CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-554

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	22-554	*Submission Date(s)*	6/24/09, 8/4/09, 8/7/09, 8/11/09, 9/17/09, 11/06/09, 12/21/09; 1/26/10; 2/3/10, 2/8/10
Brand Name		Xifaxan®	
Generic Name		Rifaximin	
PDUFA goal date		March 24, 2010 with 3 months extension	
Reviewer		Insook Kim, Ph.D.	
Team Leader		Sue-Chih Lee, Ph.D.	
OCP Division		Division of Clinical Pharmacology III	
OND Division		Division of Gastroenterology Products	
Sponsor		Salix	
Relevant IND(s)		59,133	
Submission Type; Code		Type 6 submission; (b) (4)	
Formulation; Strengths; Regimen		Immediate release oral tablet One 550 mg oral tablet twice daily 200 mg tablet approved under NDA 21-361* on May 2004 * Due to an issue during DARRTS migration, a new NDA number was granted to the current supplement.	
Indication		Maintenance of remission of Hepatic Encephalopathy in patients ≥ 18 years of age	

Table of Contents

1 Executive Summary

Rifaximin 200 mg tablet was approved for the treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in 2004. In this application, the sponsor submitted study reports to support a new indication of maintenance of remission of hepatic encephalopathy in patients ≥ 18 years of age for rifaximin. The proposed dosage regimen is one 550 mg tablet twice daily.

1.1 Recommendations

The division of Clinical Pharmacology 3 has reviewed the (b) (4). The reviewer has found that there are several unaddressed questions for the safe use of rifaximin in target patient population. Those deficiencies are mainly due to the greatly elevated systemic exposure to rifaximin in the target patient population who has hepatic impairment. However, if the clinical division found the overall safety and efficacy of rifaximin in the target patient population acceptable, those deficiencies should be addressed through labeling languages and post-marketing commitments.

Comments to the Clinical Division
Effect of rifaximin on the QT prolongation
A thorough QT study was not conducted for rifaximin. Although the systemic availability of oral rifaximin is limited, rifaximin is systemically available to an appreciable degree. The systemic exposure to rifaximin in the new patient population after 550 mg twice daily dosing is about 16-20 times higher than that in healthy subjects after 200 mg three times a day dosing, the approved treatment of patients with traveler's diarrhea. As such, the current marketing experience with rifaximin can not reasonably allay the cardiac safety issue in terms of QT prolongation potential of rifaximin in the proposed patient population. This issue remains to be addressed.

1.2 Phase IV Commitments

- Proposed Post-Marketing Commitments
    - We recommend that the effect of concomitant P-gp inhibitor(s) on rifaximin pharmacokinetics be evaluated in vivo. The study may be conducted in healthy volunteers.

    - We recommend that you conduct in vitro study(ies) to evaluate the effect of rifaximin on p-gp substrates at various concentrations which include observed plasma concentrations

- Assessment of effect of renal insufficiency
    - It is likely that the target patient population would have renal insufficiency secondary to the hepatic insufficiency. As it is possible that renal

insufficiency can affect elimination of drugs via other pathways, we recommend that the effect of renal insufficiency be assessed.

The Optional Office of Clinical Pharmacology Briefing was held on February 18, 2010 in presence of Drs. E. Dennis Bashaw and Hae-Young Ahn.

The Advisory Committee meeting with Gastrointestinal Disease Advisory Committee (GIDAC) was held on February 23, 2010.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Mass balance study report was submitted to NDA 21-361 original submission (please, see clinical pharmacology review by Dr. Kofi Kumi for more details). When radiolabeled rifaximin was orally administered, 97% of the administered dose was recovered in feces as the unchanged drug and a small amount (<1% dose) as the metabolite, 25-desacetyl rifaximin. About 0.32% of the administered dose was recovered in urine, of which 0.03% of the administered dose was present as rifaximin. Rifaximin accounted for about 18% of radioactivity in plasma. Biliary excretion of rifaximin was suggested in a separate study. Rifaximin was detected in bile after cholecystectomy in patients with intact GI mucosa. In Caco-2 cell permeability study, the apparent apical to basolateral permeability of rifaximin was comparable to that of mannitol, a low permeability drug.

Taken together, these results suggest that the oral absorption of rifaximin is limited yet once absorbed rifaximin may undergo extensive metabolism. Of note, the absolute bioavailability was not evaluated, and the relative contribution of biliary excretion and the enzymes responsible for the metabolism of rifaximin are unknown.

The proposed target population has a certain degree of hepatic impairment leading to reduced rifaximin metabolism. Therefore, the main clinical pharmacology question for this application has been if the submitted clinical pharmacology and biopharmaceutics information adequately supports safe and effective use of rifaximin in this new patient population.

Single dose and multiple dose PK

Pharmacokinetics following a single dose and multiple doses of 550 mg twice daily were characterized in healthy subjects (RFPK1007). After a single dose and after multiple doses, the median time to peak plasma concentration was 0.75 hours (Table 1). The mean Cmax was 4.04 ng/ml and 3.41 ng/ml after a single dose and multiple doses of rifaximin, respectively. After multiple doses for 7 days, the accumulation ratio based on AUC was 1.37. The mean half-life was 1.83 and 4.17 hours after a single dose and multiple doses of rifaximin, respectively. The half-life at steady-state was comparable to that under fed conditions, while it was longer than that under fasting conditions. The shorter $t_{1/2}$ after a single-dose administration under fasting condition is likely due to the low plasma concentrations during the elimination phase.

Table 1. Mean ± SD (%CV) Pharmacokinetic Parameters After a Single Dose and Multiple Doses of 550 mg Rifaximin in Healthy Subjects

	Single dose Under fasting condition (n=12)	Single dose Under fed condition (n=12)	Multiple doses 550 mg twice daily for 7 days (n=14)
Cmax (ng/mL)	4.04 ± 1.51 (37%)	4.76 ± 4.25 (89%)	3.41 ± 1.62 (47.5%)
Tmax[1]	0.75 (0.5-2.05)	1.50 (0.5-4.08)	0.76 (0.5-4.0)
AUCtau (ng·h/mL)	--	--	12.3 ± 4.76 (38.6%)
AUC_∞ (ng·h/mL)	11.1 ± 4.15 (37%)	22.5 ± 12.0 (53%)	--
CL/F (L/min)	959 ± 411 (42.8%)	--	863 ± 364 (42%)
$T_{1/2}$ (h)	1.83 ± 1.38	4.84 ± 1.34	4.17 ± 3.3

[1]Median (range)

Food effect:

A concomitant high fat meal delayed oral absorption of rifaximin and increased the mean AUC by 2 fold (Table 1).

The mean AUC was increased by 2 fold when rifaximin was administered within 30 min after a high fat meal. The median Tmax was delayed by 0.75 hours with a high fat meal and the mean Cmax did not significantly change. The Cmax with a concomitant high fat meal was more variable than without a high fat meal.

Pharmacokinetics in patients

Systemic exposure to rifaximin was significantly higher in the target patient population (who had hepatic impairment) than in healthy subjects.

The pharmacokinetics of rifaximin was evaluated in the target patient population during the open-label Phase 3 trial RFHE3002. PK blood samples were collected after dosing for 7 consecutive days in patients with Child-Pugh A and Child-Pugh B class hepatic impairment. Because the PK study was done during any time of trial 3002, the total days of dosing for patients were ≥ 7 days.

Overall, in patients with hepatic impairment the mean apparent oral clearance was reduced by 88% and the half-life was increased by 2 fold compared in healthy subjects. The mean Cmax and AUCtau were 6 fold- and 11 fold higher, respectively, than in healthy subjects (Table 2, Figure 1).

When the PK parameters were analyzed by liver function, the mean Cmax and AUCtau in patients in moderate (Child-Pugh B) hepatic impairment were 28% and 36% higher than in patients with mild (Child-Pugh A) hepatic impairment (Table 2). The mean

Cmax and AUCtau in patients increased as Model for End Stage Liver Diseases (MELD[1]) score increased (Figure 1).

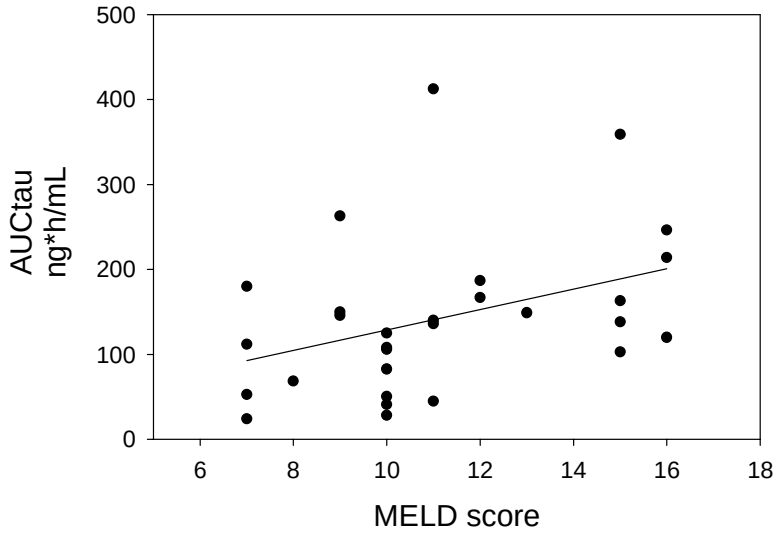
Table 2: Mean ± SD (%CV) Pharmacokinetic Parameters by Liver Function After Multiple Doses of 550 mg Rifaximin Twice Daily

	Healthy subjects (n=12)	Child-Pugh A (n=18)	Child-Pugh B (n=7)	Child-Pugh C (n=4)
AUCtau (ng*h/ml)	12.3 (4.76)	118 (67.8)	161 (101)	245.9 (119.6)
Cmax (ng/ml)	3.41 (1.62)	19.5 (11.4)	25.1 (12.6)	35.5 (12.5)
Tmax (h)	0.76 (0.5-4)	1 (0.9-10)	1 (0.97, 1)	1 (0-2)
CL/F (L/min)	863 (364)	122 (101)	70.6 (29.2)	--
T1/2 (h)	4.17 ± 3.3	8.12 ± 3.58	10.5 ± 1.5	

[1] RFPK1007 Cross-study comparison

Reviewer's comments: *The t1/2 in patients with hepatic insufficiency is considered unreliable as it was determined only after 12 hours PK sampling post-dose.*
Because of the presumed local action of rifaximin and both safety and efficacy were evaluated in patients with hepatic impairment receiving rifaximin at the proposed dosing regimen, no dosage adjustment is warranted based on the systemic exposure.

Figure 1. AUC increased with an increase in MELD score of patients



[1] MELD score was calculated as follows: MELD Score = 0.957 x Loge(creatinine mg/dL) + 0.378 x Loge(bilirubin mg/dL) + 1.120 x Loge(INR) + 0.6431

Table 3. Effect of Hepatic Impairment Scores (MELD score <11 versus 11 to 18) on Main PK parameters of Rifaximin[1]

Pharmacokinetic Parameter	Geometric Least Square Mean (ng/mL)		Ratio of Least Square Mean (B/A) (%)	90% Confidence Interval (%)	p-value	Variance Assumption	Inter-Subject CV (%)
	MELD < 11	MELD 11 to 18					
AUC_{tau} (ng•h/mL)	84.30	141.81	168.22	(110.5, 256.2)	0.0451	MELD<11 MELD 11-18	78.5 51.1
C_{max} (ng/mL)	13.70	24.41	178.12	(116.7, 271.8)	0.0283	MELD<11 MELD 11-18	89.9 48.8

Source: RFHE3002PK Appendix 16.1.9.1.7.

