 (including subjects discontinued)[b]	186/236 (78.8)	226/237 (95.4)

[a] The normal response to ACTH challenge includes 3 criteria, as defined in the cosyntropin label: 1) morning cortisol level > 5 µg/dL; 2) increase in cortisol level by ≥ 7 µg/dL above the morning (pre-challenge) level following ACTH challenge; and 3) cortisol level of > 18 µg/dL following ACTH challenge.

[b] The total subjects include 20* subjects in the budesonide arm and 2 subject in the placebo arm that was discontinued prior to week 6 due to failure of an unscheduled ACTH challenge test (i.e., their post ACTH challenge cortisol level was <18 µg/dL). (* One of these 20 subjects was discontinued after low morning cortisol levels at weeks 1 and 2 but ACTH challenge test were either not performed or not reported).

2.3.7 Does this drug prolong QT/QTc Interval?

The sponsor had requested a waiver for TQT study. The QT-IRT team has reviewed the request and agrees that a TQT study is not needed. Please see QT-IRT team review by Drs. Jiang Liu and Norman Strockbridge dated 04/09/2014.

2.4 PK Characteristics

The pharmacokinetic of budesonide 2 mg rectal foam was evaluated in healthy adult male subjects in study BUF-7/BIO and in mild to moderate ulcerative colitis patients in study BUF-4/BIO with Dr. Fallk Pharma formulation. In addition, the sponsor had collected sparse PK samples during phase 3 studies (BUCF3001 and BUCF3002) in mild to moderate active ulcerative proctitis or proctosigmoiditis patients with Salix formulation. The sponsor has conducted population PK analysis pooling all PK data from phase 3 (BUCF3001 and BUCF3002) and phase 1 (BUF-7/BIO and BUF-4/BIO) studies.

2.4.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

In Study BUF-7/BIO, serum PK of budesonide 2 mg rectal foam were evaluated in 18 healthy male subjects after administration of single dose of budesonide 2 mg rectal foam on Day 1 and BID dosing on day 2-5 rectally. The reported Cmax was 0.84 ng/ml on Day 1 and was 0.90 ng/mL on Day 5. Additionally, the AUC_{0-12} was 4.59 ng*hr/mL on Day 1 and 4.30 ng*hr/mL on Day 5 with half-life of 4.05 hours. Based on AUC_{0-12} and Cmax, there appears to be lack of significant accumulation after multiple dose administration of rectal budesonide foam. Serum budesonide PK samples in this study were stored at -20^{o}C until analysis and the concentration of budesonide was analyzed by HPLC/MS. However, the stability of serum budesonide at -20^{o}C storage condition was not established during the assay development. Therefore, it is not clear if the serum budesonide PK samples were collected and analyzed within the serum sample stability limit. In general, the applied bioanalytical method in this study was not validated in terms of stability of serum budesonide at various conditions (e.g., long term, short term, room temperature, freeze-thaw stabilities). Consequently, it is hard to interpret the result of this study and thus, the study result will not have a labeling implication.

2.4.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

PK of budesonide 2 mg rectal foam was evaluated in 12 patients with mild to moderate ulcerative colitis after single dose administration (Study BUF-4/BIO) with PK sampling up to 8 hours post-dose. However, since the stability of serum budesonide at -20^{o}C storage condition in this study was not established during the assay development and therefore, it is not clear if the serum PK samples were collected and analyzed within the serum sample stability, it is difficult to interpret the result of this study and thus, the study result will not have a labeling implication.

In addition, the sponsor had also collected sparse PK samples in phase 3 studies (BUCF 3001 and BUCF 3002) in mild to moderate active ulcerative proctitis or proctosigmoiditis (UP/UPS) patients at baseline, at week 1, 2, 4, and 6 (Day 1, 7, 14, 28 and 42) to measure the budesonide plasma concentration with a validated bioanalytical method. The sponsor has initially conducted population PK analysis pooling all PK data from phase 3 (BUCF3001 and BUCF3002) and phase 1 (BUF-7/BIO and BUF-4/BIO) studies. However, Since bioanalytical methods used in PK studies BUF-4/BIO and BUF-7/BIO with Dr. Falk formulation were not properly validated in terms of stability in storage condition, the sponsor was requested to conduct population PK analysis with just phase 3 data excluding the PK data from phase 1 studies with Dr. Fallk formulation.

The pharmacometric review was conducted in order to evaluate the population PK model (with just phase 3 sparse samples without the PK data from phase 1 studies) and ascertain pharmacokinetic parameter estimates that can be reported in the label. The sponsor's population PK model is limited by both their data and parameterization. The model was developed with sparse phase 3 data which greatly limits evaluation of the structural PK model. Consequently, Cmax should not be reported. Secondly, the model was parameterized for the elimination rate constant instead of CL. Therefore, calculating CL as a secondary parameter from this model does not remove the effect residual or inter-subject variability from Vd on the individual estimates of CL. Therefore, the reported value of %CV (640%) for CL is not reliable. CL should have been parameterized independently in the model. In such a circumstance, between subject variability and residual error may have been more accurately reported for this parameter. The estimate of AUC (4.31 ng*hr/mL with a CV% of 64%) appears reasonable and is a relevant parameter to report in the label as this value can be compared across products.

2.5 General Biopharmaceutics

2.5.1 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

Budesonide 2 mg rectal foam initially was developed by Dr. Falk Pharma and received marketing approval in Europe in 2006 (referred as Dr Falk formulation or also referred to as Budenofalk rectal foam in the submission). After (b) (4) was removed from Dr. Falk Pharma formulation and replaced by (b) (4), the new formulation was transferred to (b) (4) in USA to produce the drug product for Salix-sponsored Phase 3 studies, BUCF3001 and BUCF3002. No other changes were made to the drug product formulation during the transfer. The new formulation is referred as Salix formulation in this submission. According to the Biopharm reviewer Dr. Kelly Kitchens, the formulation change from Dr. Falk formulation to Salix formulation was minor and a vivo BE study is not needed to bridge these two formulations.

After conducting Phase 3 clinical studies BUCF3001 and BUCF3002, (b) (4) Per e-mail communication with Dr. Marie Kowblansky, CMC TL, CMC considered that the post-Phase 3 changes were not significant and TBM product formulation is the same as the Phase 3 product formulation.

2.5.2 What is the effect of food on the bioavailability of the drug when administered as drug product?

As this was a rectal formulation, food effect study was not conducted.

2.6 Extrinsic factors

2.6.1 Is the drug an inhibitor and/or an inducer of enzymes?

<u>CYP inhibition potential:</u>

Based on in vitro results showing IC50 >1130 ng/mL, budesonide rectal foam at therapeutic concentration is not expected to inhibit CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 in vivo. No data is available for CYP2C8 and CYP2C19.

The sponsor conducted an in vitro study (BUDM 0102) to evaluate the ability of budesonide to inhibit CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 in human liver microsomes. At tested concentration of up to 1130 ng/mL, there were no or little direct or time-dependent inhibition of CYP1A2, CYP2B6, CYP2C9, CYP2D6, and CYP2E1 by budesonide and the IC50 values are expected to be greater than 1130 ng/mL.

For CYP3A4/5, four marker substrate reactions (testosterone 6β-hydroxylation, midazolam 1′-hydroxylation, nifedipine oxidation and atorvastatin *ortho*-hydroxylation) were evaluated for CYP3A4/5 due to multiple binding domains within the active site. The degree of direct inhibition for the four CYP3A4/5 probes (testosterone 6β-hydroxylation, midazolam 1′-hydroxylation, nifedipine oxidation and atorvastatin *ortho*-hydroxylation) were 13%, 35%, 26% and 39% inhibition, respectively, at the highest concentration of budesonide evaluated (1130 ng/mL) and the IC50 values are expected to be greater than 1130 ng/mL. There was no evidence of time-dependent inhibition as similar effects were observed with a 30 minute preincubation.

CYP induction potential:

Based on in vitro results showing little or no effect of budesonide concentration up to 9000 nM (3875 ng/mL) on the activity or messenger RNA (mRNA) expression of CYP1A2, CYP2B6, CYP2C9, and CYP3A4, budesonide rectal foam at therapeutic concentration is not expected to induce CYP enzyme in vivo.

The sponsor conducted an in vitro study (BUDM 0103) to evaluate the ability of budesonide to induce the expression of cytochrome P450 (CYP) enzymes in primary cultures of cryopreserved human hepatocytes. Analysis of phenacetin *O*-dealkylation (marker for CYP1A2), bupropion hydroxylation (marker for CYP2B6), diclofenac 4′-hydroxylation (marker for CYP2C9) and midazolam ′ 1 –hydroxylation (marker for CYP3A4/5) by LC/MS/MS. The same hepatocytes from the same treatment groups were harvested to assess the effect of budesonide on CYP1A2, CYP2B6, CYP2C9 and CYP3A4 mRNA levels. Positive and negative controls for CYP1A2, CYP2B6, and CYP3A4 responded as anticipated. The positive control for CYP2C9, 20 μM rifampin, showed relatively small effects, namely an increase of 1.40- to 2.15-fold in CYP2C9 activity and 1.37- to 1.67-fold in CYP2C9 mRNA levels.

Budesonide caused a ≤ 1.52-fold change in CYP activity as measured by the probe substrates and a ≤ 1.48-fold change in CYP mRNA levels for all 4 CYP isozymes examined. The response to the positive control for CYP2C9 was not robust. However, because budesonide did not induce CYP1A2, CYP2B6, and CYP3A4 the conclusion that budesonide does not induce CYP2C9 is well supported.

2.6.2 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

Substrate of P-gp and BCRP:

In vitro studies showed that budesonide is not a substrate of BCRP and a weak substrate of P-gp.

To determine if budesonide (1, 10 and 100 μM) is a substrate of human efflux transporters (namely, P-gp [MDR1/ABCB1] and BCRP [ABCG2]), the bidirectional permeability of

budesonide across MDCKII-MDR1 and MDCKII-BCRP cells and control cells was measured (15, 30, 60 and 120 min incubations). As a follow up experiment, the bidirectional permeability of budesonide (10 μM) across MDCKII-MDR1 and control cells was measured (60 min incubation) in the presence and absence of the P-gp inhibitor valspodar and verapamil.

The net efflux ratio of budesonide across MDCK-MDR1 (P-gp) and control cells was 1.82, 3.27 and 1.37 at 1, 10 and 100 μM suggesting it may be a substrate of P-gp. However, in follow up experiments, the net efflux ratio was 1.19 (10 μM, 60 min incubation). In the presence of known P-gp inhibitors, valspodar (1 μM) and verapamil (60 μM), the net efflux ratio was 0.894 and 0.690. The results of the two experiments suggest budesonide may be a weak substrate of P-gp.

The net efflux ratio of budesonide across MDCK-BCRP and control cells was less than 2 at all concentrations tested (ratio of 1.12, 0.657, and 0.854 at 1, 10 and 100 μM, respectively) suggesting it is not a substrate of BCRP.

P-gp and BCRP inhibition:

In vitro studies showed that budesonide was a weak inhibitor of P-glycoprotein (IC_{50} 9.78 μM or 4.21 μg/mL) and BCRP (IC_{50} 43.1 μM or 18.6 μg/mL). Budesonide foam is not expected to inhibit these transporters in clinical use.

The ability of budesonide (0.3, 1, 3, 10, 100 μM) to inhibit human efflux transporters, namely, P-gp (MDR1/ABCB1) and BCRP (ABCG2) was evaluated by measuring the bidirectional permeability of a probe substrate (digoxin or prazosin) across a monolayer of Caco-2 and MDCKII-BCRP cells in the presence of budesonide.

At the concentrations tested (0.3 to 100 μM) budesonide inhibited P-gp and BCRP with IC50 values of 9.78 and 43.1 μM, respectively.

Substrate of OATP1B1 and OATP1B3:

In vitro studies showed that budesonide is not a substrate of OATP1B3. The results were inconclusive for OATP1B1. The results suggest budesonide is either not a substrate of OATP1B1 or a weak substrate of OATP1B1.

To determine if budesonide (0.5 and 5 μM) is a substrate of human uptake transporters (namely, OATP1B1 [OATP2/OATP-C/SLCO1B1] and OATP1B3 [OATP8/SLCO1B3]), the accumulation of budesonide in transporter-expressing and control HEK293 cells was measured (1 and 10 min incubations). As a follow up experiment, the accumulation of budesonide (1 μM, 1 min) in OATP1B1 transporter-expressing and control HEK293 cells was measured in the presence and absence of the OATP1B1 inhibitors rifampin and cyclosporine.

In incubations of 0.5 and 5 μM budesonide carried out for 1 min, the accumulation of budesonide in OATP1B1 expressing cells was more than 2-fold higher than in control cells. However the accumulation was not reproducible. In the follow up experiment, the uptake of budesonide was similar in OATP1B1 expressing and control cells and was not affected by rifampin or cyclosporine.

In incubations of 0.5 and 5 μM budesonide carried out for 1 and 10 min, the accumulation of budesonide in OATP1B3 expressing cells was similar to the accumulation in control cells suggesting budesonide is not a substrate of OATP1B3.

OATP1B1 and OATP1B3 inhibition:

In vitro studies showed that budesonide at concentrations up to 300 nM did not inhibit OATP1B1 or OATP1B3. Budesonide foam is not expected to inhibit these transporters in clinical use.

The ability of budesonide (0.3, 1, 3, 10, 30, 100 and 300 nM) to inhibit human uptake transporters, namely, OATP1B1 (OATP2/OATP-C/SLCO1B1) and OATP1B3 (OATP8/SLCO1B3) was evaluated by measuring the accumulation of probe substrates (estradiol glucuronide [OATP1B1 and OATP1B3]) in transporter-expressing and control HEK293 cells in the presence of budesonide.

Budesonide (0.3 to 300 nM) did not inhibit OATP1B1 or OATP1B3.

OCT2, OAT1, and OAT3:

No data were available for these renal transporters. However, these transporters are not expected to affects the elimination of budesonide as the product label for oral budesonide states that budesonide is not excreted renally.

2.7 Analytical Section

2.7.1 What bioanalytical methods were used to assess the concentration and were the analytical assay methods adequately validated?

The sponsor had utilized a validated LC-MS/MS method to measure the budesonide plasma samples in phase 3 studies (BUCF3001 and BUCF 3002).
In both BUF-7 and BUF-4 studies, serum budesonide samples were collected and analyzed with HLPC-MS methods that were not properly validated.

Study BUF-7/BIO (PK in healthy subjects)

- Serum budesonide levels were determined by HPLC/MS.
- Serum samples were stored at -20 ^{o}C until analyzed.
- The limit of quantification was set to 0.1 ng/ml.
- The concentrations of quality control samples were 0.2, 0.5, 1.0 ng/ml.
- 4 Calibration standards ranging from 60 to 3000 pg/ml. (unknown R2 value)
- Over the concentration range of 0.1 to 3 ng/ml within run precision varied between 0.7 and 15%; and between run precision were below 16.1% except at 0.12 ng/mL concentration (20.2%) for all three validation runs. Mean within run accuracy varied between 89% and 133 % and average accuracy was between 99% and 111% over this calibration range.
- It is not clear if the serum PK samples were collected and analyzed within stability limit. Stability of serum budesonide at -20^{o}C storage condition (as well as short term, room temperature, freeze-thaw stabilities) were not established during assay validation.
  - The study was conducted between 02/1998-08/1998
  - Sample extractions were performed from 03/08/1998 to 10/8/1998.
  - The longest possible time between sample collection and sample extraction would have been 249 days.

BUF-4/BIO (PK study in UC patients)

- Serum budesonide levels were determined by HPLC-MS/MS.

- Serum samples were stored at -20 °C until analyzed.
- The limit of quantification was set to 0.1 ng/ml.
- The concentrations quality control samples were 0.4, 4.85 and 8.32 ng/ml.
- For QC samples, the accuracy was between 95.5.6 and 108.2 %
- Calibration standard curve consisted of 8 level ranged from 1 to 10 ng/mL in human plasma, with an LLOQ of 0.1 ng/mL, and was calculated using a linear regression (weighted 1/x2). The R2 value was 0.999.
- It is not clear if the serum PK samples were collected and analyzed within stability limit. Stability of serum budesonide at -20°C storage condition was not established during assay validation.
    - The first PK sample was collected on 13 August 1999 and the last sample was collected on 6 April 2000.
    - All samples were analyzed on 17 May 2000
    - PK samples were stored at -20°C for up to 278 days prior to analysis.

Method Validation:

- Sponsor submitted a validated report for HPLC/MS bioanalytical method for measuring the concentration of budesonide in human plasma (not in human serum). This method validation report in human plasma did not provide information regarding stability of budesonide in human serum or plasma at various conditions (e.g., long term, short term, room temperature, freeze-thaw stabilities).
- Lower limit of quantification (LLQ) was established at 0.l ng/ml.
- QC samples were at 0.1, 0.4, 4.8 and 10.4 ng/ml and their within run precision varied between 4.10 and 9.10%; average and between run precision were below 7.44% for all three validation runs. Mean within run accuracy varied between 81.7% and 105.8 % and average accuracy was between 82.0% and 98.0% over this calibration range.

BUCF 3001 (sparse PK samples in patients):

- Budesonide concentrations in human plasma were determined using a validated LC/MS/MS method.
- Serum samples were stored at -70 °C until analyzed.

Assay Method	
Method Validation Report	SAL10-001
Matrix	Human Plasma
Anticoagulant	K2EDTA
Type of Extraction	Liquid/Liquid
Method of Detection	LC/MS/MS
Sample Aliquot Volume	0.150 mL
Calibration Standard Distribution	Calibration standards were interspersed throughout the bioanalytical run.
Quality Control (QC) Distribution	QC samples were distributed throughout each bioanalytical run.
Injection Sequence	The prepared samples, calibration standards and QCs were injected in a systematic order.
Analyte	Budesonide
Internal Standard	Budesonide-d8 (added to all samples except Blanks)

Regression and Weighting	Linear $1/x^2$, Mean R^2 was 0.9976	
LLOQ	0.0300 ng/mL	
ULOQ	10.0 ng/mL	
Calibration Standard Concentrations	0.0300, 0.0500, 0.250, 0.500, 1.00, 4.00, 8.00 and 10.0 ng/mL Back calculated precision ranged 2.5%-5.7% Back calculated accuracy ranged -1.3%-1.6%	
Analytical QC Concentrations	0.0700, 0.500 and 7.50 ng/mL	
Performance of Analytical QCs	Precision (%CV)	Accuracy (%Bias)
	Within-run:0.8%-11.0%	Within-run:-13%-6.0%
	Inter-run: 4.4% to 7.3%	Inter-run: -3.6% to -3.3%
Run Performance	No. of Accepted Runs	No. of Rejected Runs
	2	1

Watson Run ID 10 was rejected because the low level QCs did not meet acceptance criteria. All study samples were successfully reanalyzed in a subsequent accepted run.

Sample Storage	
Maximum Time from Receipt to Extraction (Actual)	92 days
Demonstrated Storage Stability	310 days at -70ºC
Stability Data Reference	SAL10-001 [10.2]
Samples Collected and Analyzed within Stability Limits	Yes

Incurred Sample Reanalysis (ISR)	
Incurred sample reanalysis samples were assayed in singlet in four analytical runs.	
Samples Meeting Acceptance Criteria	21 out of 21 samples (100.0%)
Incurred Sample Reanalysis was Acceptable	Yes

BUCF 3002:

- Budesonide concentrations in human plasma were determined using a validated LC/MS/MS method.
- Serum samples were stored at -70 ^{o}C until analyzed.

Assay Method	
Method Validation Report	SAL10-001
Matrix	Human Plasma
Anticoagulant	K_2EDTA
Type of Extraction	Liquid/Liquid
Method of Detection	LC/MS/MS
Sample Aliquot Volume	0.150 mL

Calibration Standard Distribution	Calibration standards were interspersed throughout the bioanalytical run.	
Quality Control (QC) Distribution	QC samples were distributed throughout each bioanalytical run.	
Injection Sequence	The prepared samples, calibration standards and QCs were injected in a systematic order.	
Analyte	Budesonide	
Internal Standard	Budesonide-d8 (added to all samples except Blanks)	
Regression and Weighting	Linear $1/x^2$, Mean R^2 was 0.9976	
LLOQ	0.0300 ng/mL	
ULOQ	10.0 ng/mL	
Calibration Standard Concentrations	0.0300, 0.0500, 0.250, 0.500, 1.00, 4.00, 8.00 and 10.0 ng/mL Back calculated precision ranged 2.1%-5.7%	
Analytical QC Concentrations	0.0700, 0.500 and 7.50 ng/mL	
Performance of Analytical QCs	Precision (%CV)	Accuracy (%Bias)
	Within-run: 0.8-9.6%	Within-run:-13%-6.0%
	Inter-run: 4.7% to 7.0%	Inter-run: -3.4% to -3.0%
Run Performance	No. of Accepted Runs	No. of Rejected Runs
	2	1

Watson Run ID 10 was rejected because the low level QCs did not meet acceptance criteria. All study samples were successfully reanalyzed in a subsequent accepted run.

Sample Storage	
Maximum Time from Receipt to Extraction (Actual)	133 days
Demonstrated Storage Stability	310 days at -70ºC
Stability Data Reference	SAL10-001 [10.2]
Samples Collected and Analyzed within Stability Limits	Yes

Incurred Sample Reanalysis (ISR)	
Incurred sample reanalysis samples were assayed in singlet in four analytical runs.	
Samples Meeting Acceptance Criteria	21 out of 21 samples (100.0%)
Incurred Sample Reanalysis was Acceptable	Yes

Method Validation:

The method of LC/MS/MS for measuring budesonide in K2EDTA human plasma in studies BUCF 3001 and BUCF 3002 was validated by [redacted] (b) (4) in [redacted] (b) (4) for quantitation range of 0.0300 to 10.0 ng/mL budesonide.

- Selectivity: Selectivity of this method for budesonide was demonstrated by screening a total of six lots of K2EDTA human plasma, purchased from [redacted] (b) (4), for

endogenous interferences. No selectivity sample exhibited a peak in the analyte channel above 20% of that found in the low level standard or a peak in the internal standard channel above 5% of that found in the matrix control sample.

- Accuracy and Precision:

Inter-run Mean	LLOQ QC 0.0300 ng/mL	Low QC 0.0700 ng/mL	Mid QC 0.500 ng/mL	High QC 7.50 ng/mL	Dil QC 50.0 ng/mL
Inter-run %CV (Precision)	6.3	4.4	5.6	3.6	
Within-run % CV (precision)	4.0-7.8	1.6-6.3	1.5-3.6	0.9-3.8	3.2
Inter-run %Bias (Accuracy)	8.3	3.6	1.8	1.7	1.2

- Recovery: Recovery was obtained for low, mid and high QC samples and it was close to 40%. The results were consistent and precise with %CV of 10.8%-13.7%.

- Carryover Effect: Analyte and internal standard carryover was evaluated by injecting an extracted blank sample following the analysis of the highest level standard used in the regression. The carryover check sample did not exhibit any peaks in the analyte channel above 20% of that found in the low level standard or any peaks in the internal standard channel above 5% of that found in the high level calibration standard.

- Calibration Curve was shown to exhibit linear curves (with weighing of $1/x^2$) between 0.0300 and 10.0 ng/mL with an average R^2 of 0.9981 for budesonide.

- Sensitivity: LLOQ for this method was 0.0300 ng/mL for budesonide. The analyte response at the LLOQ was at least five times the response for any matrix blank samples.

- Stability: budesonide in K_2EDTA human plasma in following condition were established:

Freeze-thaw cycles	Room temperature	Autosampler/extract (0-10°C)	At -70°C
4	23 hours	3 days	1015 Days

  - Budesonide stock solutions are stable in 1:1 acetonitrile:water for at least 133 days at 4ºC.
  - A working solution of budesonide is stable in 1:1 acetonitrile:water for at least 127 days at 4ºC.
  - A working solution of budesonide is stable in 1:1 acetonitrile:water for at least 23 hours at room temperature.

3 Detailed Labeling Recommendations

All recommended changes are noted by color font. Specifically, any additions are noted by underlined text in blue and any deletions are identified by ~~strikethrough text in red~~.

7.0 Drug Interaction:

(b) (4)

The active ingredient of **BRAND NAME** rectal foam, budesonide~~,~~ (b) (4) (b) (4) metabolized by the cytochrome p450 3A4 (CYP3A4) Inhibitors of CYP3A4 activity (such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, and grapefruit juice) may increase systemic budesonide concentrations. Avoid concomitant use of CYP3A4 inhibitors with UCERIS Rectal Foam. Inducers of CYP3A4 activity (such as rifampin) may reduce systemic budesonide concentrations

8.0 Use in Specific Populations

8.6 Hepatic Impairment

Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism. Discontinuing the use of UCERIS Rectal Foam should be considered in these patients [See *Warnings and Precautions* (5.4)].

12.0 Clinical Pharmacology

12.1 Mechanism of Action

(b) (4) Budesonide is a glucocorticosteroid with a (b) (4) anti-inflammatory effect.

12.2 Pharmacodynamics

Treatment with glucocorticosteroids, including UCERIS Rectal Foam, is associated with a suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-

pituitary-adrenal axis function. These effects are measured by determination of plasma cortisol concentrations and responses to adrenocorticotropin challenge (ie, ACTH stimulation test).

In the 2 placebo-controlled, 6-week studies in patients with active disease, These trials enrolled subjects with post ACTH stimulation cortisol level of >18 µg/dL at baseline. Subjects received UCERIS Rectal Foam 2 mg or a placebo twice daily for 2 weeks followed by once daily for 4 weeks. normal morning serum cortisol levels > 5 µg/dL were maintained in (b) (4) 85 and 84% of **BRAND NAME**-treated subjects and (b) (4) during Weeks 1 and 2 (twice daily treatment) and 93% and 94% during Weeks 4 and (b) (4) 6 (once daily treatment), as shown in table 2.