[1] Data submitted on 1/27/10 is not included.

In an amendment dated 1/27/10, the sponsor submitted PK parameters for four patients with Child-Pugh Class C hepatic impairment. The mean ± S.D. AUCtau and Cmax were 245.9 ±119.6 ng·h/mL *and 35.5 ±12.5* ng/ml, *respectively. The AUC and Cmax were higher by 20- and 10-fold higher than those in healthy subjects and 2- and 1.8-fold higher than those in patients with Child-Pugh Class A hepatic impairment.*

Protein Binding: hepatic encephalopathy patients vs. healthy subjects

Rifaximin is moderately bound to protein and protein binding of rifaximin was slightly lower in patients with hepatic impairment.

Protein binding was evaluated in healthy subjects and patients with a history of hepatic encephalopathy. In healthy subjects, the average protein binding ratio was 67.5% ranging from 62.5% to 72.8%. On the other hand, the average ratio of protein binding in patients with hepatic impairment after administration of 550 mg rifaximin twice daily was 62% ranging from 55.3 to 68.2%. The plasma concentration of rifaximin when the protein binding was measured ranged from 14 to 52 ng/ml in patients and < 10 ng/ml in healthy subjects.

Drug interaction:

- ***Effect of rifaximin on concomitant drugs which are substrates of CYP3A4:***

  No clinically meaningful effect of rifaximin is expected on co-administered drugs which are primarily metabolized by CYP3A4 in healthy subjects.

  However, it is unknown if rifaximin in the target population, who have elevated rifaximin systemic exposure, would cause clinically meaningful drug interaction with other drugs which are metabolized by CYP3A4 enzyme.

Rifaximin induces CYP3A4 enzyme activity in vitro. When Rifaximin 550 mg was administered three times daily for 7 days and 14 days, the AUC of midazolam, a probe substrate of CYP3A4 was 3.8% and 8.8% lower, respectively than when midazolam was

administered alone, and Cmax of midazolam also decreased 4-5% when rifaximin was administered for 7-14 days prior to midazolam administration.

Reviewer's comments: *This degree of drug interaction is not considered clinically meaningful. Although the dosage regimen of rifaximin in this study i.e., three times a day, is different from the proposed dosage regime i.e. twice a day, the same conclusion is applicable to the proposed twice a day dosage regimen as this study was conducted under more stringent condition and resulted in no significant effect.*

The induction of CYP3A4 by rifaximin may be dose- and treatment-duration dependent. Because the drug interaction was evaluated in healthy volunteers whose systemic exposure to rifaximin is much lower than in the target population, it is still unknown if rifaximin would induce CYP3A4 activity in target patient population with elevated systemic exposure to rifaximin (Table 4).

Table 4. Comparison of Mean Peak Plasma Concentrations

Study	Dosage regimen	Cmax (ng/mL)	Cmax (μM)	In vivo CYP3A4 induction
RFDI1002* +	7 days 200 mg TID	1.21	0.00154	None
RFDI1008+	7 days 550 mg TID	3.61	0.00459	< 25%
	14 days 550 mg TID	3.89	0.00495	< 25%
RFHE3002PK	7+ days 550 mg BID Child-Pugh A Child-Pugh B	 19.5 25.1	 0.0248 0.0319	Not evaluated

**submitted in NDA 21-361 original submission*
+in healthy volunteers

Reviewer's comments: *In the presence of 0.2 μM rifaximin, which is about 6-10 fold higher than the observed mean peak plasma concentration of rifaximin in patients, CYP3A4 enzyme activity was increased by 1.5 fold in vitro and the potency of induction was about 50% of rifampin, a strong CYP3A4 inducer. The CYP3A4 induction was not studied at lower rifaximin concentrations.*

- ***Effect of P-glycoprotein inhibitors on rifaximin permeability in vitro***
  In the presence of P-glycoprotein (P-gp) inhibitors, the efflux ratio (ER) of rifaximin decreased by 2-12 fold. Other transporters may be involved in efflux transport of rifaximin:

The membrane permeability of rifaximin was evaluated in Caco-2 cell monolayer system. The apparent permeability of rifaximin from apical to basolateral direction was about $1*10^{-6}$ cm/sec and it was comparable to that of Mannitol. Rifaximin was greatly more permeable from basolateral to apical side. The efflux ratio of rifaximin at 5 μM was 45-135 while the efflux ratio of digoxin, a substrate of P-gp was 11-12. This results show

that one or more transporters may be involved in the transport of rifaximin through Caco-2 monolayers.

In the presence of P-gp inhibitors i.e. 60 μM verapamil and 0.5 μM GF120918, the efflux ratio of rifaximin decreased by 2-12 fold to 10-30.

- ***Effect of rifaximin on the permeability of P-gp substrate (digoxin) in vitro***
  In the presence of Rifaximin at 50 μM, the efflux ratio of digoxin decreased from 11-12 to 2-6. However, the inhibition potential of rifaximin at the clinical use concentrations was not evaluated.

The efflux ratio of digoxin decreased from 11-12 to 2-6 in presence of rifaximin at 50 μM. Known P-gp inhibitor, verapamil and GF120918 reduced the efflux ratio of digoxin to 1. This result suggests that rifaximin at 50 μM has a potential to inhibit efflux transport of concomitant drugs which are P-gp substrates in vivo but its inhibitory potency is expected to be lower than that of verapamil.

Reviewer's comments: *Nevertheless, this effect was studied only at one concentration which was much higher than the concentrations in the GI tract or the highest Cmax of 66 nM observed in a patient with moderate liver impairment. Additional study at lower concentrations of rifaximin will be helpful to determine if in vivo drug interaction study is warranted.*

Exposure (Dose)-Response Relationship

Rifaximin for the proposed indication is presumably acting locally in the intestine. As such the systemic exposure may be more relevant to safety than efficacy. Nevertheless, because only one dose level was studied in the target population for the proposed indication, there is insufficient information to draw a conclusion about the exposure-response relationship in terms of safety and efficacy.

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Rifaximin (Xifaxan®) was approved in 2004 for the treatment of patients with traveler's diarrhea using a dosing regimen of 200 mg three times daily for 3 days (NDA 21-361). In this application, the sponsor is pursuing the use of rifaximin 550 mg BID for maintenance of remission of hepatic encephalopathy in patients ≥ 18 years of age. The 200 mg tablet approved under the parent NDA 21-361 and a new NDA number was granted to the current supplement due to system migration to DARRTS (Type 6 submission).

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Structure

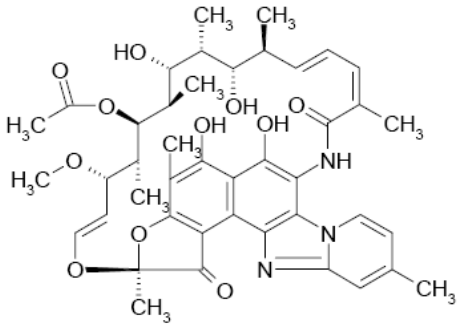


Figure 1. Rifaximin

Molecular formula: $C_{43}H_{51}N_3O_{11}$

Molecular weight: 785.89

Figure 2. Structure of rifaximin

Xifaxan 550 mg tablet is an immediate release tablet and compositionally proportional to the approved 200 mg tablet. Rifaximin is practically insoluble in water. The solubility of rifaximin in 100 mM sodium phosphate buffer at pH 7.4 was (b) (4)
On the other hand, in presence of 0.25% sodium dodecyl sulfate (SDS), the solubility of rifaximin increased about 100 folds to (b) (4)

Table 5. Solubility of Rifaximin in Typical Dissolution Medium

Dissolution Medium	Solubility (mg/mL)
0.1 N Hydrochloric Acid	(b) (4)
22 mM Sodium Acetate, pH 4.5	
50 mM Potassium Phosphate, pH 6.8	
50 mM Potassium Phosphate, pH 7.4	
100 mM Sodium Phosphate, pH 7.4	

Table 6. Solubility of Rifaximin in 100 mM Sodium Phosphate Buffer, pH 7.4 Containing Increasing Quantities of SDS

Dissolution Medium	Solubility (mg/mL)
100 mM Sodium Phosphate, pH 7.4, 0.25% SDS [a]	(b) (4)
100 mM Sodium Phosphate, pH 7.4, 0.5% SDS [a]	
100 mM Sodium Phosphate, pH 7.4, 0.8% SDS [a]	
100 mM Sodium Phosphate, pH 7.4, 1.0% SDS [a]	

Reference: VALRPT-43, Revision 0

a SDS = Sodium dodecyl sulfate

Table 7. Solubility of rifaximin at different pH

Solvent system	Solubility (mg/l)
Purified water pH 4 buffer solution pH 7 buffer solution pH 10 buffer solution	(b) (4)

There was a dramatic increase in solubility to (b) (4) at pH 10 from (b) (4) at pH 7. There was no remarkable difference in solubility between at pH 4.5 and pH 7.4.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Rifaximin is a non-aminoglycoside semi-synthetic antibiotic derived from rifamycin SV; it is a structural analog of rifampin. The mechanism of action of rifaximin depends on the inhibition of DNA-dependent RNA polymerase of the target microorganisms, leading to the suppression of initiation of chain formation in RNA synthesis. Rifaximin binds to the beta-subunit of the bacterial DNA dependent RNA polymerase, resulting in inhibition of bacteria protein synthesis.

Hepatic encephalopathy, also known as hepatic coma or portal-systemic encephalopathy (PSE) is a serious, rare, complex, episodic, neuropsychiatric syndrome associated with advanced liver disease. HE may occur at any age, but the peaks parallel those of fulminant liver disease (peak = 40's), and cirrhosis (peak = late 50's). Both genders are affected in roughly equal proportions, reflecting the underlying liver disease. Hepatic encephalopathy may be associated with acute liver failure, portal-systemic bypass with no intrinsic hepatocellular disease, or cirrhosis and portal hypertension with portal-systemic shunting of blood. Hepatic encephalopathy associated with the latter is most common.

Hepatic encephalopathy is manifested as a continuum of mental status deterioration, psychomotor dysfunction, impaired memory, increased reaction time, sensory abnormalities, poor concentration, disorientation, and coma. Changes may be observed in personality, consciousness, behavior, and neuromuscular function. Neuromotor signs may include hyperreflexia, rigidity, myoclonus, and asterixis (a coarse, myoclonic “flapping” muscle tremor). The clinical diagnosis of overt HE in subjects with advanced liver disease and portal-systemic shunting is based on two concurrent types of symptoms: impaired mental status (as generally defined by Conn Score) and symptoms of impaired neuromotor functioning (asterixis).

The etiology and pathogenesis of hepatic encephalopathy are not known. The main tenet for the pathogenesis of HE is that nitrogenous substances derived from endogenous bacterial metabolism in the GI tract adversely affect brain function. Compounds gain

access to the systemic circulation as a result of decreased hepatic function or portalsystemic shunts. Once in brain tissue, the compounds produce alterations of neurotransmission that affect consciousness and behavior. Other gut derived neurotoxins have also been implicated. Some of these neurotoxins also accumulate and alter CNS function and include mercaptans, phenols, manganese, short chain fatty acids, bilirubin, and a variety of neuroactive medications

Rifaximin is proposed for the maintenance of remission of Hepatic Encephalopathy in patients aged 18 years or older.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Oral administration of one 550 mg tablet twice a day

2.2 General Clinical Pharmacology

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

For the proposed indication, target patient population has a varying degree of hepatic impairment, which could lead to increased systemic exposure of rifaximin. In support of the proposed indication, the sponsor submitted three in vivo and two in vitro clinical pharmacology related studies. The three in vivo studies are (1) Study RFPK1007 to characterize single dose and multiple dose pharmacokinetics and to evaluate food effect in healthy subjects, (2) Study RFPK1008 to assess drug interaction with midazolam in healthy volunteers, and (3) Study RFHE3002PK to determine the effect of different degrees of hepatic impairment on the pharmacokinetics of rifaximin. The two in vitro studies were conducted to evaluate if rifaximin is a substrate and/or inhibitor of efflux transporter(s) and to evaluate protein binding in blood samples from PK studies. The sponsor also submitted the final study report of RFPK1002 titled “A two-way crossover scintigraphic evaluation of the disintegration of two batches or rifaximin” and used it to support twice daily dosing frequency. The RFPK1002 is considered only supportive as it was a comparative study for 200 mg tablets.