(b) (4) At baseline (predose), 84% of subjects in the **BRAND NAME** group had a normal response to the ACTH challenge and at Week 6, (b) (4) 63% of subjects had a normal response to the ACTH challenge; in the placebo group, these values were 86% and (b) (4) 76%, respectively, as shown in table 2. ACTH stimulation test was not performed during twice daily treatment period (Weeks 1 and 2).

Table 2: Proportion of Subjects with Normal Endogenous Cortisol Levels (> 5 µg/dL) During the Study and Proportion of Subjects with Normal Response to ACTH Challenge

Cortisol Parameter	**BRAND NAME Rectal Foam 2 mg/25 mL N = 268 n (%)**	**Placebo N = 278 n (%)**
Total cortisol > 5 µg/dL (lower limit of normal range)		
Baseline	259/268 (96.6)	275/278 (98.9)
Week 1	224/263 (85.2)	264/269 (98.1)
Week 2	216/257 (84.0)	263/266 (98.9)
Week 4	218/235 (92.8)	243/249 (97.6)
Week 6	211/224 (94.2)	234/241 (97.1)
Normal response to ACTH challenge[a]		
Baseline	222/266 (83.5)	238/278 (85.6)
Week 6[b]	148/(b) (4) 236 (62.7)	180/(b) (4) 237 (75.9)

[a] The normal response to ACTH challenge includes 3 criteria, as defined in the cosyntropin label: 1) morning cortisol level > 5 µg/dL; 2) increase in cortisol level by ≥ 7 µg/dL above the morning (pre-challenge) level following ACTH challenge; and cortisol level of > 18 µg/dL following ACTH challenge.

[b] Includes 20 subjects in the Uceris arm and 2 subjects in the placebo arm who discontinued prior to week 6 due to adverse events related to low cortisol or abnormal response to ACTH challenge.

12.3 Pharmacokinetics

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Based on population pharmacokinetic analysis from sparse PK samples from phase 3 studies, the estimated AUC0-12 following administration of Uceris Rectal Foam 2 mg BID was 4.31 ng*hr/mL with a CV of 64% in target patient population.

Distribution

(b) (4) the volume of distribution (Vss) of budesonide varies between 2.2 and 3.9 L/kg in healthy subjects and in patients. Plasma protein binding is estimated to be 85 to 90% in the concentration range of 1 to 230 nmol/L, independent of gender. The erythrocyte/plasma partition ratio at clinically relevant concentrations is approximately 0.8.

Metabolism

(b) (4)

Following absorption, budesonide is subject to first-pass metabolism. In vitro experiments in human liver microsomes demonstrate that budesonide is rapidly and extensively biotransformed, mainly by CYP3A4, to its 2 major metabolites, 6β-hydroxy budesonide and 16αhydroxy

prednisolone. The glucocorticoid activity of these metabolites is negligible (<1/100) in relation to that of the parent compound.

In vivo investigations with intravenous doses in healthy subjects are in agreement with the in vitro findings and demonstrate that budesonide has a high plasma clearance, 0.9-1.8 L/min. These high plasma clearance values approach the estimated liver blood flow, and, accordingly, suggest that budesonide is a high hepatic clearance drug.

Excretion

Budesonide is excreted in urine and feces in the form of metabolites. After oral as well as intravenous administration of micronized [^{3}H]-budesonide, approximately 60% of the recovered radioactivity is found in urine. The major metabolites, including 6β-hydroxybudesonide and 16α-hydroxyprednisolone, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide is detected in urine.

(b) (4)

Special Populations

Hepatic Impairment

In patients with liver cirrhosis, systemic availability of orally administered budesonide correlates with disease severity and is, on average, 2.5-fold higher compared with healthy controls. Patients with mild liver disease are minimally affected. Patients with severe liver dysfunction were not studied. Absorption parameters are not altered, and for the intravenous dose, no significant differences in CL or VSS are observed. The effect of hepatic impairment on the pharmacokinetics of UCERIS Rectal Foam have not been studied.

Renal Impairment

The pharmacokinetics of budesonide in patients with renal impairment has not been studied. Intact budesonide is not renally excreted, but metabolites are to a large extent, and might therefore reach higher levels in patients with impaired renal function. However, these metabolites have negligible corticosteroid activity as compared with budesonide.

Drug-Drug Interactions

Budesonide is metabolized via CYP3A4. Potent inhibitors of CYP3A4 can increase the plasma levels of (b) (4) budesonide (b) (4). Co-administration of ketoconazole (inhibitor of CYP 3A4) results in an eight-fold increase in AUC of oral budesonide, compared to budesonide alone. Grapefruit juice, an inhibitor of gut mucosal CYP3A, approximately doubles the systemic exposure of oral budesonide. Conversely, induction of CYP3A4 can result in the lowering of budesonide plasma levels. The effect of CYP3A4 inhibitors and inducers on the pharmacokinetics of UCERIS Rectal Foam have not been studied. [*See Dosage and Administration* (2) *and Drug Interactions* (7)].

Oral contraceptives containing ethinyl estradiol, which are also metabolized by CYP3A4, do not affect the pharmacokinetics of oral budesonide. Budesonide does not affect the plasma levels of oral contraceptives (ie, ethinyl estradiol).

In vitro interactions studies performed with budesonide showed that budesonide did not inhibit human cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2D6, or CYP2E1 at

concentrations ranging from 0.11 to 1130 ng/mL. Isoenzyme CYP3A4 was inhibited at the highest concentration tested but IC_{50} was >1130 ng/mL. UCERIS Rectal Foam is not expected to inhibit these enzymes in clinical use. No significant induction of CYP1A2, CYP2B6, CYP2C9 or CYP3A4/5 expression was observed in human hepatocytes in vitro at budesonide concentration up to 9000 nM (3.88 µg/mL).

In an in vitro study, budesonide was not a substrate of human transporters OATP1B3 and may be a weak substrate of OATP1B1. Budesonide at concentration up to 300 nM (129 ng/mL) did not inhibit OATP1B1 or OATP1B3.

Budesonide was not a substrate of BCRP and a weak substrate of P-glycoprotein. Budesonide was a weak inhibitor of P-glycoprotein (IC_{50} 9.78 µM or 4.21 µg/mL) and BCRP (IC_{50} 43.1 µM or 18.6 µg/mL). Budesonide foam is not expected to inhibit these transporters in clinical use.

4 Appendices

4.1 Individual Studies

Trial BUF-7/BIO

Title: Pharmacokinetics and Pharmacodynamics of Budesonide after rectal Application of BUDENOFALK Foam to Healthy Male Subjects

Sponsor: Dr. Falk Pharma GmbH

Clinical Site: Medical University Clinic BERGMANNSHEIL, Bochum

Analytical Site: [redacted] (b) (4)

Study Date: 02/1998-08/1998

Phase of Study: Phase 1 study

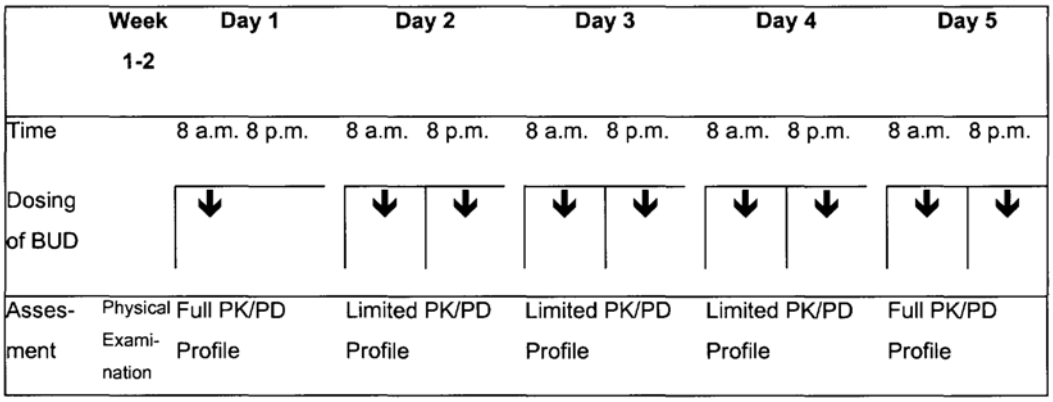
OBJECTIVE:

- To investigate the pharmacokinetics of a single rectal dose of Budenofalk foam (2 mg budesonide over 24 hours) in 18 healthy volunteers
- To assess the pharmacokinetics in the same subjects at steady state after administration of 2 mg budesonide as Budenofalk foam, given rectally b.i.d. over 5 days
- To assess the observed systemic effects on lymphocytes and granulocytes, and on serum cortisol.

STUDY DESIGN:

This was an open-label study to assess the pharmacokinetic of budesonide after administration of Budenofalk foam (2 mg budesonide) in canister in 18 eligible healthy male volunteers after administration of a single dose on day 1 (8. a.m) and b.i.d. dosing (at 8 a.m and 8 p.m) at days 2-5 rectally. Subjects were instructed to shake the can vigorously before use (similar to the instructions provided for BUCF3001/3002). Drug was administered following overnight fasting on Day 1. On day 2-4, the subjects received a breakfast after blood drawing and drug administration. On day 1 and 5, the subjects remained fasted and received a standardized lunch at 1:00 p.m., i.e. 5 hours after the application, at 07:00 p.m. they received a standardized dinner. Further, the subjects received on day 1 and 5 at 10:00a.m., 04:00p.m. and 06:00 p.m. 250 ml mineral water.

Full pharmacokinetics and pharmacodynamic parameters (cortisol, lymphocytes and granulocytes) were assessed over 24 hours on Day 1 and 5 while only the 8.a.m. and 8.p.m. time points were included on day 2-4.



Key inclusion criteria:
Healthy males subjects age between 21-40 with good health with a body weight not exceeding Broca indices 0.8 - 1.2

Key exclusion criteria:
- Previous or present gastro-intestinal, hepatic, or renal disease; or other states known to impair absorption, distribution, transformation or excretion of drugs,
- Females
- Allergy to budesonide

Study Population:
This study had 19 healthy volunteers enrolled and 18 of them completed the study as planned.
In volunteers 1-4 at day 1, the foam container released not a sufficient amount of foam, therefore the volunteers 1, 3 and 4 repeated day 1 later. Volunteer 2 was excluded from the study as he was not available for the repeat of study session 1. Subsequently, Volunteer 2 was replaced by Volunteer 19. Volunteer 5 had a worse headache / migraine at day 1 ~ 8:00 p.m. and he received an aspirin and a leucocytosis followed, therefore he repeated the 5 day dosing regimen two weeks later. The headache was considered not to be drug related.

Table- 1. Summary of Demographic

Parameter		Total (N=18)
Age (years)	Mean ±SD Min, Max	25.9 ± 2.9 20-31
Gender n (%)	Male Female	18 (100%) 0 (0%)
Race n (%)	Not provided	
Ethnicity n (%)	Hispanic or Latino Not Hispanic or Latino	
Height (cm)	Mean ±SD	180.4 ± 5.5
Weight (kg)	Mean ±SD	75.6 ± 6.0

Pharmacokinetic Measurements:
PK Blood Samples:
Full pharmacokinetic and pharmacodynamic profiles were established on day 1 and 5, while only the 8.a.m. and 8.p.m. time points were included on day 2-4.
Blood samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 36, 48, 60, 72, 84, 96, 96.5, 97, 97.5, 98, 99, 100, 101' 102, 104, 106, 108, 108.5, 109, 109.5, 110, 112, 113, 114, 116, 118, 120 h after the first dosing. Serum was separated from cellular material by sedimentation and subsequent centrifugation. Serum samples were stored at -20 ^{o}C until analyzed

PK Analysis:
Pharmacokinetic parameter estimates were calculated using Kinetica® software with non-compartmental methods.

Graphical presentation of the data is based on average concentration. Time points were not included in the graphical representation at which more than 1/3 of the data points were below the limit of detection. For the evaluation of the first day, data below the limit of detection were not considered. For the multiple dosing situations on day 5, data below the limit of detection were taken as % of the limit of detection

Bioanalytical Method:

- Serum budesonide levels were determined by HPLC/MS.
- Serum samples were stored at -20 ^{o}C until analyzed.
- The limit of quantification was set to 0.1 ng/ml.
- The concentrations of quality control samples were 0.2, 0.5, 1.0 ng/ml.
- 4 Calibration standards ranging from 60 to 3000 pg/ml. (unknown R2 value)
- It is not clear if the serum PK samples were collected and analyzed within stability limit. Stability of serum budesonide at -20^{o}C storage condition was not established during assay validation.
    - The study was conducted between 02/1998-08/1998
    - Sample extractions were performed from 03/08/1998 to 10/8/1998.
    - The longest possible time between sample collection and sample extraction would have been 249 days.