The clinical efficacy and safety of rifaximin for the proposed indication were evaluated in a pivotal phase 3 trial: a multi-center, randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety and tolerability of rifaximin 550 mg bid for 6 months in preventing hepatic encephalopathy (RFHE3001) and a long-term extension study: a multi-center, open-label trial to evaluate the long-term safety and tolerability of rifaximin 550 mg bid in subjects with a history of hepatic encephalopathy (RFHE3002).

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical studies?

The primary efficacy parameter for double-blind, placebo controlled study RFHE3001 was the occurrence of an episode of breakthrough overt HE during treatment. Breakthrough overt HE was defined as an increase of the Conn score to Grade ≥ 2 (i.e. 0 or 1 to ≥ 2) or an increase in Conn and asterixis score of 1 grade each for those subjects who entered the study with a Conn score of 0 (Table 8, 9).

Table 8: Conn Score – West Haven Criteria

Conn score 0	No personality or behavioral abnormality detected
Conn score 1	Trivial lack of awareness, euphoria or anxiety; shortened attention span; impairment of addition or subtraction.
Conn score 2	Lethargy; disorientation for time; obvious personality change; inappropriate behavior.
Conn score 3	Somnolence to semi-stupor, responsive to stimuli; confused; gross disorientation; bizarre behavior.
Conn score 4	Coma; unable to test mental state

Table 9: Asterixis Grade

Grade 0	No tremors
Grade 1	Rare flapping motions
Grade 2	Occasional, irregular flaps
Grade 3	Frequent flaps
Grade 4	Almost continuous flapping motions

Efficacy endpoints are to be discussed at the AC meeting scheduled on February 23, 2010.

Venous ammonia

Elevaton in blood ammonia, a key secondary endpoint in RFHE3001, is suggested to be associated with the CNS effects underlying overt HE. Comparison of changes from baseline to end of study in venous ammonia levels showed statistically significant, greater improvement over the course of the study in the rifaximin group when compared to placebo (p = 0.0391).

Reviewer's comments: *The comparison of change venous ammonia level from baseline to end of study after each treatment appears to be misleading as the treatment duration differs among subjects regardless of treatments.*

In a phase 2 dose-ranging study RFHE9702, the blood ammonia was also measured at baseline and after 7 days of rifaximin treatment. A decrease in mean blood ammonia level was observed only in 600 mg daily dose cohort (200 mg t.i.d.) while no change was observed at 1200 mg and 2400 mg daily dose cohorts. It was noted that the mean baseline blood ammonia concentration was higher for the higher dose cohorts (143.5 mM and 183.3 mM for 1200 mg and 2400 mg cohorts, respectively) compared to that for 600 mg dose cohort (132.8 mM).

Reviewer's comments: *The arterial ammonia level is generally considered as a better measure than venous ammonia level. The relevance of blood ammonia level to the incidence of hepatic encephalopathy was discussed at GIDAC AC meeting and is still in*

debate. Therefore, the clinical utility of venous ammonia data is unclear for this application.

2.2.3. Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Rifaximin was measured in plasma using a validated HPLC-MS/MS method to assess pharmacokinetic parameters (Please, see section 2.5.)

2.2.4 Exposure-Response Evaluation

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

Rifaximin for the proposed indication is presumably acting locally in the intestine. As such the systemic exposure may be more relevant to safety than efficacy. Nevertheless, because only one dose level was studied in the target population for the proposed indication, there is insufficient information to draw a conclusion about the exposure-response relationship in terms of safety and efficacy.

Dose selection for the pivotal phase 3 trials

Dose selection was based on results of a Phase 2 trial although the design of that trial was not optimal for the purpose.

The total daily dose of 1100 mg for Phase 3 trials was determined based on published literature and a supportive dose ranging study conducted in active HE patients with an endpoint of Portal Systemic Encephalopathy (PSE) Index (RFHE9702). In RFHE9702, daily dose of 600 mg, 1200 mg and 2400 mg in three divided doses were administered to patients with grade I, II, or III hepatic encephalopathy for 7 days and the efficacy was assessed by PSE Index which is a composite score of Mental State (Conn score), asterixis grade, Number Connection Test Score, Electroencephalography (EEG) score and venous ammonia levels.

There was no statistically significant difference among three dose groups based on PSE Index at the end of the treatment which was a pre-specified primary endpoint (Table 10). On the other hand, the change of PSE Index from baseline after 7 days of rifaximin treatment tended to be greater for1200 mg and 2400 mg daily dose cohorts than for 600 mg dose cohort. The mean change of PSE Index from baseline to end of treatment was -6.4%, -10.3%, and -10.7% in 600 mg, 1200 mg, and 2400 mg rifaximin dose cohorts, respectively. The total daily dose of 1200 mg was further studied in supportive Phase 3 trials in active HE patients (RFHE9901, 9701).

Table 10. Mean PSE Index at baseline and after 7 days of treatment

Rifaximin daily dose		PSE Index (%)					Adjusted mean from analysis of covariance	
		N	Mean	St dev	Min	Max	Mean	95% CI
600 mg	Day 1	14	37.8	11.4	25.0	64.3		
	Day 7 or withdrawal	17	31.9	16.9	3.6	67.9	32.4	22.9, 42.7
1200 mg	Day 1	16	38.4	13.8	21.4	75.0		
	Day 7 or withdrawal	18	28.2	18.9	7.1	82.1	30.8	22.7, 39.2
2400 mg	Day 1	16	41.7	8.5	17.9	50.0		
	Day 7 or withdrawal	16	31.0	14.2	7.1	57.1	25.8	18.8, 34.4

Because there was no control group in the Phase 2 trial, it is unknown if the minimum effective dose was identified. Nonetheless, the contribution of this information to the current dose rationale is limited due to differences in the target population (acute HE patients vs. patients with a history of HE), the primary efficacy endpoint (PSE index vs. the occurrence of an episode of breakthrough overt HE), treatment duration ($\leq$14 days versus 6 months), and dosing frequency (three times a day versus twice a day) between these supportive studies and RFHE 3001 trial.

Safety Analysis in Subgroup by Liver Function:

No apparent increase in the incidence of treatment-emergent adverse events (TEAE) under rifaximin treatment by decrease in liver function was observed. Nonetheless, it should be noted that the safety database for patients with severe hepatic impairment is relatively limited (please, see Clinical Review by Dr. Lara Dimick for more details)

Based on the increasing trend of systemic exposure to rifaximin with worsening the liver function, a subgroup analysis of adverse events by liver function based on MELD score and Child-Pugh Class was conducted by the sponsor.

Notably, a higher rate of death was reported in patients with severe hepatic impairment under rifaximin treatment in RFHE 3001 compared to placebo group and groups with mild and moderate hepatic impairment (Table 11). It is unknown if this could be attributed to other confounding factors or potentially higher systemic exposure to rifaximin. The detailed review of safety signal by liver function is deferred to the clinical reviewer.

The incidence of treatment-emergent adverse events (TEAE) increased as the liver function decreased (Table 11). Nonetheless, the incidence of TEAE increased in placebo groups as well and the TEAE rate was similar between rifaximin treatment group and placebo group among patients with the same Child-Pugh Class liver function. Based on the current information, there is no obvious correlation with the degree of liver impairment and incidence of adverse event.

Reviewer's comments*: It should be noted, however, that the relatively limited safety data is available for patients with severe liver impairment. A similar trend in the incidence of TEAE and treatment-emergent serious adverse events (TESAE) was observed by hepatic function based on MELD score* (Table *12). Please, see review by Dr. Lara Dimick for more details.*

Table 11 Treatment-Emergent Adverse Events By Baseline Child-Pugh Class And Treatment Population (RFHE3001).

Child-Pugh Class	Class A		Class B		Class C		Total	
Treatment	Placebo (n=56) n (%)	Rifaximin (n=46) n (%)	Placebo (n=72) n (%)	Rifaximin (n=65) n (%)	Placebo (n=14) n (%)	Rifaximin (n=17) n (%)	Placebo (n=142) n (%)	Rifaximin (n=128) n (%)
Death	2 (3.6)	2 (4.3)	8 (11.1)	3 (4.6)	1 (7.1)	3 (17.6)		
TEAE[1] in any organ system	39 (69.6)	29 (63)	66 (91.7)	57 (87.7)	13 (92.9)	16 (94.1)	118 (83.1)	102 (79.7)
TESAE [2]	23 (41.1)	13 (28.3)	26 (36.1)	25 (38.5)	7 (50)	8 (47.1)	56 (39.4)	46 (35.9)

[1]From Table 4.1. Summary of treatment-emergent adverse events by baseline Child-Pugh Class and treatment population submitted on 12/21/09

[2]From Table 4.3. Summary of treatment-emergent serious adverse events by baseline Child-Pugh Class and treatment population submitted on 12/21/09

Table 12 Treatment-Emergent Adverse Events By Baseline MELD score And Treatment Population (RFHE3001).

MELD score	≤ 10		≥11 , ≤18		19 ≤	
Treatment	Placebo (n=48) n (%)	Rifaximin (n=34) n (%)	Placebo (n=96) n (%)	Rifaximin (n=94) n (%)	Placebo (n=14) n (%)	Rifaximin (n=12) n (%)
TEAE in any organ system	28 (58.3)	21 (61.8)	84 (87.5)	80 (85.1)	14 (100)	11 (91.7)
TE-SAE	12 (25)	6 (17.6)	42 (43.8)	38 (40.4)	9 (64.3)	7 (58.3)

2.2.4.3 Does this drug prolong the QT or QTc interval?

A thorough QT study was not conducted for rifaximin.

2.2.5 Pharmacokinetic Characteristics

2.2.5.1 What are the PK characteristics of rifaximin?

Mass balance study report was submitted to NDA 21-361 original submission (please, see clinical pharmacology review by Dr. Kofi Kumi for more details). When radiolabeled rifaximin was orally administered, 97% of the administered dose was recovered in feces

as the unchanged drug and a small amount (<1% dose) as the metabolite, 25-desacetyl rifaximin (n=3-4; Table 13). About 0.32% of the administered dose was recovered in urine, of which 0.03% of the administered dose was present as rifaximin. Rifaximin accounted for about 18% of radioactivity in plasma. Biliary excretion of rifaximin was suggested in a separate study. Rifaximin was detected in bile after cholecystectomy in patients with intact GI mucosa. After administration of 400 mg twice a day for 2 days, six out of 13 patients had measurable rifaximin in bile and the concentration of rifaximin in these patients was from 4.5 to 16.5 µg/mL. Seven patients had either non-detectable or trace amount of rifaximin in bile. In Caco-2 cell permeability study, the apparent apical to basolateral permeability of rifaximin was comparable to that of mannitol, a low permeability drug.

Taken together, these results suggest that the oral absorption of rifaximin is limited yet once absorbed rifaximin may undergo extensive metabolism. Of note, the absolute bioavailability was not evaluated, and the relative contribution of biliary excretion and the enzymes responsible for the metabolism of rifaximin are unknown.

Table 13. Mass balance study (NDA 21-361 original submission).

Parameter	Rifaximin	Parameter	Total Radioactivity[a]
C_{max} (ng/mL)	4.3 ± 2.8	C_{max} (ng equivalents/mL)	30.2 ± 7.4
T_{max} (h)	1.25[b]	T_{max} (h)	1.5[b]
AUC_{0-t} (ng•h/mL)	19.5 ± 16.5	AUC_{0-t} (ng equivalents•h/mL)	61.8 ± 20.0
% Dose Excreted in Urine	0.030 ± 0.020	% Dose Excreted in Urine	0.32 ± 0.05
		% Dose Excreted in Feces	96.62± 5.67

Source: RFPK9801 Tables 3, 4, and 5.

AUC_{0-t} = area under the concentration-time curve from time 0 (predose) to the last quantifiable concentration-time point; C_{max} = maximum concentration; SD = standard deviation; T_{max} = time to maximum concentration

a N=3 except for C_{max} and T_{max}

b Median values

Reviewer's comments: *Enzymes responsible for the metabolism of rifaximin are unknown.*

Protein binding: Rifaximin is moderately protein bound and in vivo protein binding of rifaximin was about 9% lower in patients with hepatic impairment.

Rifaximin is moderately protein bound. In healthy subjects, the average protein binding ratio after administration of 550 mg rifaximin twice daily was 67.5% ranging from 62.5% to 72.8%. Rifampin, a structural analog of rifaximin is about 80% protein bound.

One the other hand, the average ratio of protein binding in patients with hepatic impairment after administration of 550 mg rifaximin twice daily was 62.0 % ranging from 55.3 to 68.2%.

Reviewer's comments: *A blood sample for protein binding was collected 0.5-2 hour post-dose in healthy volunteers and at 2 hours post-dose in 75% patients (9 out of 12). In three patients out of 12 patients, the samples were collected from 4-10 hours post-dose. The plasma concentration of rifaximin when the protein binding was measured ranged from 14 to 52 ng/ml in patients and < 10 ng/ml in healthy subjects.*

This suggests that about 9% more free drug will be available in patients with hepatic impairment than in healthy subjects at given plasma concentrations. The lower protein binding in patients with hepatic impairment may be attributed to a lower plasma protein due to reduced liver function.

2.2.5.2 What are the single dose and multiple dose PK parameters?

Pharmacokinetics following a single dose and after multiple doses of 550 mg twice daily were characterized in healthy subjects (RFPK1007). After a single dose and multiple doses, the median time to peak plasma concentration was 0.75 hours (Table 14). The mean Cmax was 4.04 ng/ml and 3.41 ng/ml after a single dose and multiple doses of rifaximin, respectively. After multiple doses for 7 days, the accumulation ratio based on AUC was 1.37. The mean half-life was 1.83 and 4.17 hours after a single dose and multiple doses of rifaximin, respectively. The half-life at steady-state was comparable to that under fed conditions, while it was longer than that under fasting conditions. The shorter $t_{1/2}$ after a single-dose administration under fasting condition is likely due to the low plasma concentrations during the elimination phase.

Table 14. Mean ± SD (%CV) Pharmacokinetic Parameters After a Single Dose and Multiple Doses of 550 mg Rifaximin in Healthy Subjects

	Single dose Under fasting condition (n=12)	Single dose Under fed condition (n=12)	Multiple doses 550 mg twice daily for 7 days (n=14)
Cmax (ng/mL)	4.04 ± 1.51 (37%)	4.76 ± 4.25 (89%)	3.41 ± 1.62 (47.5%)
Tmax[1]	0.75 (0.5-2.05)	1.50 (0.5-4.08)	0.76 (0.5-4.0)
AUCtau (ng·h/mL)	--	--	12.3 ± 4.76 (38.6%)
AUC_∞ (ng·h/mL)	11.1 ± 4.15 (37%)	22.5 ± 12.0 (53%)	--
CL/F (L/min)	959 ± 411 (42.8%)	--	863 ± 364 (42%)
$T_{1/2}$ (h)	1.83 ± 1.38	4.84 ± 1.34	4.17 ± 3.3

[1]Median (range)

Reviewer's comments: *The dose-proportionality of rifaximin PK was not formally studied.*

2.2.5.3 How does the PK of rifaximin in healthy volunteers compare to that in patients?

Systemic exposure to rifaximin was significantly higher in the target patient population (who had hepatic impairment) than in healthy subjects.

The pharmacokinetics of rifaximin was evaluated in the target patient population during the open-label Phase 3 trial RFHE3002. PK blood samples were collected after dosing for 7 consecutive days in patients with Child-Pugh A and Child-Pugh B class hepatic

impairment. Because the PK study was done during any time of trial 3002, the total days of dosing for patients were ≥ 7 days.

Overall, in patients with hepatic impairment the mean apparent oral clearance was reduced by 88% and the half-life was increased by 2 fold compared in healthy subjects. The mean Cmax and AUCtau were 6 fold- and 11 fold higher, respectively, than in healthy subjects (Table 15, Figure 3).

When the PK parameters were analyzed by liver function, the mean Cmax and AUCtau in patients in moderate (Child-Pugh B) hepatic impairment were 28% and 36% higher than in patients with mild (Child-Pugh A) hepatic impairment (Table 15). The mean Cmax and AUCtau in patients increased as MELD (Model of End Stage Liver Diseases) score increased (Figure 3).

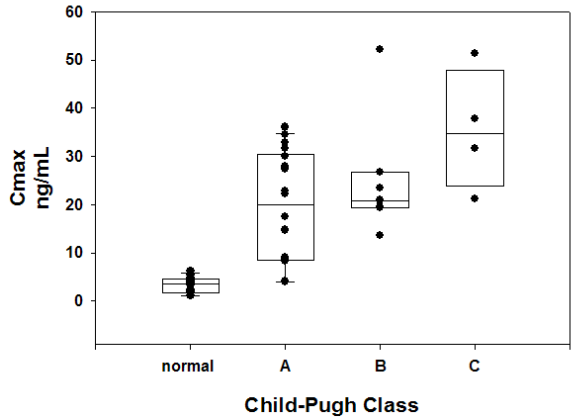
Table 15: Mean ± SD (%CV) Pharmacokinetic Parameters After Multiple Doses of 550 mg Rifaximin Twice Daily

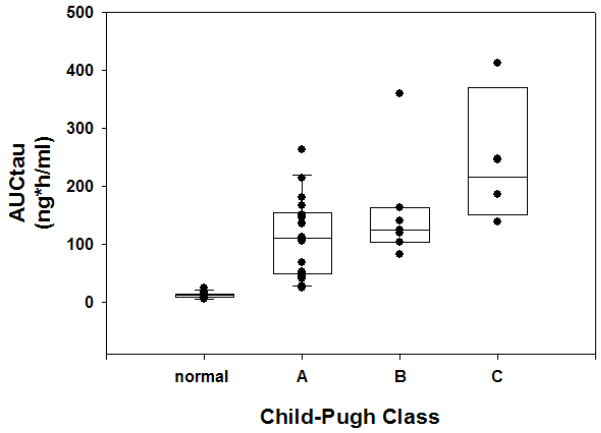
	Healthy subjects (n=12)	Child-Pugh A (n=18)	Child-Pugh B (n=7)	Child-Pugh C (n=4)
AUCtau (ng*h/ml)	12.3 (4.76)	118 (67.8)	161 (101)	245.9 (119.6)
Cmax (ng/ml)	3.41 (1.62)	19.5 (11.4)	25.1 (12.6)	35.5 (12.5)
Tmax (h)	0.76 (0.5-4)	1 (0.9-10)	1 (0.97, 1)	1 (0-2)
CL/F (L/min)	863 (364)	122 (101)	70.6 (29.2)	--

[1] RFPK1007 Cross-study comparison

Reviewer's comments: *The sponsor submitted PK information for patients with Child-Pugh C class hepatic impairment in an amendment dated 1/26/10. The mean AUCtau was 245. 9 (± 119.6) ng*h/ml and Cmax was 35.5 (± 12.5) ng/ml. The mean AUC and Cmax in patients with Child-Pugh C class hepatic impairment was 52% and 41% higher, respectively, than those in patients with Child-Pugh B Class hepatic impairment.*

Figure 3. AUCtau and Cmax by Child-Pugh Class liver function





2.2.5.9 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The dose-proportionality was not formally studied for rifaximin.

2.2.5.10 How do the PK parameters change with time following chronic dosing?

PK after multiple doses was predictable from PK after a single-dose administration of rifaximin. The accumulation factor after 7 days of 550 mg rifaximin BID dosing was 1.34.

2.2.5.11 What is the inter-subject variability of PK parameters in volunteers and patients?

An inter-subject coefficient of variability (CV%) for AUCtau and Cmax ranging from approximately 50 to 63%. The variability observed in healthy subjects i.e. CV% of 45% to 60%.

2.3 Intrinsic Factors

2.3.1 What is the effect of gender and hepatic impairment on PK and what is the impact of any differences in exposure on safety responses?

Gender effect:

The AUC and Cmax were slightly higher in healthy female subjects than in healthy male subjects (Table 16). It may be due to a lower body weight of female subjects than male subjects.

Table 16. PK parameters in healthy subjects by gender (RFPK1007)

	550 mg single dose[1]	at steady-state 550 mg BID

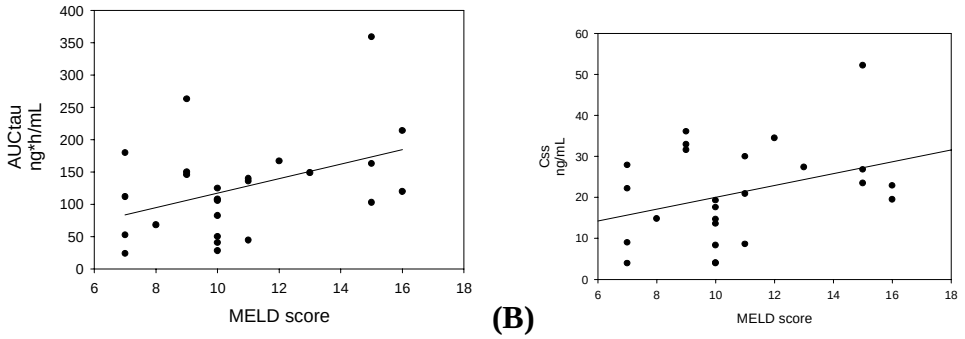
	Cmax (ng/ml)	AUCi (ng·h/mL)	Cmax (ng/ml)	AUCtau (ng·h/mL)
Male (n=6)	3.12 ± 1.19	9.73 ± 4.27	2.95 ± 1.63	10.71 ± 4.13
Female (n=8)	4.70 ± 1.55	11.53 ± 4.32	3.67 ± 1.54	13.07 ± 5.33

[1]Male (n=5), Female (n=7)

In the RCT Study population, the pattern and frequencies of TEAEs were similar between the rifaximin and placebo groups for both male and female subjects (Please, see Clinical Review by Dr. Lara Dimick for more details).
During the randomized placebo-controlled trial RFHE3001, the overall incidence of treatment-emergent adverse events (TEAE) was 82.2% (88/107) and 82.7% (62/72) in placebo-treated males and rifaximin-treated males, respectively. The overall incidence of TEAE in female subjects treated with placebo and rifaximin was 84.6% (44/52) and 78.5% (51/65), respectively. In general, the frequency of other TEAEs was comparable between gender subgroups.

Hepatic insufficiency (please see section 2.2.5.3.)
The systemic exposure increases as the liver function worsen (Figure 4).