Method Validation:

- The bioanalytical method of HPLC/MS for measuring the concentration of serum budesonide this study was not validated in terms of stability of serum budesonide at various conditions (e.g., long term, short term, room temperature, freeze-thaw stabilities).

- Over the concentration range of 0.1 to 3 ng/ml within run precision varied between 0.7 and 15%; and between run precision were below 16.1% except at 0.12 ng/mL concentration (20.2%) for all three validation runs. Mean within run accuracy varied between 89% and 133 % and average accuracy was between 99% and 111% over this calibration range.

RESULTS:

Pharmacokinetics:

Figure 1: Mean (± S.D.) serum concentrations of budesonide after rectal administration of 2 mg budesonide as Budenofalk foam given as a single rectal dose on day 1 and twice daily on day 2-5 in healthy male subjects.

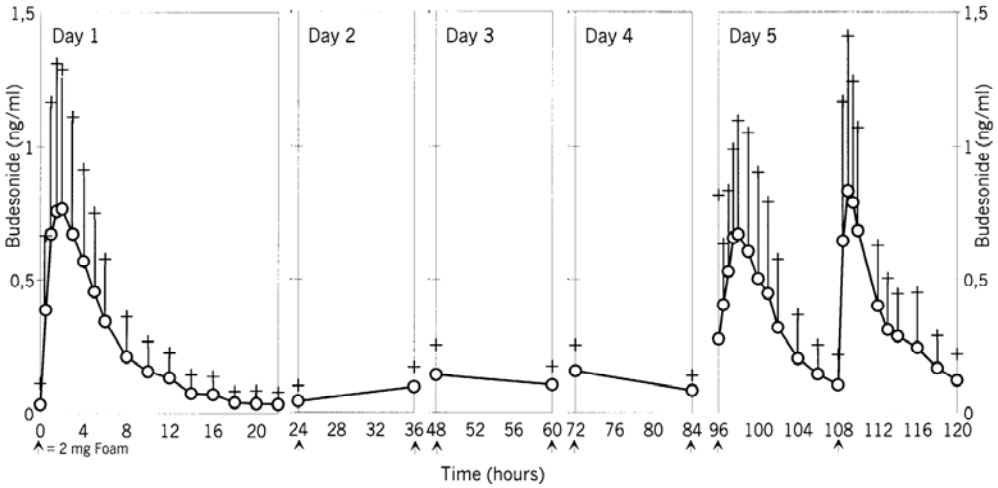


Table 2: Mean (+S.D.) pharmacokinetic parameters of 2 mg budesonide after rectal administration as Budenofalk foam, given as a single rectal dose on day 1 and twice daily on day 2 to 5 in healthy males.

	Day 1		Day 5		t-test
	Mean	S.D.	Mean	S.D.	p
n	18		18		
Dose (mg)	2.0		2.0		
$t_{½}$ (h)	4.05	1.28			
k_e (h^{-1})	0.19	0.07			
MRT (h)	6.36	1.73			
AUC_{0-12h} (ng*h/ml) or AUC_{ss} (ng*h/ml)	4.59	2.94	4.30	2.58	0.299
AUC_{∞} or AUC_{ss} (ng*h/ml)	5.36	3.60	4.30	2.58	0.051
AUC_{∞}/D (ng*h/(ml*mg) or AUC_{ss}/D (ng*h/(ml*mg)	2.68	1.80	2.15	1.29	0.051
Cl/f (L/min)	9.33	8.36	10.10	5.14	0.346
T_{max} (h)	2.14	1.28	1.81	0.88	0.172
C_{max} (ng/ml)	0.84	0.55	0.90	0.49	0.313
C_{max}/D (ng/(ml*mg)	0.42	0.28	0.45	0.24	0.313
$C_{average}$ (ng/ml)			0.36	0.21	

In addition to the PK parameters, the sponosr had also evalauted the PD parameters such as lymphocytes, granulocytes and cortisol. Since phase 3 studies (BUCF3001and BUCF 3002) had already assessed the effect of budosonide rectal foam on cortisol level, the PD parameters were not reviewed in this study.

SAFETY:
According to the sponsor, there was no drug related adverse event were documented in this study.

***Reviewer's Conclusion*:**

- *Based on the provided PK data (AUC0-12 and Cmax **)** on Day 1 and Day 5, there appears to be lack of significant accumulation in after multiple dose administration of rectal budesonide foam.*
- *However, it is hard to interpret the study result in this study as stability of serum budesonide was not properly established in the storage condition -20°C. Therefore, the study result will not have labeling implication.*

Trial: BUF-4/BIO

Title: A prospective, open, single centre clinical phase I study to evaluate the colonic spread and the pharmacokinetics of budesonide foam in patients with mildly to moderately active ulcerative colitis

Sponsor: Dr. Falk Pharma GmbH

Clinical Site: Clinical Department of Pharmacology,
Vienna University Medical School,
A-1090 Vienna, Austria

Analytical Site: (b) (4)

Study Date: 08/1999-04/2000

Phase of Study: Phase 1 study

OBJECTIVE:
The primary objective was:

- To establish the spread of budesonide foam in patients with mildly to moderately active ulcerative colitis.

The secondary objectives were:

- To investigate the persistence of the spread and homogeneity of the distribution of the test medication,
- To evaluate the time of retention of the budesonide foam,
- To investigate the serum pharmacokinetic profile of budesonide following application of foam formulation in patients with mildly to moderately active ulcerative colitis, and its pharmacodynamic effects on blood cells,
- To evaluate the acceptance of the foam by the patients,
- To study the safety and tolerability of the formulation as assessed by the incidence of adverse events and standard safety laboratory evaluations following single drug application.

Test Product; Dose and Mode of Administration
The ^{99M}Tc-labelled budesonide-foam test preparation was supplied in spray cans; each container was sufficient for seven actuations. One actuation corresponds to 2 mg budesonide, generating a volume of about 20 ml. The study medication was administered rectally.

STUDY DESIGN:
This was an open-label, single dose, single center, uncontrolled, exploratory phase 1 study to evaluate the colonic spread of a single 2 mg dose of ^{99m}Tc-labelled budesonide foam in canister (about 20 ml, equivalent to one pump actuation) in 12 patients with mildly to moderately active ulcerative colitis and inflammation in the rectum and colon. Subjects were instructed to shake the can vigorously before use (similar to the instructions provided for BUCF3001/3002). A single application of ^{99m}Tc-labelled budesonide foam was inserted into the rectum in the morning, after defecation. Patients were then asked to remain in a supine position for 4 hours. Gamma scintigraphic examination was performed immediately after dosing and at 0.05, 0.5, 1, 2, 4, and 6

hours to determine the extent of distribution of the foam within the colon. In addition, blood samples were collected immediately before and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours after dosing for pharmacokinetic and pharmacodynamic analysis.

Key inclusion criteria:
Male and non-pregnant and non-lactating female patients, 19-70 years of age, with a diagnosis of mildly to moderately active ulcerative colitis and a Disease Activity Index (DAI) ≥ 4 at baseline

Key exclusion criteria:

- Patients who had used steroids or non-steroidal anti-inflammatory drugs within two weeks prior to the start of the study
- Patients who were using concomitant drugs which could have influenced the underlying disease or interacted with budesonide
- Patients who had a contraindication to corticoid treatment or a known intolerance of budesonide and/or other glucocorticoid drugs

Study Population:
This study had 12 patients enrolled and all of them completed the study as planned. None was prematurely withdrawn from the study.

Table- 1. Summary of Demographic

Parameter		Total (N=12)
Age (years)	Mean ±SD Min, Max	41 ± 11.2 28-58
Gender n (%)	Male Female	8 4
Race n (%)	White	12
Height (cm)	Mean ±SD	174 ± 13.3
Weight (kg)	Mean ±SD	80.7 ± 14.2

Scintigraphic Evaluation:
The ^{99m}Tc-labelled budesonide-foam test preparation was supplied in spray cans. The foam was labelled by the addition of an aqueous ^{99m}Tc-Sulfur-colloid to the foam generating solution. According to the sponsor, ^{99m}Tc was selected after it had been established that this isotope does not alter the presentation or consistency of the budesonide foam formulation. As this was a single dose study, the sponsor's believed that the patients' exposure to radiation was negligible due to:

- low dose administered (3 MBq),
- local administration and short duration (< 24 h) of residence in the bowel,
- reasonably short decay half-life of ^{99m}Tc (6.02 h).

Scintigraphic imaging was performed using a single head, large field of view gamma camera equipped with a low energy high resolution collimator. Planar images from anterior and posterior were taken with the patient in supine position. Acquisition time per image was 5 minutes with the abdomen and pelvic region within the field of view. Images were taken at 0.05, 0.5, 1, 2, 4, and 6 hours after application of the ^{99m}Tc labelled foam. Patients remained in supine position and did not move for 4 hours. For better anatomical orientation, additional images after each time point using radioactive markers were performed. The markers were placed over the xiphoid, the umbilicus and the left spina iliaca anterior superior. ^{57}Co point sources with a gamma energy close to ^{99m}Tc were to be used as markers.

The gamma camera scans were to be analysed by two separate assessors, who both independently evaluated the radioactivity, the homogeneity, the persistence and the spread of the foam throughout each of the following seven abdominal regions: transverse colon, proximal third of descending colon, middle third of descending colon, distal third of descending colon, proximal half of sigmoid colon, distal half of sigmoid colon and rectum.

Radioactivity:
The radioactivity in each region was to be expressed as a fraction of the total radioactivity in the abdomen as a whole at each time point. Radioactivity in the whole abdomen was defined as the total count from the assessment with maximum count of the sum of all sections at one of the time point during the time period of t = 0.05 and 6 hours.
In the first step of the evaluation, irregular regions were to be drawn for different anatomical segments of the colon. Standard software routine (GMS software 3.0, Toshiba) was to be used and total counts within the different regions were to be calculated. Only regions with clearly visible activity were to be taken into consideration. To correct in part for attenuation differences for the different anatomical regions, counts from anterior and posterior images were to be added and the result to be expressed as percentage of the total colonic activity. Data were not to be corrected for physical decay.
To calculate the spread of the foam within the colon, an inter-two-point length measurement and scale display algorithm, which is part of the standard GMS software, was to be used. Starting with the most distal activity (the anus), the length of the spread of the foam was to be approximated by straight lines along the colonic activity. The scale was to be calibrated in centimeters.

Homogeneity:
Homogeneity was to be classified by visual inspection as 0 = absent, 1 = not homogenous, and 2 = homogeneous. Analysis of homogeneity of foam in the colon was to be done by listing the patient's individual values and by frequency counts. These data were to be analysed descriptively for exploratory purposes only.

Persistence:
The persistence of the test drugs in the bowel segments was to be evaluated by comparing the 4 and 6 hours scans with the best scan up to 2 hours. The persistence was to be scored as 0 = absent, 1 = poor, 2 = fair, 3 = good. Analysis of persistency of foam in the colon was to be done by listing the patient's individual values and by frequency counts. These data were to be analysed descriptively for exploratory purposes only.

Pharmacokinetic:
Pharmacokinetic serum concentration were determined at t = 0, 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, and 8 hours following the dose administration. At each sampling time point, a 10 ml blood sample was to be taken for the preparation of serum. Pharmacokinetic parameter estimates were calculated using computer programme PC Modfit (Version 1.25) was with non-compartmental methods.

Parameter	Method	Sample	Volume [ml]	Scheduled Day/Time
Pharmacokinetics	Scintillation counting	Whole blood	2 ml each	Day 2 at t=0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 h
	HPLC-MS	Serum (serum monovettes)	10 ml each	Day 2 at t=0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 h
Pharmacodynamics	Coulter-counter and differential blood counts	EDTA blood	2 ml each	Day 2 at t=0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 h

Bioanalytical Method:

- Serum budesonide levels were determined by HPLC-MS/MS.
- Serum samples were stored at -20 ^{o}C until analyzed.
- The limit of quantification was set to 0.1 ng/ml.
- The concentrations quality control samples were 0.4, 4.85 and 8.32 ng/ml.
- For QC samples, the accuracy was between 95.5.6 and 108.2 %
- Calibration standard curve consisted of 8 level ranged from 1 to 10 ng/mL in human plasma, with an LLOQ of 0.1 ng/mL, and was calculated using a linear regression (weighted 1/x2). The R2 value was 0.999.
- It is not clear if the serum PK samples were collected and analyzed within stability limit. Stability of serum budesonide at -20^{o}C storage condition was not established during assay validation.
    - The first PK sample was collected on 13 August 1999 and the last sample was collected on 6 April 2000.
    - All samples were analyzed on 17 May 2000
    - PK samples were stored at -20°C for up to 278 days prior to analysis.

Method Validation:

- Sponsor submitted a validated report for HPLC/MS bioanalytical method for measuring the concentration of budesonide in human plasma (not in human serum). This method validation report in human plasma did not provide information regarding stability of budesonide in human serum or plasma at various conditions (e.g., long term, short term, room temperature, freeze-thaw stabilities).
- Lower limit of quantification (LLQ) was established at 0.l ng/ml.
- QC samples were at 0.1, 0.4, 4.8 and 10.4 ng/ml and their within run precision varied between 4.10 and 9.10%; average and between run precision were below 7.44% for all three validation runs. Mean within run accuracy varied between 81.7% and 105.8 % and average accuracy was between 82.0% and 98.0% over this calibration range.

RESULTS:

Exposure:

The extent of exposure was based on the difference of weight of the budesonide foam can before and after drug application. Data were available for 11 of the 12 patients because the weight of the can before administration for patient 03 was not measured.

Table 2: Treatment Exposure

Patient #	Weight of dispensed foam (g)	Administered budesonide dose (mg)
01	1.0	1.7
02	1.8	3.0
03	-	-
04	1.2	2.0
05	1.1	1.8
06	1.3	2.2
07	1.3	2.2
08	1.4	2.3
09	1.1	1.8
10	1.2	2.0
11	1.0	1.7
12	1.3	2.2
Mean (SD)	1.2 (0.23)	2.1 (0.38)

Pharmacokinetics:

Figure 1: Mean(± S.D.) serum concentrations of budesonide vs. time

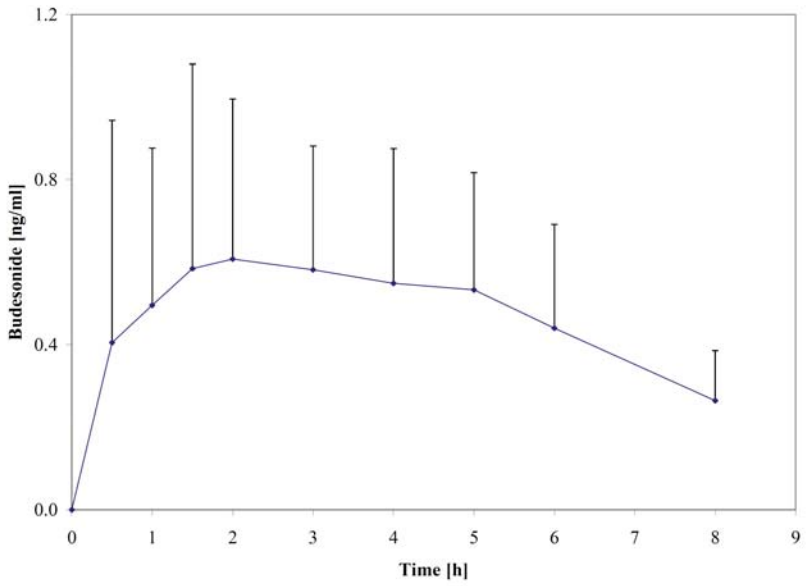


Table 3: Pharmacokinetic parameters of 2 mg budesonide in human serum after rectal administration of 2 mg budesonide foam

Patient #	t_{max}	C_{max}	AUC(0-8h)	AUC(0-24h)	k	$t_{1/2}$
	h	ng/ml	ng.h/ml	ng.h/ml	1/h	h
1	1.5	0.383	2.38	3.39	0.180	3.84
2	4.0	1.000	5.57	7.45	0.240	2.88
3	2.0	0.754	3.92	5.96	0.139	4.99
4	6.0	0.626	2.75	.	.	.
5	4.0	1.220	6.33	7.29	0.392	1.77
6	3.0	0.165	0.918	1.84	0.086	8.08
7	2.0	1.200	4.63	5.13	0.352	1.97
8	5.0	0.428	2.07	.	.	.
9	3.0	0.567	2.68	3.05	0.317	2.18
10	1.5	1.790	7.27	9.73	0.160	4.33
11	3.0	0.499	2.85	4.38	0.155	4.47
12	2.0	0.574	3.08	3.61	0.299	2.32
Mean	3.08	0.767	3.70	5.18	0.232	3.66
SD	1.43	0.456	1.89	2.42	0.103	1.83
Max	6.00	1.790	7.27	9.73	0.392	8.08
Min	1.50	0.165	0.918	1.84	0.086	1.77
Median	3.00	0.600	2.97	4.75	0.210	3.41

Half-lifes were not determined for patient 04 and 08 due to insufficient data point at terminal phase. In addition, due to double peak profiles that were observed in several subjects (5 out 12 subjects) and due to insufficient data points up to 8 h postdose, the terminal phase half-life times could only be estimated with some degree of uncertainty. Therefore, the extrapolated areas up to 24 h postdose, which depend on a well-defined terminal phase half-life, could also only be estimated with some degree of uncertainty.

As serum concentrations were determined up to 8 h following the time of administration, an extrapolation was made to estimate the AUC(0-24h) using the following formula which relies on a well-defined terminal phase half-life being available:

AUC (0-24h) = AUC (0-Ttast) + Clast *I* k* (l-$e^{-k(24-Tlast)}$)

Scintigraphic Evalution:

Figure 2: Overall Spread of Budesonide Foam

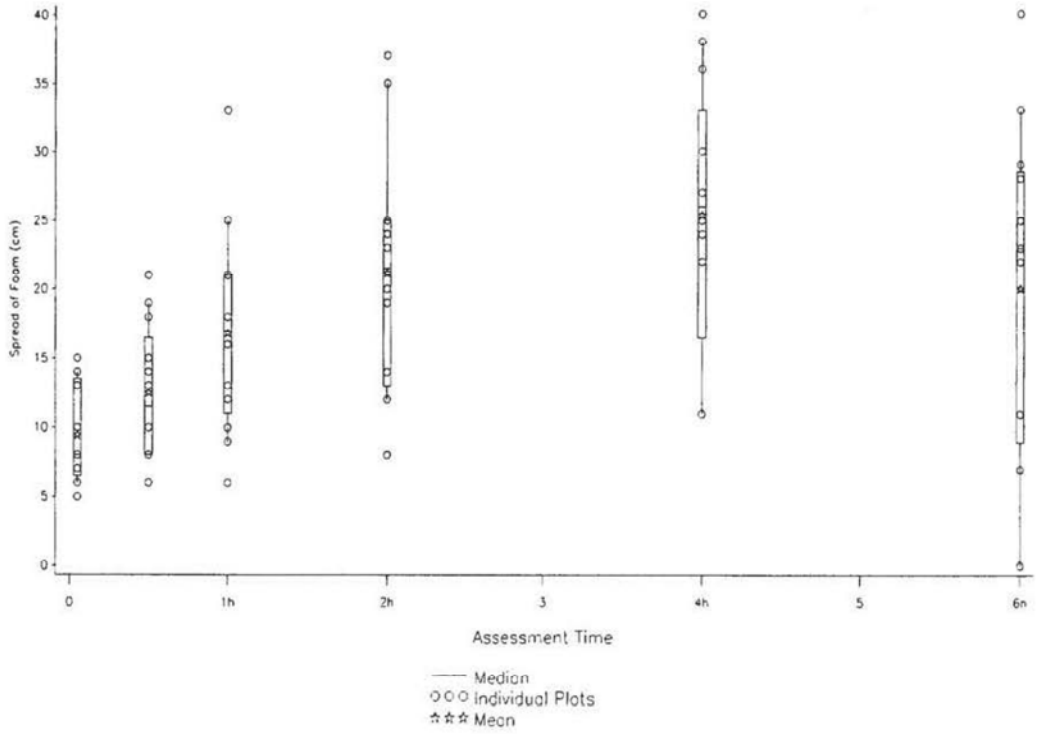
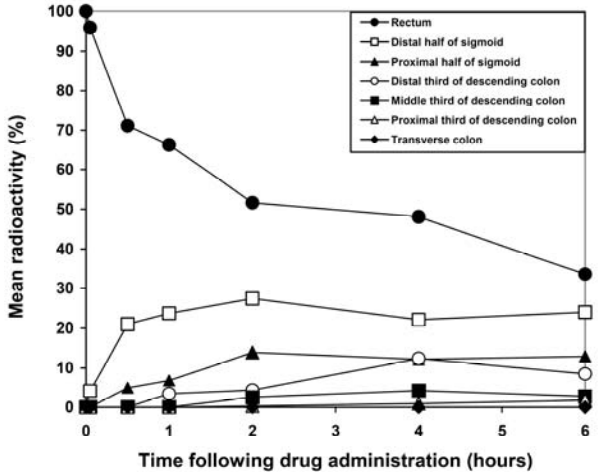


Table 4: Spread of foam in patients

			Disease		Length and time (h) of maximum spread
'atient	**Sex**	**Age**	**Diagnosis**	**Extent of Inflammation (cm)**	**Foam**
1	Male	28	Left-sided UC	Upper half desc. colon (70cm)	11cm (4h)
2	Male	31	Left-sided UC	Upper half desc. colon (60cm)	40cm (4h)
3	Male	50	Left-sided UC	Upper half desc. colon (80cm)	12cm (1h)
4	Female	45	Left-sided UC	Upper half desc. colon (85cm)	36cm (4h)
5	Female	42	Left-sided UC	Upper half desc. colon (50cm)	25cm (4h)
6	Male	54	Proctosigmoiditis	Sigmoid colon (22cm)	33cm (6h)
7	Male	38	Left-sided UC	Upper half desc. colon (90cm)	29cm (6h)
8	Male	28	Left-sided UC	Upper half desc. colon (33cm)	30cm (4h)
9	Male	31	Left-sided UC	Upper half desc. colon (50cm)	18cm (0.5h)
10	Female	58	Left-sided UC	Upper half desc. colon (50cm)	27cm (4h)
11	Male	34	Left-sided UC	Upper half desc. colon (end of inflammation not seen)	23cm (6h)
12	Female	56	Left-sided UC	Upper half desc. colon (60cm)	38cm (4h)

Figure 3: Spread of Budesonide Foam Across the Colon:



The maximal budesonide spread ranged between 11 and 40 cm. the budesonide foam progressively spread with time towards the descending colon, reached a maximum spread (±SD) of 25.4 ± 10.3 cm at 4 h.

Since Homogeneity and Persistence were subjective and exploratory measures only, these parameters were not reviewed.

SAFETY:

Safety was assessed by the incidence of emergent adverse events, haematological and biochemical changes, vital signs and physical examination. During the study (4 to 6 days follow-up according to patients), 16 adverse events were reported by a total of five patients. None of the adverse events was considered as serious. All were considered to be unrelated to the study drug. Some new abnormal laboratory values were observed, but none were considered to be clinically relevant. There was a slight decrease in blood pressure one day after budesonide administration (Visit 2), but this decrease was considered unlikely to be related to the study drug. According to the sponsor, there was death, serious adverse event or other significant adverse event occurred during the study.

***Reviewer's Conclusion*:**

- *Although the PK parameter in UC patients in this study appears to be similar to that of healthy male subjects in study BUF-7/BIO, it is difficult to interpret the result of this study and make direct comparison. Budesonide serum PK samples in this study BUF-4 were stored at -20^{o}C until analysis and the concentration of budesonide was analyzed by HPLC-MS/MS. However, the stability of serum budesonide at -20^{o}C storage condition was not established during the assay development in both study BUF-7 in healthy subjects and study BUF-4 in UC patients. Therefore, it is not clear if the serum PK samples were collected and analyzed within stability limit in both studies.*
- *In addition, the PK samples were only collected up to 8 hours and were not sufficient to adequately characterize the terminal phase.*
- *Since this scintigraphy study was exploratory in nature, data from this scintigraphy study is not recommended to be included in the label.*

Trials BUCF3001:

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of Budesonide Foam (2 mg/25 mL BID for 2 Weeks, Followed by 2 mg/25 mL QD for 4 Weeks) Versus Placebo in Subjects with Active Mild to Moderate Ulcerative Proctitis or Proctosigmoiditis.

Objectives:

Primary: To establish the efficacy profile of rectally administered budesonide foam administered as 2 mg/25 mL BID for 2 weeks followed by 2 mg/25 mL QD for 4 weeks, as compared to an equivalent volume of rectally administered placebo foam over the same dosing schedule, in subjects who presented with a diagnosis of active mild to moderate ulcerative proctitis (UP) or proctosigmoiditis (UPS).

Secondary: To confirm the safety with budesonide foam following 6 weeks of dosing in subjects with active mild to moderate UP or UPS.

Methodology:
This was a Phase 3, randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of budesonide foam in subjects with active mild to moderate proctitis or proctosigmoiditis. Subjects were randomized to study treatment in a 1:1 ratio to receive either 2 mg/25 mL budesonide foam BID for 2 weeks followed by 2 mg/25 mL QD for 4 weeks, or placebo foam BID for 2 weeks followed by placebo foam QD for 4 weeks.

The study consisted of the following 4 phases: Screening (Visit 1; Day -21 to Day -7), Run-In/Stabilization (Visit 2; Days -7 to Day -1), Treatment (Visits 3-7; Days 1-42), and Follow-up or End of Study (Visit 8; Day 56; 14 ± 2 days). The total duration of the study was up to approximately 11 weeks, depending on the timing of study visits.

Number of subjects (planned and analyzed): Approximately 280 subjects were planned for randomization and dosing. Actual enrollment included 265 randomized subjects, all of whom received study drug and were included in the intent-to-treat and safety analyses. A total of 257 subjects were included in the per protocol population.