Figure 4. (A) AUC and (B) Cmax increased with an increase in MELD score of patients



(A) **(B)**

2.4 Extrinsic Factors

2.4.1 What is the effect of a high fat diet on PK of rifaximin and what is the impact of any differences in exposure on response?

Food effect: ***A concomitant high fat meal delayed oral absorption of rifaximin and increased the mean AUC by 2 fold.***
The mean AUC was increased by 2 fold when rifaximin was administered within 30 min after a high fat meal. The median Tmax was delayed by 0.75 hours with a high fat meal and the mean Cmax was not significantly different. The Cmax with a concomitant high fat meal was more variable than without a high fat meal (Table 17).

Table 17. Effect of Food on Rifaximin PK following a single 550 mg dose of rifaximin (n=14)

Parameter	Fasting	Fed
Cmax (ng/mL)	4.04 ± 1.51	4.76 ± 4.25
Tmax (h)	0.75 (0.5-2.05)	1.50 (0.5-4.08)
AUCi (ng*h/ml)	11.1 ± 4.15	22.5 ± 12.0
T1/2 (h)	1.83 ± 1.38	4.84 ± 1.34

Reviewer's comments: *During the Phase 3 trials, no specific instruction as to the meal intake was given so patients were taken rifaximin regardless of food intake. During the PK study in patients, a light meal was ingested immediately after the 1 hour post-dose blood sampling following overnight fasting.*

2.4.2 Drug-Drug Interactions

2.4.2.1 Is the drug a substrate of CYP enzymes?

The enzymes responsible for metabolism of rifaximin were not studied.

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

- ***Effect of rifaximin on concomitant drugs which are substrates of CYP3A4:***

  No clinically meaningful effect of rifaximin is expected on co-administered drugs which are metabolized by CYP3A4 <u>in healthy subjects</u>.

  However, it is unknown if rifaximin in the patients with a history of HE, who have elevated rifaximin systemic exposure, would cause clinically meaningful drug interaction with other drugs which are metabolized by CYP3A4 enzyme.

<u>Inhibition of CYP enzymes</u>

CYP enzyme activity in vitro was not significantly inhibited in presence of rifaximin at 2-200 ng/mL concentrations and IC50 was estimated > 200 ng/mL (NDA 21-361 original submission. Please see Clinical pharmacology review by Dr. Kofi Kumi for more details). The mean Cmax in patients with Child-Pugh C class hepatic impairment was 35.5 (± 12.5).

<u>Induction of CYP enzymes</u>

Rifaximin, a structural analog of rifampin induced CYP3A4 in vitro (NDA 21-361 original submission. Please see Clinical pharmacology review by Dr. Kofi Kumi for more details). The potency of in vitro induction of CYP3A4 was about <50% of rifampin at given concentration (Table 18).

Table 18. In vitro CYP3A4 Induction (fold increase in CYP3A4 activity) Based On Rate of Testosterone-6β-hydroxylation (from Clinical Pharmacology review for NDA 21-361 original submission)

Conc. (μM)	Rifaximin	Rifampin
0.2	1.5	3
1.0	1.7	3.7
10	1.8	4
20	1.3	3
50	0.15#	3.2

appeared to alter the morphology of the hepatocytes as observed by light microscopy. Taken from original Clinical Pharmacology review for NDA 21-361.

The in vivo drug interaction via CYP3A4 induction by rifaximin was studied in study RFPK1008 in healthy subjects. When Rifaximin 550 mg was administered three times daily for 7 days and 14 days, the AUC of midazolam, a probe substrate of CYP3A4 was 3.8% and 8.8% lower, respectively than when midazolam was administered alone, and Cmax of midazolam also decreased 4-5% when rifaximin was administered for 7-14 days prior to midazolam administration.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

- ***Effect of P-glycoprotein inhibitors on rifaximin permeability in vitro***
  In the presence of P-glycoprotein (P-gp) inhibitors, the efflux ratio (ER) of rifaximin decreased by 2-12 fold. Other transporters are likely involved in efflux transport of rifaximin:

The membrane permeability of rifaximin was evaluated in Caco-2 cell monolayer system. The apparent permeability of rifaximin from apical to basolateral direction was about $1*10^{-6}$ cm/sec and it was comparable to that of Mannitol. Rifaximin was greatly more permeable from basolateral to apical side. The efflux ratio of rifaximin at 5 μM was 45-135 while the efflux ratio of digoxin, a substrate of P-gp was 11-12. These results show that one or more transporters may be involved in the transport of rifaximin through Caco-2 monolayers.

In the presence of P-gp inhibitors i.e. 60 μM verapamil and 0.5 μM GF120918, the efflux ratio of rifaximin decreased by 2-12 fold (Table 19).

Table 19. Inhibition of Rifaximin transport by P-gp inhibitors

	ER	$ER_{Verapamil}$	$ER_{GF120918}$
Round 1	134.54 ± 0.1	10.89 ± 0.2	16.48 ± 0.17
Round 2	78.53 ± 0.32	11.56 ± 0.28	29.68 ± 0.11

Round: Independent experiment on different days

- ***Effect of rifaximin on the permeability of P-gp substrate (digoxin) in vitro***

In the presence of Rifaximin at 50 μM, the efflux ratio of digoxin decreased from 11-12 to 2-6. However, the inhibition potential of rifaximin at the therapeutic concentrations was not evaluated.

The efflux ratio of digoxin decreased from 11-12 to 2-6 in presence of rifaximin at 50 μM. Known P-gp inhibitors, verapamil and GF120918 reduced the efflux ratio of digoxin to 1 (Table 20). This result suggests that rifaximin at 50 μM has a potential to inhibit efflux transport of concomitant drugs which are P-gp substrates in vivo but its inhibitory potency is expected to be lower than that of verapamil.

Reviewer's comments: *Nevertheless, this effect was studied only at one concentration which was much higher than the highest Cmax of 66 nM observed in a patient with moderate liver impairment. Additional study at lower concentrations of rifaximin will be helpful to determine if in vivo drug interaction study is warranted. GF120918 also inhibits BCRP transporter.*

Table 20. Inhibition of Digoxin Transport by Rifaximin

	ER	$ER_{Rifaximin}$
Round 1	11.35 ± 0.31	4.77 ± 0.27
Round 2	11.74 ± 0.32	1.99 ± 0.44
Round 3	12.32 ± 0.21	6.36 ± 0.28

2.4.2.5 Are there other transporter pathways that may be important?

The P-gp inhibitor could not reduce the efflux ratio of rifaximin to unity suggesting potentially other efflux pumps may be involved in efflux of rifaximin. Interaction between rifaximin and other transporters was not studied.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

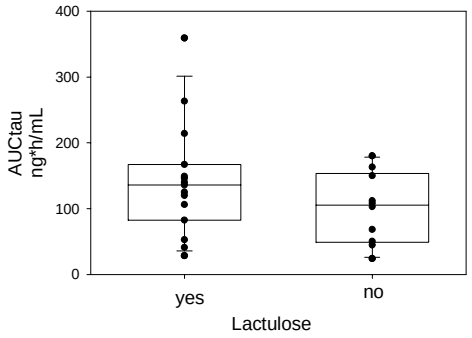
Effect of Concomitant Lactulose Use

Lactulose is a standard of care for patients with hepatic encephalopathy and in the pivotal RFHE3001 trial, 91% patients based on patient's diary used lactulose concomitantly.

Fifteen patients out of total 25 patients who participated in PK substudy were on concomitant lactulose therapy during the PK study. The mean systemic exposure in patients with concomitant lactulose use was higher than that in patients without concomitant lactulose regardless of liver function (Figure 5). The mean AUC in patients with concomitant lactulose was 142 ng*h/mL (61% CV) and that in patients without concomitant lactulose was 106 hg*h/mL (44% CV). Of note, 33% (5 out of 15) of patients who used lactulose concomitantly had moderate hepatic impairment and 20% (2 out of 10) of patients who did not use lactulose had moderate hepatic impairment. It is

unknown if the slightly higher systemic exposure observed is due to an interaction between rifaximin and lactulose.

Figure 5. Mean AUC in patients with a history of HE by concomitant lactulose use



Reviewer's comments: *Because of confounding factors such as hepatic insufficiency, a firm conclusion about effect of lactulose can not be drawn. The bacterial degradation of lactulose results in an acidic pH converting NH_3 to NH_4^+. It is proposed that the conversion of NH_3 to NH_4^+ inhibits the diffusion of NH_3 into the blood. Since the solubility of rifaximin is not significantly different between pH 4.5 and pH 7.4, the increasing trend in AUC of rifaximin with concomitant lactulose is unlikely due to an increase in solubility.*

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

Induction of CYP3A4 in vivo by rifaximin in the target patient population

The induction of CYP3A4 by rifaximin may be dose- and treatment-duration dependent. The drug interaction study RFDI1008 which was conducted in healthy volunteers could not address the issue in the target population whose plasma concentration of rifaximin is $\geq$ 5 fold higher than in healthy subjects (Table 20).

Table 20. Comparison of Mean Peak Plasma Concentrations

Study	Dosage regimen	Cmax (ng/mL)	Cmax (μM)	In vivo CYP3A4 induction
RFDI1002* +	7 days 200 mg TID	1.21	0.00154	None
RFDI1008+	7 days 550 mg TID	3.61	0.00459	< 25%
	14 days 550 mg TID	3.89	0.00495	< 25%
RFHE3002PK	7+ days 550 mg BID Child-Pugh A Child-Pugh B	 19.5 25.1	 0.0248 0.0319	Not evaluated

**submitted in NDA 21-361 original submission*

+in healthy volunteers

Inhibition of P-gp transporter by rifaximin at therapeutic plasma concentrations

The effect of rifaximin on efflux ratio of P-gp substrate was studied only at one concentration which was much higher than the observed mean peak plasma concentration in patients. Therefore, it is unknown if rifaximin has P-gp inhibitory effect at therapeutic plasma concentrations. Additional study at lower concentrations of rifaximin will be helpful to determine if in vivo drug interaction study is warranted.

Effect of P-gp inhibitor(s) on rifaximin systemic exposure in vivo

The efflux ratio of rifaximin in vitro was significantly reduced in presence of P-gp inhibitors. The in vivo drug interaction between rifaximin and P-gp inhibitor(s) was not evaluated.

2.5 Analytical Section

2.5.1 How was rifaximin identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The active moiety rifaximin was measured in plasma by using a validated HPLC-MS/MS assay method with acceptable precision and accuracy. The final report of bioanalytical assay method validation; PF00104 titled "Validation of a method for the determination of rifaximin in human plasma containing sodium heparin using high performance liquid chromatography with mass spectrometric (MS/MS) detection" was submitted. A partial validation (PF08B-0253 titled "Partial Validation of a Method for the Determination of Rifaximin in Human Plasma using High-Performance Liquid Chromatography with Mass Spectrometric Detection") was further performed to lower the standard curve range and to modify the extraction procedure and chromatography

2.6.3 What is the range of the standard curve? What are the lower limit of quantification (LLOQ)? What is the accuracy and precision at LLOQ?

The standard curve was established at concentrations ranging from 0.5 to 200 ng/ml. The LLOQ was 0.5 ng/mL and the accuracy and precision at LLOQ were 0.6-12.2% and 3.2-5.8%, respectively (Table 21).

Table 21.