Test Product, Dose and Mode of Administration, Batch Number:
Budesonide foam, 2 mg/25 mL BID for 2 weeks, followed by 2 mg/25 mL QD for 4 weeks For the first 2 weeks following Randomization, subjects were instructed to administer a dose of study drug each morning, and again at approximately 12 hours post the first morning dose. After 14 days of treatment, subjects were instructed to administer one dose of study drug in the evening at bedtime for the remainder of the treatment period (28 days). Batch Numbers: BGD-C, CAN-C.

Duration of Treatment:
Total duration of the study was up to approximately 11 weeks. The study consisted of the following phases: Screening Phase (Visit 1; Day -21 to Day -7), Run-In/Stabilization (Visit 2; Days -7 to Day -1), Treatment Phase (Visits 3-7; Days 1-42), Observation Period (14 ± 2 days, which occurred after treatment was completed), and Follow-up or End of Study (Visit 8; Day 56).

Reference Therapy, Dose and Mode of Administration, Batch Number:
Placebo foam, 25 mL BID for 2 weeks, followed by QD for 4 weeks with dosing as described for budesonide. Batch numbers: BGE-C, CDC-C.

Results:

Disposition and Demographics Results
A total of 265 subjects were randomized to 1 of 2 double-blind treatment groups and received at least 1 dose of study drug: 133 subjects to budesonide foam 2 mg/25 mL and 132 subjects to placebo. All of these subjects received at least 1 dose of study drug. Overall, 85% of subjects completed the study (budesonide 81%, placebo 88%). The most common reasons for early discontinuation from the study were AEs (budesonide 10%, placebo 5%), "other" (3%, 5%; of which lack of efficacy was the most common [2%, 5%]), and subject request (5%, 2%).

The mean (SD) age of subjects overall was 42 (13.6) years with ≥ 94% of subjects in each group < 65 years of age. While both treatment groups had more female subjects than male subjects, the difference in these proportions was larger in the placebo group (males 39%, females 61%) than in the budesonide group (46%, 54%). Most subjects were White (budesonide 87%, placebo 93%) and 16% overall were Hispanic or Latino. The 2 treatment groups were similar with respect to mean weight and body mass index.

Efficacy results: See Clinical review.

HPA safety results:

HPA assessment procedures:

Prior to enrollment, subjects were administered an ACTH challenge test given as 250 µg dose administered intramuscularly in the morning between 8 – 10 am at baseline. Subjects were required to have a 30 minute post ACTH challenge cortisol level >18 µg/dL to be enrolled into the trial.

Morning serum cortisol level were measured in all subjects at baseline, week 1, week 2, week 4, and week 6. If morning cortisol level in any subject were <5 µg/dL, they were administered and unscheduled ACTH challenge test after stopping the treatment for at least 24 hours. If a subject fail the unscheduled ACTH challenge test (i.e., having the 30 minute post ACTH challenge cortisol level <18 µg/dL), that subject would be discontinued from the trial.

A final ACTH challenge test was administered to all subjects still in the trial at week 6.

Cortisol Assay:

The bioanalyses of serum cortisol were performed by two central laboratories:

(b) (4)

(b) (4) used the commercial competitive solid-phase radioimmunoassay systems Immulite 2000 and Immulite 2500. Adequate in-house validation was done for both systems at (b) (4) The analytical range was 1 – 50 µg/dL. Precisions and accuracy was within ±15% except for precision of the lowest standard (1.1 µg/dL) where intra-assay precision on the Immulite 2500 was 18.86%. Storage stability at room temperature was documented for 5 days. 3 samples (<0.1%) were received outside of the 5-day stability window.

(b) (4) used the commercial competitive solid-phase radioimmunoassay system Immulite 2000. The manufacturer's validated range was 1 – 50 µg/dL. Storage stability at 2 – 8 ºC was noted as 7 days. No specific in-house validation was conducted at (b) (4). The sponsor

provided external QC report by (b) (4) showing comparable performance with peers instruments and internal QC results during the time frame of trial samples analysis showing adequate precision and accuracy of the QC samples. The sponsor stated all trial samples were received within the 7-day stability window.

Results:

There were initial decreases in serum cortisol levels at Weeks 1 and 2 that gradually returned toward baseline levels by Week 6 in the budesonide group (Figure 1). At Week 6, mean (± SD) changes from baseline in total serum cortisol were -15.09 (± 181.146) nmol/L in the budesonide group and 5.35 (± 177.620) nmol/L in the placebo group (Table 1). The greater decreases in serum cortisol levels during Weeks 1 and 2, compared with Weeks 4 and 6, are likely due to BID dosing during the first 2 weeks and QD dosing during the subsequent 4 weeks. Mean total serum cortisol had returned to 96% of baseline levels at Week 6. It should be noted that 11 subjects from the budesonide arm that had failed an unscheduled ACTH challenge test prior to weeks 6 were discontinued from the trial and could partly contributed to the apparent return to baseline cortisol level (only 1 subject in the placebo arm were discontinued for the same reason).

Serum cortisol levels > 5 μg/dL (138 nmol/L) were maintained in at least 84% of subjects in the budesonide and placebo treatment groups at Weeks 1, 2, 4, and 6 (Table 2). The proportion of subjects who maintained serum cortisol levels > 5 μg/dL was lower in the budesonide group than in the placebo group at Weeks 1 and 2 (BID treatment phase): 84% budesonide versus 98% placebo at Week 1 and 85% versus 98%, respectively, at Week 2. During the QD treatment phase (Weeks 3 through 6) this difference between treatments was attenuated and similar percentages of budesonide-treated and placebo-treated subjects had serum cortisol levels > 5 μg/dL by Week 6 (96% and 97%, respectively). As noted above, 12 subjects (mainly from the budesonide arm) who had failed the unscheduled ACTH challenge test were discontinued from the trial prior to week 6 and may partly contributed to this apparent attenuation in the budesonide arm.

Table 3 shows a further breakdown of the proportion of subjects with low, normal, and high morning serum cortisol levels. Most subjects in the budesonide arm that were outside of the normal range were on the low side.

The normal response to ACTH challenge at week 6 includes 3 criteria, as defined in the cosyntropin label: 1) morning cortisol level > 5 μg/dL (prechallenge); 2) increase in cortisol level by ≥ 7 μg/dL (193 nmol/L) above the morning (pre-challenge) level following ACTH challenge; and 3) cortisol level of > 18 μg/dL (500 nmol/L) following ACTH challenge. At baseline, 80% of subjects in the budesonide foam group had a normal response to the ACTH challenge and at Week 6, 70% of subjects had a normal response to the ACTH challenge; this difference was similar in the placebo group (86% and 78%), respectively. However, if one take into account subjects who were discontinued prior to week 6 due to failure of the unscheduled ACTH challenge test, the baseline vs. week 6 rates were 80% and 64% for budesonide and 86% and 77% for placebo; A larger difference was seen (a decrease of 16% for budesonide vs a decrease of 9% for placebo).

Table 1: Change from baseline in mean serum cortisol levels (safety population)

Total Serum Cortisol, nmol/L	Placebo N = 131	Budesonide foam 2 mg/25 mL N = 134
Baseline	N = 131	N = 134
Mean (SD)	361.04 (124.93)	364.60 (148.095)
Week 1	N = 126	N = 130
Mean (SD)	364.01 (141.95)	305.52 (148.80)
Mean change from Baseline (SD)	5.94 (136.738)	-60.45 (170.565)
Week 2	N = 127	N = 126
Mean (SD)	360.37 (131.07)	295.83 (149.57)
Mean change from Baseline (SD)	-3.55 (134.531)	-65.90 (163.052)
Week 4	N = 118	N = 117
Mean (SD)	361.75 (136.15)	331.38 (145.67)
Mean change from Baseline (SD)	-1.89 (137.682)	-38.61 (153.403)
Week 6	N = 115	N = 109
Mean (SD)	367.86 (154.19)	356.27 (153.37)
Mean change from Baseline (SD)	5.35 (177.620)	-15.09 (181.146)

Figure 1: Mean ± SD cortisol values by visit and treatment group (safety population)

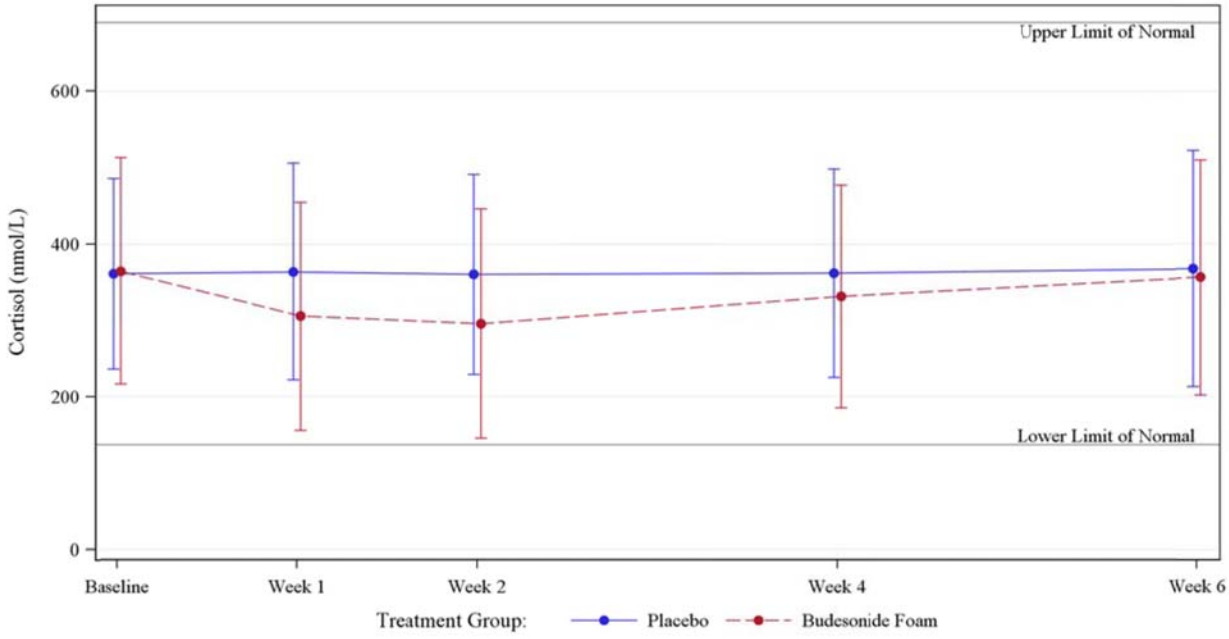


Table 2: Proportion of Subjects with Normal Endogenous Cortisol Levels (> 5 µg/dL) During the Study and Proportion of Subjects with Normal Response to ACTH Challenge

Cortisol Parameter	Budesonide Foam 2 mg/25 mL N = 134 n (%)	Placebo N = 131 n (%)
Total cortisol > 5 µg/dL (lower limit of normal range)		
Baseline	130/134 (97.0)	129/131 (98.5)
Week 1	112/134 (83.6)	123/126 (97.6)
Week 2	109/129 (84.5)	125/127 (98.4)
Week 4	108/117 (92.3)	115/118 (97.5)
Week 6	106/110 (96.4)	111/115 (96.5)
Normal response to ACTH challenge[a]		
Baseline	105/132 (79.5)	113/131 (86.3)
Week 6	75/107 (70.1)	88/113 (77.9)
Week 6 (including subjects discontinued)[b]	75/118 (63.6)	88/114 (77.2)
Cortisol Following ACTH Challenge > 18 µg/dL		
Baseline	128/132 (97.0)	129/131 (98.5)
Week 6	95/107 (88.8)	109/113 (96.5)
Week 6 (including subjects discontinued)[b]	95/118 (80.5)	109/114 (95.6)

[a] The normal response to ACTH challenge includes 3 criteria, as defined in the cosyntropin label: 1) morning cortisol level > 5 µg/dL; 2) increase in cortisol level by ≥ 7 µg/dL above the morning (pre-challenge) level following ACTH challenge; and 3) cortisol level of > 18 µg/dL following ACTH challenge.

[b] The total subjects include 11 subjects in the budesonide arm and 1 subject in the placebo arm that was discontinued prior to week 6 due to failure of an unscheduled ACTH challenge test (i.e., their post ACTH challenge cortisol level was <18 µg/dL).