Summary of Pre-Study and During-Study Validation Results for the Determination of Rifaximin in Human Plasma

	Pre-Study Validation	During-Study Validation
Standard Concentrations (ng/mL)	0.500, 1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 100.0, 200.0	0.500, 1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 100, 200
Linear Range (ng/mL)	0.500 to 200.0	0.500 to 200
Linearity (mean r^2)	0.9997	1.00
LLOQ (ng/mL)	0.500	0.500
Intra-assay Precision (CV%) at LLOQ	5.8	NA
Inter-assay Precision (CV%) at LLOQ	3.2	5.97
Intra-assay Accuracy (% Deviation) at LLOQ	12.2	NA
Inter-assay Accuracy (% Deviation) at LLOQ	0.6	-1.40
QC Concentrations (ng/mL)	1.50, 15.0, 160.0	1.50, 15.0, 160
Intra-assay Precision (CV%) of Quality Control Samples at Low, Medium, and High	4.7 to 8.9	NA
Inter-assay Precision (CV%) of Quality Control Samples at Low, Medium, and High	2.0 to 7.1	7.99 to 13.7
Intra-assay Accuracy (% Deviation) of Quality Control Samples at Low, Medium, and High	0.7 to 3.5	NA
Inter-assay Accuracy (% Deviation) of Quality Control Samples at Low, Medium, and High	-1.6 to 4.2	-8.13 to 3.33
Number of repeated samples	NA	56
% Recovery (internal standard)	106.2 (89.8)	NA
Stability		
In heparinized human plasma stored at room temperature	Stable for at least 24 hours	NA
In heparinized human plasma stored at -20°C	Stable for at least 83 days	NA
In heparinized human plasma subjected to freeze-and-thaw cycles	Stable for at least 3 cycles	NA
In injection solution stored at 5°C	Stable for at least 70 hours	NA

NA - Not Applicable.

3 Detailed Labeling Recommendations

Reviewer's recommendation is underlined.

Reviewer's recommendation

7. DRUG INTERACTIONS

In vitro studies have shown that rifaximin did not inhibit cytochrome P450 isoenzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 at concentrations ranging from 2 to 200 ng/mL. Rifaximin is not expected to inhibit these enzymes under clinical uses.

In vitro study has suggested that rifaximin induces CYP3A4. In patients with normal liver function, rifaximin (b) (4) However, it is unknown whether rifaximin can have a significant effect on the pharmacokinetics of concomitant CYP3A4 substrates in patients with reduced liver function which leads to elevated rifaximin concentrations.

In vitro study suggested that rifaximin is a substrate of p-glycoprotein. (b) (4)

8.7 Hepatic Insufficiency

Following administration of rifaximin 550 mg twice daily to patients with a history of hepatic encephalopathy, the systemic exposure (i.e. AUCtau) of rifaximin was about 10-, 13-, and 20 fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic (b) (4) compared to that in healthy volunteers. No dosage adjustment is recommended because rifaximin is presumably acting locally. Nonetheless, caution should be exercised when rifaximin is administered to patients with severe hepatic (b) (4) [see *Clinical Pharmacology (12.3) and Clinical Studies (14.2)*].

12.3 Pharmacokinetics

Absorption

Systemic absorption of rifaximin (XIFAXAN Tablets 200 mg three times a day) was also evaluated in 13 subjects challenged with shigellosis on Days 1 and 3 of a three-day course of treatment. Rifaximin plasma concentrations and exposures were low and variable. There was no evidence of accumulation of rifaximin following repeated administration for 3 days (9 doses). Peak plasma rifaximin concentrations after 3 and 9 consecutive doses ranged from 0.81 to 3.4 ng/mL on Day 1 and 0.68 to 2.26 ng/mL on Day 3. Similarly, $AUC_{0\text{-last}}$ estimates were 6.95 ± 5.15 ng•h/mL on Day 1 and 7.83 ± 4.94 ng•h/mL on Day 3. XIFAXAN Tablets are not suitable for treating systemic bacterial infections because of the limited systemic exposure after oral administration [see *Warnings and Precautions (5.1)*].

After a single dose and multiple doses of rifaximin 550 mg in healthy subjects, the mean time to reach peak plasma concentration was about an hour. The pharmacokinetic parameters were highly variable and the accumulation ratio based on AUC was 1.37.

The pharmacokinetics of rifaximin in patients with a history of hepatic encephalopathy (HE) was evaluated after administration of XIFAXAN Tablets, 550 mg two times a day. The PK parameters were associated with a high variability and mean rifaximin exposure (AUC_τ) in patients with a history of HE (147 ng•h/mL) was approximately 11.9-fold higher than that observed in healthy subjects following the same dosing regimen (12.3 ng•h/mL). When PK parameters were analyzed based on Child-Pugh Class A, B, and C, the mean AUC_τ was 10-, 13-, and 20 fold higher, respectively, compared to that in healthy subjects (Table 3).

Table 3. Mean (± SD) Pharmacokinetic Parameters of Rifaximin at Steady-State in Patients with a History of Hepatic Encephalopathy by Child-Pugh Class[1]

	Healthy Subjects (n=14)	Child-Pugh		
		A (n=18)	B (n=7)	C (n=4)
AUCtau (ng·h/mL)	12.3 ± 4.8	118 ± 67.8	161 ± 101	(b) (4)
Cmax (ng/mL)	3.4 ± 1.6	19.5 ± 11.4	25.1 ± 12.6	35.5 ± 12.5
Tmax* (h)	0.8 (0.5, 4.0)	1 (0.9, 10)	1 (b) (4)	1 (0, 2)

[1]Cross-study comparison with PK parameters in healthy subjects
[2]Median (range)

Food Effect

A high fat meal consumed 30 minutes prior to rifaximin dosing delayed the mean time to peak plasma concentration from 0.75 to 1.5 hours and increased the systemic exposure (AUC) of rifaximin by 2 fold (Table 4).

Table 4. Mean ±S.D. Pharmacokinetic parameters after a single dose administration of 550 mg rifaximin in healthy subjects under fasting and fed condition (N=12)

	Fasting	Fed
C_{max} (ng/mL)	4.1 ± 1.5	4.8± 4.3
T_{max} (h)*	0.8 (0.5-2.1)	1.5 (0.5-4.1)
Half-Life (h)	1.8 ± 1.4	4.8 ± 1.3
AUC (ng·h/mL)	11.1 ± 4.2	22.5 ± 12

*Median (range)

XIFAXAN Tablets can be administered with or without food [see *Dosage and Administration (2.3)*].

Distribution

Rifaximin is moderately bound to human plasma protein. In vivo, the mean protein binding ratio was 67.5% in healthy subjects and 62% in patients with hepatic impairment when 550 mg rifaximin was administered.

(b) (4)

Metabolism and Excretion

(b) (4)

In a separate study, rifaximin was detected in bile after cholecystectomy in patients with intact GI mucosa suggesting biliary excretion of rifaximin.

Hepatic (b) (4)

The systemic exposure of rifaximin was elevated in patients with hepatic impairment compared to (b) (4) healthy subjects. The mean AUC in patients with Child-Pugh C class hepatic impairment was 2 fold higher than in patients with Child-Pugh A class hepatic impairment (See Table (b) (4)

Drug Interactions

In vitro drug interaction studies have shown that rifaximin, at concentrations ranging from 2 to 200 ng/mL, did not inhibit human hepatic cytochrome P450 isoenzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4.

In an *in vitro* study, rifaximin was shown to induce CYP3A4 at concentration 0.2 µM.

In vitro study suggests that rifaximin is a substrate for P-glycoprotein. In the presence of p-glycoprotein inhibitor verapamil, the efflux ratio of rifaximin was reduced greater than 50% in vitro. Effect of p-glycoprotein inhibitor on rifaximin was not evaluated in vivo.

The inhibitory effect of rifaximin on p-gp transporter was observed (b) (4) The effect of rifaximin on p-gp transporter was not evaluated in vivo.

Midazolam

The effect of rifaximin 200 mg administered orally every 8 hours for 3 days and for 7 days on the pharmacokinetics of a single dose of either midazolam 2 mg intravenous or midazolam 6 mg orally was evaluated in healthy subjects. No significant difference was observed in the metrics of systemic exposure or elimination of intravenous or oral midazolam or its major metabolite, 1'-hydroxymidazolam, between midazolam alone or together with rifaximin. Therefore, rifaximin was not shown to significantly affect intestinal or hepatic CYP3A4 activity for the 200 mg three times a day dosing regimen.

After Rifaximin 550 mg was administered three times a day for 7 days and 14 days to healthy subjects, the mean AUC of single midazolam 2 mg orally was 3.8% and 8.8% lower, respectively than when midazolam was administered alone. The mean Cmax of midazolam was also decreased by 4-5% when rifaximin was administered for 7-14 days prior to midazolam administration. This degree of interaction is not considered clinically meaningful.

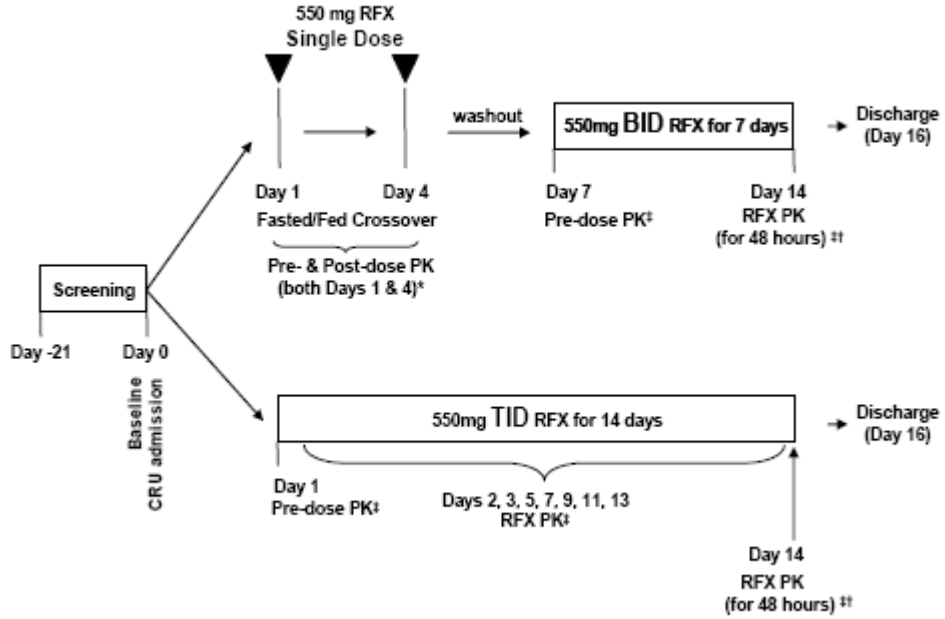
(b) (4)

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

4.2. Individual Study Review

RFPK 1007
Title: A phase 1, randomized, open-label, single-dose and multiple-dose, two-part study to evaluate the oral bioavailability of rifaximin 550 mg tablets with a high-fat meal or after fasting and during twice daily and 3 times daily dosing in healthy volunteers

Study design scheme



RFX PK = Rifaximin pharmacokinetic measurements

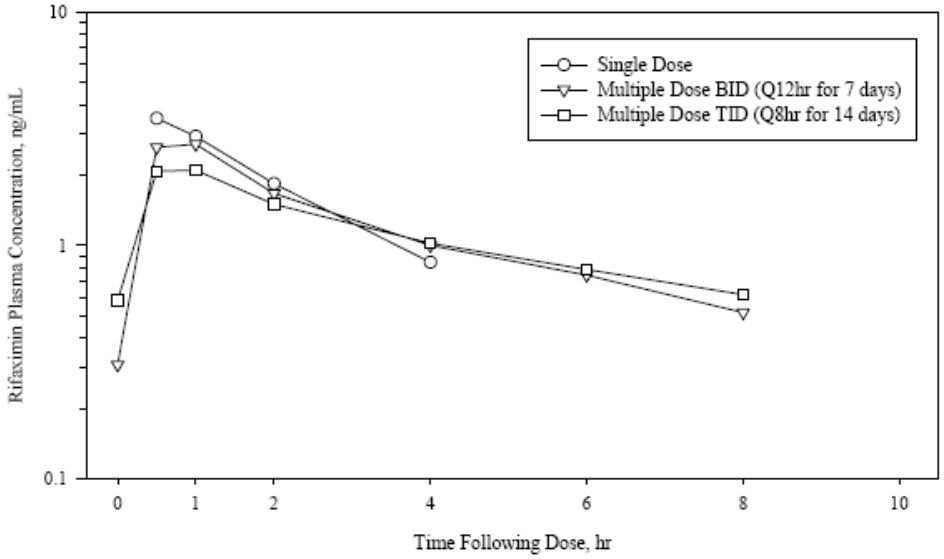
PK sampling: at pre-dose, and at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours dose dose.

Mean (SD) plasma PK parameters of Rifaximin 550 mg: Single-dose (fasted), multiple-dose BID and multiple-dose TID

Rifaximin Parameters	Single-Dose Fasted N = 12	Multiple-Dose BID N = 14	Multiple-Dose TID N = 14
C_{max} (ng/mL)	4.04 (1.51)	3.41 (1.62)	2.39 (1.28)
C_{min} (ng/mL)	NA	0.275 (0.333)	0.513 (0.359)
T_{max} (h)[a]	0.75 (0.50-2.05)	0.76 (0.50-4.00)	1.00 (0.50-2.03)
AUC_{0-t} (ng*h/mL)	8.83 (3.45)	11.5 (6.44)	11.6 (5.07)
AUC_{tau} (ng*h/mL)	10.4 (3.47)	12.3 (4.76)	9.30 (2.70)
AUC_{Total} (ng*h/mL)[b]	NA	24.6 (9.53)	27.9 (8.09)
$AUC_{0-\infty}$ (ng*h/mL)	11.1 (4.15)	NA	NA
CL/F (L/min)	959 (411)	863 (364)	1060 (304)
Rc	NA	1.37 (0.582)	NA
λz (h-1)	0.380 (0.255)	0.166 (0.120)	0.123 (0.0987)
t½ (h)[c]	1.83 (1.38)	4.17 (3.30)	5.63 (5.27)

Source: RFPK1007 Tables 14.2.1.1.2, 14.2.1.1.3, 14.2.1.3.1, 14.2.1.3.3, 14.2.1.3.4, and 14.2.1.3.5.
λz = terminal rate constant; Rc = accumulation ratio
a Median (range).
b AUC_{Total} = total daily AUC as determined by AUC_{tau} times the daily dosing frequency; therefore, BID AUC_{Total} = AUC_{tau} times 2 and TID AUC_{Total} = AUC_{tau} times 3; tau = 12 h for single dose and BID dosing, and tau = 8 h for TID dosing.
c Harmonic mean (pseudo SD) based on jackknife variance; NA, not applicable.
Notes: Arithmetic mean ± SD values are shown for rifaximin pharmacokinetic parameters. The same subjects received single-dose fasted/fed and multiple-dose BID regimens in the crossover study design (Part A), and a separate cohort of subjects received the TID regimen in Part B of the study. For the single-dose fasted group, N = 12 for most parameters because 2 subjects were excluded from the calculations due to rifaximin concentrations that were below the LLOQ; and N = 11 for the λz and t½ because a third subject was excluded from reporting of λz and t½ since in these subjects, only 2 plasma concentrations, in the terminal log-linear phase, were above the assay's LLOQ. In addition, N = 12 for determination of Rc because single dose AUC_{tau} values were paired with multiple dose BID AUC_{tau} values and only 12 subjects had paired AUC_{tau} values for single dose and for multiple-dose BID regimens.

Rifaximin mean plasma concentration-time profiles following single fasted and multiple BID and TID 550 mg oral doses



Mean values for C_{max} were lower in the multiple-dose TID regimen (2.39 ng/mL) when compared with multiple-dose BID (3.41 ng/mL) and single-dose regimens (4.04 ng/mL). Oral clearance values were not significantly different between BID dosing and single doses or between BID and TID dosing. Systemic exposure, as measured by $AUC_{0-\infty}$ or AUC_{tau}, was similar across treatment regimens. Mean values were 11.1 ($AUC_{0-\infty}$), 12.3 (AUC_{tau}), and 9.3 (AUC_{tau}) ng*h/mL in subjects who received the single-dose, multiple-dose BID, and multiple-dose TID regimens, respectively.

Although the total administered TID daily dose was 1.5-fold larger during TID dosing than during BID dosing, the daily exposure (AUC_{Total}) after TID administration was only modestly (approximately 13%) higher than that after the BID regimen. Mean AUC_{Total} values were 24.6 and 27.9 ng•h/mL for the BID and TID regimens, respectively.

Reviewer's comments: *The TID dosage regimen is being studied for Irritable Bowel Syndrome indication and yet is not studied for the proposed indication in patients with a history of hepatic encephalopathy. The mean Cmax was lower after multiple doses of twice daily 550 mg rifaximin compared after a single dose of 550 mg rifaximin and it was even lower under three times daily dosage regimen than under twice daily dosage regimen. The apparent oral clearance was about 23% higher under the TID regimen. As the multiple dose PK under TID dosage regimen and under BID dosage regimen was determined after 14 days and 7 days of dosing, respectively. In other study RFDI1008, the AUCtau and Cmax after 14 days of 550 mg TID dosing were 14.4 ng*h/ml and 3.89 ng/ml, respectively.*

In study RFDI1008, a time-dependent decrease in systemic exposure of midazolam was observed indicating a weak time-dependent induction of CYP3A4 enzyme mediated metabolism. It is unknown if rifaximin is a substrate of any cytochrome P450 enzymes and the decrease in Cmax may be attributed to an increase in first-pass metabolism of rifaximin due to induction of enzymes following multiple doses.

RFPK1007: Effect of a high fat diet on PK of rifaximin 550 mg

Food significantly delayed the mean time to peak plasma concentration of rifaximin from 0.75 to 1.5 hr, and increased rifaximin systemic exposure by approximately 2-fold as determined by AUC. The mean C_{max} was highly variable and was not significantly different between with or without food.

Reviewer's comments: *Similar effect of food on PK of rifaximin was observed previously with two 200 mg tablets (RFPK9901). The 200 mg rifaximin tablet is* (b) (4) *to 400 mg rifaximin tablet. The food effect on AUC was consistent for both strengths, a high fat meal significantly increased Cmax of 200 mg tablet by 2.5 fold given as 400 mg dose while it was variable for 550 mg tablet.*

Effect of Food on Rifaximin PK following a single 550 mg dose of rifaximin (n=14) and following a single 400 mg dose of rifaximin (n=14)

Parameter	550 mg Dose; RFPK1007		400 mg Dose; RFPK9901	
	Fasting	Fed	Fasting	Fed
C_{max} (ng/mL)	4.04 ± 1.51	4.76 ± 4.25	3.80 ± 1.32	9.63 ± 5.93
T_{max} (h)	0.75 (0.50-2.05)[a]	1.50 (0.50-4.08)[a]	1.21 ± 0.47	1.90 ± 1.52
$t_{1/2}$ (h)	1.83 ± 1.38[b]	4.84 ± 1.34[b]	5.85 ± 4.34	5.95 ± 1.88
$AUC_{0-\infty}$ (ng•h/mL)	11.1 ± 4.15	22.5 ± 12.0	18.35 ± 9.48	34.70 ± 9.23
% Excreted in urine	Not collected	Not collected	0.023 ± 0.009	0.051 ± 0.017

Source: RFPK1007 Table 14.2.1.1.2; RFPK9901 Table 14.2.1.

a Expressed as median and range

b Expressed as harmonic mean and pseudo standard deviation on jackknife variance

Formulation of rifaximin 550 mg and 200 mg tablet

Component	mg/200mg Tablet [a]	mg/550mg Tablet	% (w/w) of Tablet Core
(b) (4)			
Rifaximin	200	550	(b) (4)
Sodium starch glycolate, NF	(b) (4)		
Glyceryl distearate, NF (Glycerol palmitostearate)			
Colloidal silicone dioxide, NF			
Microcrystalline cellulose, NF			
Talc, USP			
(b) (4)			
ApproximateTotal Tablet Weight	**363**	**999**	

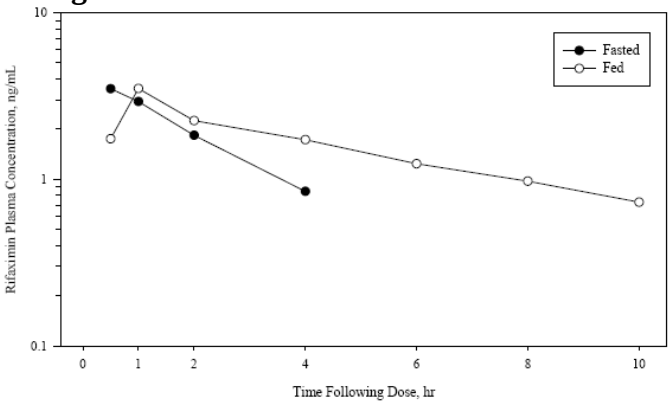
[a] Xifaxan® (rifaximin) Tablets, 200 mg (NDA 21-361, approved in May 2004)

[b] Tablets are coated to an approximate weight gain of (b) (4) of the core tablet weight.

[c] (b) (4) is used as the solvent when mixing the coating solution. It is removed during the coating process.

NA = Not Applicable

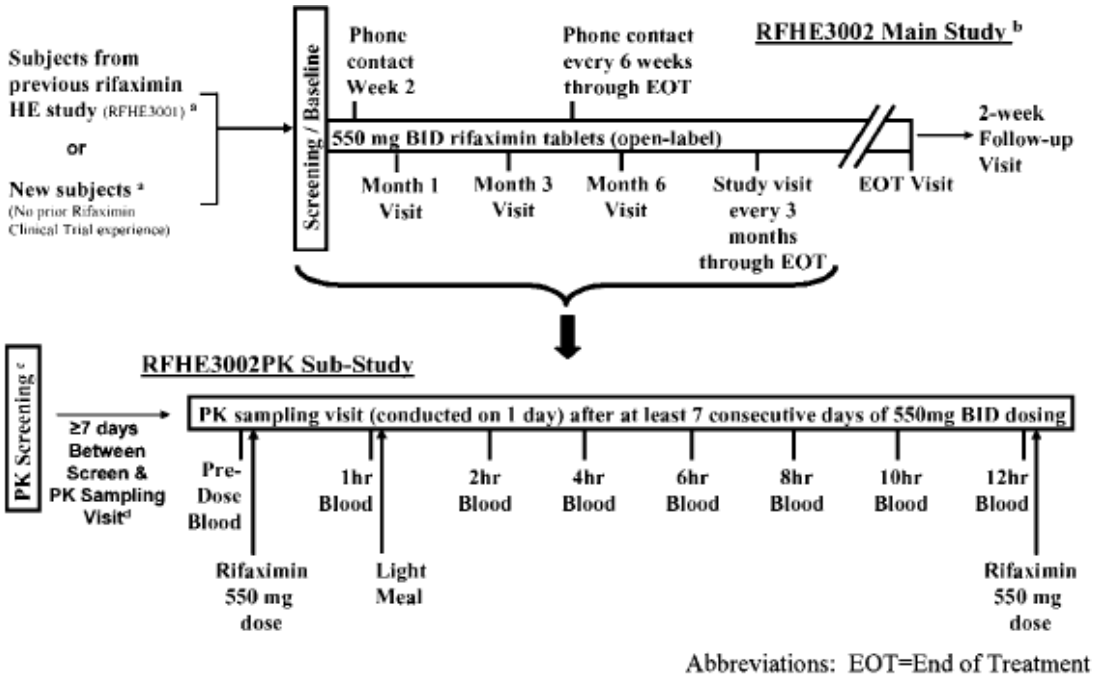
Rifaximin mean plasma concentration-time profiles following single fasted or fed 550 mg oral doses



RFHE3002PK

Title: An Open-Label Sub-Study to Evaluate the Pharacokinetics of Rifaximin During Long-Term Treatment in Subjects with Impaired Liver Function

Study design: RFHE3002PK was a pharmacokinetic substudy of the Phase 3 study RFHE3002, a multicenter, open-label trial to evaluate the long-term safety and tolerability of rifaximin 550 mg tablets taken BID in subjects with a history of HE. The pharmacokinetic evaluable population included 25 subjects (17 male, 8 female, aged 45 through 68 years) including 18 subjects (72%) with mild hepatic impairment (Child-Pugh A) and 7 subjects with moderate hepatic impairment (Child-Pugh B). Compliance of taking consecutive 7 days of dosing was ensured in patients participated in PK substudy.