Table 3: Proportions of Subjects with Low, Normal, and High Serum Cortisol Levels During the Study (Safety Population)

Visit	Result	Placebo N = 131 n (%)	Budesonide foam 2 mg/25 mL N = 134 n (%)
Baseline		N = 131	N = 134
	Low	2 (1.5)	4 (3.0)
	Normal	127 (96.9)	128 (95.5)
	High	2 (1.5)	2 (1.5)
Week 1		N = 126	N = 134
	Low	1 (0.8)	22 (16.4)
	Normal	119 (94.4)	110 (82.1)
	High	6 (4.8)	2 (1.5)
Week 2		N = 127	N = 129
	Low	2 (1.6)	20 (15.5)
	Normal	123 (96.9)	108 (83.7)
	High	2 (1.6)	1 (0.8)
Week 4		N = 118	N = 117
	Low	3 (2.5)	9 (7.7)
	Normal	112 (94.9)	104 (88.9)
	High	3 (2.5)	4 (3.4)
Week 6		N = 115	N = 110
	Low	4 (3.5)	4 (3.6)
	Normal	107 (93.0)	105 (95.5)
	High	4 (3.5)	1 (0.9)

Trial BUCF3002:

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of Budesonide Foam (2 mg/25 mL BID for 2 Weeks, Followed by 2 mg/25 mL QD for 4 Weeks) Versus Placebo in Subjects with Active Mild to Moderate Ulcerative Proctitis or Proctosigmoiditis.

Objectives:

Primary: To establish the efficacy profile of rectally administered budesonide foam administered as 2 mg/25 mL BID for 2 weeks followed by 2 mg/25 mL QD for 4 weeks, as compared to an equivalent volume of rectally administered placebo foam over the same dosing schedule, in subjects who presented with a diagnosis of active mild to moderate ulcerative proctitis (UP) or proctosigmoiditis (UPS).

Secondary: To confirm the safety with budesonide foam following 6 weeks of dosing in subjects with active mild to moderate UP or UPS.

Methodology:

This was a Phase 3, randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of budesonide foam in subjects with active mild to moderate proctitis or proctosigmoiditis. Subjects were randomized to study treatment in a 1:1 ratio to receive either 2 mg/25 mL budesonide foam BID for 2 weeks followed by 2 mg/25 mL QD for 4 weeks, or placebo foam BID for 2 weeks followed by placebo foam QD for 4 weeks.

The study consisted of the following 4 phases: Screening (Visit 1; Day -21 to Day -7), Run-In/Stabilization (Visit 2; Days -7 to Day -1), Treatment (Visits 3-7; Days 1-42), and Follow-up or End of Study (Visit 8; Day 56; 14 ± 2 days). The total duration of the study was up to approximately 11 weeks, depending on the timing of study visits.

Number of subjects (planned and analyzed): Approximately 280 subjects were planned for randomization and dosing. Actual enrollment included 281 randomized subjects, all of whom received study drug and were included in the intent-to-treat and safety analyses. A total of 273 subjects were included in the per protocol population.

Test Product, Dose and Mode of Administration, Batch Number:

Budesonide foam, 2 mg/25 mL BID for 2 weeks, followed by 2 mg/25 mL QD for 4 weeks For the first 2 weeks following Randomization, subjects were instructed to administer a dose of study drug each morning, and again at approximately 12 hours post the first morning dose. After 14 days of treatment, subjects were instructed to administer one dose of study drug in the evening at bedtime for the remainder of the treatment period (28 days). Batch Numbers: BGD-C, CAN-C.

Duration of Treatment:

Total duration of the study was up to approximately 11 weeks. The study consisted of the following phases: Screening Phase (Visit 1; Day -21 to Day -7), Run-In/Stabilization (Visit 2; Days -7 to Day -1), Treatment Phase (Visits 3-7; Days 1-42), Observation Period (14 ± 2 days, which occurred after treatment was completed), and Follow-up or End of Study (Visit 8; Day 56).

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo foam, 25mL BID for 2 weeks, followed by QD for 4 weeks with dosing as described for budesonide. Batch numbers: BGE-C, CDC-C.

Results:

Disposition and Demographics Results
A total of 281 subjects were randomized to 1 of 2 double-blind treatment groups: 134 subjects to budesonide foam 2 mg/25 mL and 147 subjects to placebo. All of these subjects received at least 1 dose of study drug. Overall, 85% of subjects completed the study (budesonide 86%, placebo 85%). The most common reasons for early discontinuation from the study were AEs (budesonide 10%, placebo 4%), subject request (3%, 5%), and "other" (2%, 5%), of which lack of efficacy was the most common (0, 3%).

The mean (SD) age of subjects overall was 43 (13.4) years with ≥ 90% of subjects in each group < 65 years of age. While both treatment groups had more female subjects than male subjects, the difference in these proportions was larger in the placebo group (males 43%, females 57%) than in the budesonide group (46%, 54%). Most subjects were White (budesonide 89%, placebo 92%) and 11% overall were Hispanic or Latino. The 2 treatment groups were similar with respect to mean weight and BMI.

Efficacy results: See Clinical review.

HPA safety results:

HPA assessment procedures:

Prior to enrollment, subjects were administered an ACTH challenge test given as 250 µg dose administered intramuscularly in the morning between 8 – 10 am at baseline. Subjects were required to have a 30 minute post ACTH challenge cortisol level >18 µg/dL to be enrolled into the trial.

Morning serum cortisol level were measured in all subjects at baseline, week 1, week 2, week 4, and week 6. If morning cortisol level in any subject were <5 µg/dL, they were administered and unscheduled ACTH challenge test after stopping the treatment for at least 24 hours. If a subject fail the unscheduled ACTH challenge test (i.e., having the 30 minute post ACTH challenge cortisol level <18 µg/dL), that subject would be discontinued from the trial.

A final ACTH challenge test was administered to all subjects still in the trial at week 6.

Cortisol Assay:

The bioanalyses of serum cortisol were performed by two central laboratories:

(b) (4)

(b) (4) used the commercial competitive solid-phase radioimmunoassay systems Immulite 2000 and Immulite 2500. Adequate in-house validation was done for both systems at (b) (4) The analytical range was 1 – 50 µg/dL. Precisions and accuracy was within ±15% except for precision of the lowest standard (1.1 µg/dL) where intra-assay precision on the Immulite 2500 was 18.86%. Storage stability at room temperature was documented for 5 days. 3 samples (<0.1%) were received outside of the 5-day stability window.

(b) (4) used the commercial competitive solid-phase radioimmunoassay system Immulite 2000. The manufacturer's validated range was 1 – 50 µg/dL. Storage stability at 2 – 8 ºC was noted as 7 days. No specific in-house validation was conducted at (b) (4). The sponsor

provided external QC report by (b) (4) showing comparable performance with peers instruments and internal QC results during the time frame of trial samples analysis showing adequate precision and accuracy of the QC samples. The sponsor stated all trial samples were received within the 7-day stability window.

Results:

There were initial decreases in serum cortisol levels at Weeks 1 and 2 that gradually returned toward baseline levels by Week 6 in the budesonide group (Figure 2). At Week 6, mean (± SD) changes from baseline in total serum cortisol were 9.59 (± 182.93) nmol/L in the budesonide group and -9.29 (± 148.66) nmol/L in the placebo group (Table 4). The greater decreases in serum cortisol levels at Weeks 1 and 2, compared with Weeks 4 and 6, are likely due to BID dosing during the first 2 weeks and QD dosing during the subsequent 4 weeks. Total serum cortisol had returned to approximately baseline levels at Week 6. It should be noted that 9 subjects from the budesonide arm that had failed an unscheduled ACTH challenge test prior to weeks 6 were discontinued from the trial and could partly contributed to the apparent return to baseline cortisol level (only 1 subject in the placebo arm were discontinued for the same reason).

Reviewer's notes: Eight subjects in the budesonide arm of this trial failed the unscheduled ACTH challenge test and were discontinued from the trial prior to week 6. One subject (1306-0011) had low morning cortisol level of <28 nmol/L at week 1 and also low level of 47 nmol/L at week 2. There was no mention of an unscheduled ACTH testing at either week 1 or week 2. The subject was discontinued from treatment at week 4 due to reason of low cortisol level. This subject, with 2 consecutive weeks of low morning cortisol level would have likely fail an ACTH challenge test and was considered as such for purpose of calculating rate of HPA suppression by this reviewer. Thus this reviewer uses the value of 9 subjects instead of 8 subjects when considering this population.

Serum cortisol levels > 5 μg/dL (138 nmol/L) were maintained in at least 84% of subjects in the budesonide and placebo treatment groups at Weeks 1, 2, 4, and 6 (Table 5). The proportion of subjects who maintained serum cortisol levels > 5 μg/dL was lower in the budesonide group than in the placebo group at Weeks 1 and 2 (BID treatment phase): 87% budesonide versus 99% placebo at Week 1 and 84% versus 99%, respectively, at Week 2. During the QD treatment phase (Weeks 3 through 6) this difference between treatments was attenuated and the percentages of budesonide-treated and placebo-treated subjects who had serum cortisol levels > 5 μg/dL by Week 6 (92% and 98%, respectively) were generally similar to those at baseline (96% and 99%, respectively). As noted above, 10 subjects (mainly from the budesonide arm) who had failed the unscheduled ACTH challenge test were discontinued from the trial prior to week 6 and may partly contributed to this apparent attenuation in the budesonide arm.

Table 6 shows a further breakdown of the proportion of subjects with low, normal, and high morning serum cortisol levels. Most subjects in the budesonide arm that were outside of the normal range were on the low side.

The normal response to ACTH challenge includes 3 criteria, as defined in the cosyntropin label: 1) morning cortisol level > 5 μg/dL (prechallenge); 2) increase in cortisol level by ≥ 7 μg/dL (193 nmol/L) above the morning (pre-challenge) level following ACTH challenge; and 3) cortisol level of > 18 μg/dL (500 nmol/L) following ACTH challenge. At baseline, 87% of subjects in the budesonide foam group had a normal response to the ACTH challenge and at Week 6, 67% of subjects had a normal response to the ACTH challenge; in the placebo group, these values were 85% and 75%, respectively. If one take into account subjects who were discontinued prior to

week 6 due to failure of the unscheduled ACTH challenge test, the baseline vs. week 6 rates were 87% and 62% for budesonide and 85% and 75% for placebo; A larger difference was seen (a decrease of 25% for budesonide vs a decrease of 10% for placebo).

Table 4: Change from baseline in mean serum cortisol levels (safety population)

Total Serum Cortisol, nmol/L	Placebo N = 147	Budesonide Foam 2 mg/25 mL N = 134
Baseline	N = 147	N = 134
Mean (SD)	373.38 (145.53)	349.58 (139.78)
Week 1	N = 143	N = 122
Mean (SD)	371.46 (135.99)	310.77 (141.16)
Mean change from Baseline (SD)	0.63 (108.69)	-36.15 (148.00)
Week 2	N = 139	N = 124
Mean (SD)	365.37 (139.09)	298.56 (142.13)
Mean change from Baseline (SD)	-10.89 (119.60)	-50.76 (157.37)
Week 4	N = 131	N = 116
Mean (SD)	366.81 (146.22)	335.30 (135.80)
Mean change from Baseline (SD)	-7.12 (137.70)	-17.00 (142.70)
Week 6	N = 126	N = 112
Mean (SD)	369.86 (145.46)	369.12 (161.98)
Mean change from Baseline (SD)	-9.29 (148.66)	9.59 (182.93)

Figure 2: Mean ± SD cortisol values by visit and treatment group (safety population)

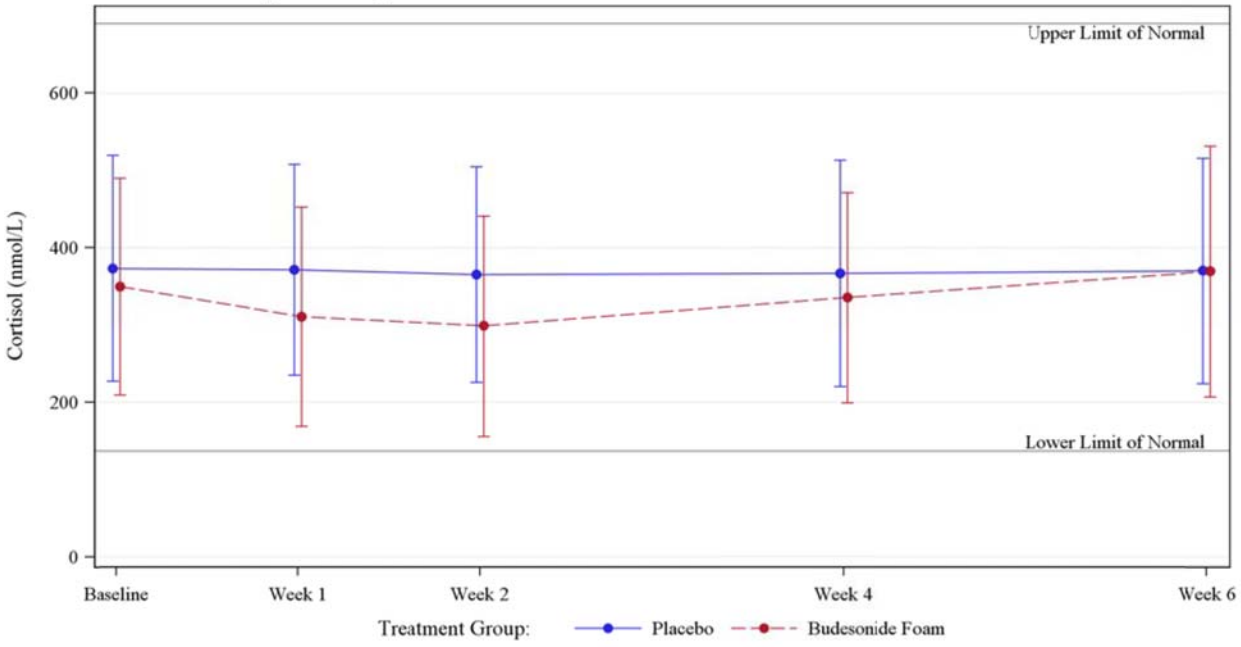


Table 5: Proportion of Subjects with Normal Endogenous Cortisol Levels (> 5 µg/dL) During the Study and Proportion of Subjects with Normal Response to ACTH Challenge

Cortisol Parameter	Budesonide Foam 2 mg/25 mL N = 134 n (%)	Placebo N = 147 n (%)
Total cortisol > 5 µg/dL (lower limit of normal range)		
Baseline	129/134 (96.3)	146/147 (99.3)
Week 1	112/129 (86.8)	141/143 (98.6)
Week 2	107/128 (83.6)	138/139 (99.3)
Week 4	110/118 (93.2)	128/131 (97.7)
Week 6	105/114 (92.1)	123/126 (97.6)
Normal response to ACTH challenge[a]		
Baseline	117/134 (87.3)	125/147 (85.0)
Week 6	73/109 (67.0)	92/122 (75.4)
Week 6 (including subjects discontinued)[b]	73/118 (61.9)	92/123 (74.8)
Cortisol Following ACTH Challenge > 18 µg/dL		
Baseline	133/134 (99.3)	146/147 (99.3)
Week 6	91/109 (83.5)	117/122 (95.9)
Week 6 (including subjects discontinued)[b]	91/118 (77.1)	117/123 (95.1)

[a] The normal response to ACTH challenge includes 3 criteria, as defined in the cosyntropin label: 1) morning cortisol level > 5 µg/dL; 2) increase in cortisol level by ≥ 7 µg/dL above the morning (pre-challenge) level following ACTH challenge; and 3) cortisol level of > 18 µg/dL following ACTH challenge.

[b] The total subjects include 9* subjects in the budesonide arm and 1 subject in the placebo arm that was discontinued prior to week 6 due to failure of an unscheduled ACTH challenge test (i.e., their post ACTH challenge cortisol level was <18 µg/dL). (* One of these 9 subjects was discontinued after low morning cortisol levels at weeks 1 and 2 but ACTH challenge were either not performed or not reported).

Table 6: Proportions of Subjects with Low, Normal, and High Serum Cortisol Levels During the Study (Safety Population)

Visit	Result	Placebo N = 147 n (%)	Budesonide foam 2 mg/25 mL N = 134 n (%)
Baseline		N = 147	N = 134
	Low	1 (0.7)	4 (3.0)
	Normal	142 (96.6)	127 (94.8)
	High	4 (2.7)	3 (2.2)
Week 1		N = 143	N = 129
	Low	2 (1.4)	17 (13.2)
	Normal	135 (94.4)	110 (85.3)
	High	6 (4.2)	2 (1.6)
Week 2		N = 139	N = 128
	Low	1 (0.7)	20 (15.6)
	Normal	134 (96.4)	107 (83.6)
	High	4 (2.9)	1 (0.8)
Week 4		N = 131	N = 118
	Low	3 (2.3)	7 (5.9)
	Normal	125 (95.4)	108 (91.5)
	High	3 (2.3)	3 (2.5)
Week 6		N = 126	N = 114
	Low	3 (2.4)	8 (7.0)
	Normal	117 (92.9)	102 (89.5)
	High	6 (4.8)	4 (3.5)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DILARA JAPPAR
08/15/2014

DOANH C TRAN
08/15/2014

JUSTIN C EARP
08/18/2014

NITIN MEHROTRA
08/18/2014

SUE CHIH H LEE
08/18/2014

OCP reviewed the data for ACTH stimulation tests performed in two pivotal Phase 3 studies. For efficacy and other aspects of safety of the proposed product, please see the review by Dr. Zana Marks of DGIEP.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205613 **Applicant: Salix** **Stamp Date: 11/15/2013**

Drug Name: Budesonide **Submission Type: 505(b)(1)**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted PK and PD comparability data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Please refer to filing memo section "Product and proposed dose" for more details about the drug product.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors	X			PopPK analysis was conducted.

	that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Request pediatric waiver (0-< (b) (4) years) and deferral ((b) (4) years)
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__Yes_____

Please convey the following IR to the sponsor:

- Submit (or provide the location of) the full bioanalytical assay validation reports for assays (i.e., HPLC-MS/MS assays) that were used to analyze the pharmacokinetic samples from clinical studies conducted in Europe and USA. Please refer to the following guidance for more information.

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf

- Please submit the following datasets and codes/scripts for independent review related population PK report entitled "population pharmacokinetics of budesonide foam":
  - All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
  - Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- It is noted that different drug product formulations were in the Europe (Studies BUF-7/BIO and BUF-4/BIO used Dr. Falk Pharma formulation) and USA (Studies BUCF3001 and BUCF3002 used a modified new formulation). Please explore the formulation impact on PK in the above reference population PK analysis.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**205613**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**DCP III**	**Generic Name**	**Budesonide**
Medical Division	**DGIEP**	**Drug Class**	**Non-halogenated synthetic glucocorticoid**
OCP Reviewer	**Lanyan Fang, Ph.D.**	**Indication(s)**	**active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge**
OCP Team Leader	**Sandhya Apparaju, Ph.D. (Acting)**	**Dosage Form**	**rectal foam**
Pharmacometrics Reviewer	**Lanyan Fang, Ph.D.**	**Dosing Regimen**	**1 metered dose (2 mg) administered twice daily for 2 weeks followed by 1 metered dose administered once daily for 4 weeks**
Pharmacometrics Team Leader	**Nitin Mehrotra, Ph.D.**	**Route of Administration**	**rectal**
Date of Submission	**11/15/2013**	**Sponsor**	**Salix**
Estimated Due Date of OCP Review	**TBD**	**Priority Classification**	**standard**
PDUFA	**9/15/2014**	**Dosing Strength**	**2 mg per metered dose**

Clinical Pharmacology and Biopharmaceutical Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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Reference Bioanalytical and Analytical Methods	X	2		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	1		BUF-7/BIO
Patients-				
single dose:	X	1		BUF-4/BIO
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	X	3		
Subpopulation studies -				
ethnicity:	X			popPK assessment
gender:	X			popPK assessment
Age:				
pediatrics:				
Body Weight	X			popPK assessment
geriatrics:				
renal impairment:	X			popPK assessment
hepatic impairment:	X			popPK assessment
Immunogenicity:				
PD -				
Phase 2:				
Phase 3:	X	2		BUF-6/UCA BUF-9/UCA
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	1		BUF-5/UCA
Phase 3 clinical trial:	X	2		BUCF3001 BUCF3002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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Population Analyses -				
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability	X			The applicant estimated the absolute BA based on published systemic exposures after i.v. administration of budesonide. (Page 36, BUF-7/BIO CSR)
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			The applicant compared the systemic exposures following administration of budesonide rectal foam versus in-house budesonide capsule formulation from other studies. (Table 4, BUF-7/BIO CSR)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
PK and PD comparability:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				

Pediatric development plan	X			
Literature References	X	1		Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid Eur. J. Respir. Dis., 1982, 63 (suppl.122): 86-95.
Total Number of Studies	X	13		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing memo

MOA and Indication:

This is an original 505(b)(1) submission for budesonide rectal foam containing 2 mg budesonide (per metered dose), a non-halogenated synthetic glucocorticoid, as the active ingredient. It is a mixture of the two epimers (22R and 22S) differing in the position of an acetal chain. Both epimers are active glucocorticoids applied in a mixture of approximately 1:1. The 22R-epimer is approximately (b) (4) than the 22S-epimer. Budesonide rectal foam is thought to have local anti-inflammatory effect in the colon.

Budesonide rectal foam is indicated for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.

Clinical versus To-be-marketed (TBM) Product Formulations and Proposed Dose:

Budesonide rectal foam is formulated as an emulsion which is filled into an aluminum can with an aerosol propellant. The drug product development process is summarized herein. Budesonide 2 mg rectal foam (also referred to as Budenofalk rectal foam in the submission) was developed by Dr. Falk Pharma and received marketing approval in Europe in 2006. After (b) (4) was removed from Dr. Falk Pharma formulation and replaced by (b) (4) the new formulation was transferred to (b) (4) in USA to produce the drug product for Salix-sponsored Phase 3 studies, BUCF3001 and BUCF3002. No other changes were made to the drug product formulation during the transfer. After conducting Phase 3 clinical studies BUCF3001 and BUCF3002, (b) (4) Per e-mail communication with Dr. Marie Kowblansky, CMC TL, CMC considered that the post-Phase 3 changes were not significant and TBM product formulation is the same as the Phase 3 product formulation.

TBM product is available in one strength, 2 mg budesonide per metered dose. The dosing regimen is 1 metered dose administered rectally twice daily for 2 weeks followed by 1 metered dose administered once daily for 4 weeks.

PK:

The pharmacokinetics of budesonide rectal foam were characterized in healthy adult male subjects (Study BUF-7/BIO) and patients (Studies BUCF3001 and BUCF3002). The applicant claimed that systemic budesonide exposures were generally low and no budesonide accumulation in serum after twice-daily dosing for 4 consecutive days. Based on published systemic exposures of budesonide capsule formulation from other studies, the applicant estimated the relative bioavailability (versus budesonide capsule) as 15.3% after a single dose and 13.8% after multiple dosing (2 mg twice daily [BID] x 4 days). The applicant conducted population PK analysis to evaluate the PK characteristics in healthy subjects and intended patients as well as impact of covariates on PK.

Hypothalamic-pituitary-adrenal (HPA) Axis Suppression

As a glucocorticoid product, budesonide rectal foam has the potential to suppress the HPA axis which is a side effect. As such, the applicant conducted adrenocorticotropin challenge (i.e., ACTH stimulation test) studies in the two Phase 3 trials (BUCF3001 and BUCF3002) at baseline and at Week 6. Pending further review of the study results, the reported data were cited in this filing memo. In the budesonide rectal foam group, at baseline (predose), 84% of subjects had a normal response to the ACTH challenge and at Week 6, 69% of subjects had a normal response to the ACTH challenge; in the placebo group, these values were 86% and 77%, respectively.

DDI assessment

No clinical DDI studies were conducted. The applicant conducted *in vitro* metabolism studies and claimed no significant interactions with transporters (P-glycoprotein, BCRP, OATP1B1, and OATP1B3). Additionally, the applicant claimed that budesonide does not inhibit human CYPs 1A2, 2B6, 2C9, 2D6, 2E1, or 3A4/5 to a clinically significant extent, nor does it significantly induce the expression of CYP1A2, CYP2B6, CYP2C9 or CYP3A4 in cultured human hepatocytes.

Overall Clinical Program

The clinical development program for budesonide rectal foam includes the following studies sponsored by Dr. Falk Pharma: BUF-7/BIO in healthy adults; and BUF-4/BIO (phase 1), BUF-5/UCA (phase 2b), BUF-6/UCA (phase 3), and BUF-9/UCA (phase 3) in subjects with active ulcerative proctitis (UP) or ulcerative proctosigmoiditis (UPS). These studies were included in the European marketing application for Budenofalk (budesonide) foam approved in 2006. Two Salix-sponsored studies, BUCF3001 and BUCF3002 (pivotal, randomized, double-blind, placebo-controlled, phase 3) in subjects with active UP or UPS, are also part of the clinical development program. An overview of the clinical studies conducted during development program of budesonide rectal foam is attached in the Appendix.

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology III finds NDA205613 (budesonide rectal foam) fileable from clinical pharmacology's perspective. Since the applicant didn't submit the full bioanalytical assay validation report for review, we will convey the following IR to the applicant:

- Submit (or provide the location of) the full bioanalytical assay validation reports for assays (i.e., HPLC-MS/MS assays) that were used to analyze the pharmacokinetic samples from clinical studies conducted in Europe and USA. Please refer to the following guidance for more information.

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf

Additionally, we will convey the below IRs related to the population PK report to the applicant:

- Please submit the following datasets and codes/scripts for independent review related population PK report entitled "population pharmacokinetics of budesonide foam":
    - All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    - Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- It is noted that different drug product formulations were in the Europe (Studies BUF-7/BIO and BUF-4/BIO used Dr. Falk Pharma formulation) and USA (Studies BUCF3001 and BUCF3002 used a modified new formulation). Please explore the formulation impact on PK in the above reference population PK analysis.

Appendix: List of studies (sponsor's Table 18 from the summary of clin pharm findings)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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/s/

LANYAN FANG
01/14/2014

NITIN MEHROTRA
01/14/2014

SANDHYA K APPARAJU
01/14/2014

YOW-MING C WANG
01/14/2014