PK sampling: PK blood samples were collected at predose, and at 1, 2, 4, 6, 8, 10, and 12 hours after dosing following overnight fasting.

Reviewer's comments: *Previously the sponsor agreed to study PK in 10 patients for each Child-Pugh class. However, due to difficulty in recruiting patients with Child-Pugh C in PK substudy, no hepatically impaired subjects from Child-Pugh category C were enrolled in RFHE3002PK. In RFHE3002 trial, a total of 31 patients were in Child-Pugh C category and 17 of them were randomized to rifaximin arm.*

Subject Demographics and baseline characteristics-all enrolled subjects

Characteristic	N = 25
N	25
Mean(± SD) age, years	58 (± 5.34)
Sex: n (%)	
Male	17 (68.0)
Female	8 (32.0)
Race: n (%)	
White	22 (88.0)
Black or African American	3 (12.0)
Child-Pugh Score: n (%)	
A	18 (72.0)
B	7 (28.0)
MELD Score: n (%)	
< 11	15 (60.0)
11 - 18	10 (40.0)
Conn Score	
Grade 0	22 (88.0)
Grade 1	3 (12.0)

Bioanalytical assay
Rifaximin in plasma was analyzed by an adequately validated bioanalytical assay method using LC/MS/MS. In-study QC was done at 1.5, 5, and 12 ng/ml and the accuracy and precision ranged from -1.67 to 0.667% and from 4.58 to 5.84%, respectively. The calibration curve ranging from 0.5 to 15 ng/ml was used for determination of plasma concentrations of rifaximin.

Results
PK parameters were estimated by using a Non-Compartmental Model.

Mean ± SD (% CV) plasma pharmacokinetic parameters of Rifaximin subjects with liver impairment

	Child-Pugh A (n=18)	Child-Pugh B (n=7)	Healthy subjects (n=14)[1]
AUCtau (ng*h/ml)	118 ± 67.8 (57%)	161 ± 101 (62.7%)	12.3 ± 4.76
Cmax (ng/ml)	19.5 ± 11.4 (58.5%)	25.1 ± 12.6 (50.2%)	3.41 ± 1.62
Cmin (ng/ml)	5.13 ± 4.01 (78%)	7.90 ± 5.35 (67.7%)	0.275 ± 0.333
Tmax (h)	1 (0.9-10)	1 (0.97, 1)	0.76 (0.5-4)
$T_{1/2}$ (h)	8.12 ± 3.58 (44.1%)	10.5 ± 1.5 (14.3%)	4.17 ± 3.3
CL/F (L/min)	122 ± 101 (82.8%)	70.6 ± 29.2 (41.4%)	863 ± 364

[1] **From RFPK1007**

Mean AUCtau and Cmax were 36% and 29% higher, respectively in patients with Child-Pugh B class hepatic impairment than in patients with Child-Pugh A class hepatic impairment.

In cross-study comparison to healthy subjects (RFPK1007), mean AUCtau was 9.6- and 13.1-folds higher, respectively in patients with Child-Pugh A and Child-Pugh B class hepatic impairment.

In cross-study comparison to healthy subjects (RFPK1007), mean Cmax was 5.7-and 7.4-folds higher, respectively in patients with Child-Pugh A and Child-Pugh B class hepatic impairment.

Effect of Hepatic Impairment Scores (Child-Pugh A versus Child-Pugh B) on main PK parameters of rifaximin

Pharmacokinetic Parameter	Geometric Least Square Mean (ng/mL)		Ratio of Least Square Mean (B/A) (%)	90% Confidence Interval (%)	p-value	Variance Assumption	Inter-Subject CV (%)
	Child-Pugh A	Child-Pugh B					
AUC_{tau} (ng*h/mL)	92.44	139.80	151.2	(98.8, 231.5)	0.1092	Child-Pugh A Child-Pugh B	81.8 49.6
C_{max} (ng/mL)	15.41	23.11	149.9	(98.8, 227.5)	0.1096	Child-Pugh A Child-Pugh B	91.5 43.6

Source: RFHE3002PK Appendix 16.1.9.1.2.

When the liver function was assessed based on MELD (Measurement of End-stage Liver Disease), 3 out of 18 patients with Child-Pugh A class and all patients with Child-Pugh B class hepatic impairment had MELD score from 11 to 18.

Effect of Hepatic Impairment Scores (MELD score <11 versus 11 to 18) on Main PK parameters of Rifaximin

Pharmacokinetic Parameter	Geometric Least Square Mean (ng/mL)		Ratio of Least Square Mean (B/A) (%)	90% Confidence Interval (%)	p-value	Variance Assumption	Inter-Subject CV (%)
	MELD < 11	MELD 11 to 18					
AUC_{tau} (ng•h/mL)	84.30	141.81	168.22	(110.5, 256.2)	0.0451	MELD<11 MELD 11-18	78.5 51.1
C_{max} (ng/mL)	13.70	24.41	178.12	(116.7, 271.8)	0.0283	MELD<11 MELD 11-18	89.9 48.8

Source: RFHE3002PK Appendix 16.1.9.1.7.

Reviewer's comments:

Notably, one subject 0875-0011 had 2 folds higher AUC and Cmax than the mean AUC and Cmax in other patients with Child-Pugh B class liver impairment. The subject was initially classified in Child-Pugh C and had MELD score 20 at baseline during

RFHE3001 trial. When the subject was rolled over to the RFHE3002 long-term extension study after completion of 6 months treatment, she was classified in Child-Pugh B and had MELD score 15 at baseline suggesting that the history of severe hepatic impairment may have influenced the PK of rifaximin in this subject.

Relationship between AUCtau of rifaximin and covariates-Parsimonious model

Effect	Final Multivariate Model			
	Estimate	95% CI	p value	Standard-Error
Intercept	8.4175	(5.0768 ; 11.7582)	<0.0001	1.6064
Albumin	-0.0573	(-0.1130 ; -0.0017)	0.0440	0.0268
Total Bilirubin	0.0173	(-0.0035 ; 0.0381)	0.0988	0.0100
INR	-1.7432	(-3.1909 ; -0.2956)	0.0206	0.6961

Covariate analyses indicated that biochemical markers of impaired hepatic function ie elevated albumin, total bilirubin, and international normalized ratio values correlated with elevated rifaximin systemic exposure (AUC_{tau}, and C_{max}) and decreased oral clearance (CL/F) in this study.

Reviewer's comments: *Total bilirubin and INR are common factors in calculating MELD score and Child-Pugh score. Serum albumin and serum creatinine is factored only in Child-Pugh score or MELD score, respectively.*

Lactulose Use

During the PK substudy, 62% of patients who participated in the substudy took lactulose concomitantly. Highly variable yet there is a trend of increase in systemic exposure in patients who took lactulose concomitantly during the PK substudy. The dosage regimen of lactulose use is inconsistent and for a few patients, the dose is unclear.

Systemic exposure of rifaximin with or without concomitant lactulose use during the PK substudy

	Child-Pugh A		Child-Pugh B	
Concomitant Lactulose	+lactulose N=10	-lactulose N=7*	+lactulose N=5	-lactulose N=2
Cmax	21.7 (12.4) (57%)	17.8 (10.4) (58%)	25.1 (15.4) (61%)	25.2
AUCtau	130.3 (75.7) (58%)	99 (55.3) (56%)	165.3 (110.3) (67%)	133

RFDI1008 A Phase 1, Single Arm. Open-Label Study to Evaluate the Effect of Rifaximin 550 mg Tablets TID on the Pharmacokinetics of Orally Administered Midazolam in Healthy Male and Female Volunteers

Study RFDI1008 was a single-site, single-arm, open-label, drug-interaction study that examined the effect of rifaximin 550 mg tablets (administered orally TID for a daily dose of 1650 mg) on orally administered midazolam 2 mg (administered as midazolam HCl syrup 2 mg/mL) when dosed for 7 and 14 consecutive days, respectively. A total of 24 subjects (14 male, 10 female, aged 22 through 42 years) received rifaximin and 20 subjects completed the study.

Effect of multiple dose rifaximin (550 mg TID) on midazolam PK

Midazolam Parameters	Geometric Least Squares Mean	Geometric Mean Ratios[a]	90% Confidence Interval for Geometric Mean Ratios[c] Lower	Upper	p-value[b]	Power[c]
C_{max} (ng/mL)						
Day 1 (midazolam alone)	10.2					
Day 9 (midazolam + 7 days rifaximin)	9.73	95.31	81.76	111.09	0.6010	77.6
Day 16 (midazolam + 14 days rifaximin)	9.67	94.77	79.97	112.30	0.5972	70.0
AUC_{0-t} (ng•h/mL)						
Day 1 (midazolam alone)	20.7					
Day 9 (midazolam + 7 days rifaximin)	19.8	95.47	78.96	115.43	0.6834	61.5
Day 16 (midazolam + 14 days rifaximin)	19.1	92.36	75.28	113.32	0.5171	56.1
$AUC_{0-\infty}$ (ng•h/mL)						
Day 1 (midazolam alone)	22.8					
Day 9 (midazolam + 7 days rifaximin)	22.0	96.19	79.62	116.20	0.7314	61.9
Day 16 (midazolam + 14 days rifaximin)	20.8	91.25	75.01	111.01	0.4363	59.2

Source: RFDI1008 Tables 14.2.1.1.3

a Geometric mean ratios of midazolam + rifaximin (test) to midazolam alone (reference); expressed as a percent.

b P-value for testing difference in natural log-transformed parameter between midazolam + rifaximin (test) and midazolam alone (reference) using the 2 one-sided t-test procedure and an analysis of variance model with a fixed effect for treatment

c Expressed as a percent.

PK parameters of 1'-hydroxymidazolam with and without concomitant rifaximin treatment

1'-Hydroxymidazolam Parameter	Study Day	Treatment	Geometric Least Squares Mean	GMR[a]	90% CI for GMR		p-value[b]	Power[c]
					Lower	Upper		
C_{max}, ng/mL	1	Midazolam Alone	4.63					
	9	Midazolam + 7 Days Rifaximin	4.77	103.01	87.61	121.11	0.7597	73.6
	16	Midazolam + 14 Days	4.26	91.90	77.48	109.00	0.4097	69.6
AUC_{0-t}, ng·hr/mL	1	Midazolam Alone	7.15					
	9	Midazolam + 7 Days Rifaximin	8.14	113.82	95.25	136.00	0.2285	66.4
	16	Midazolam + 14 Days	6.65	93.03	75.44	114.73	0.5652	54.4
$AUC_{0-\infty}$, ng·hr/mL	1	Midazolam Alone	8.87					
	9	Midazolam + 7 Days Rifaximin	9.73	109.75	95.02	126.76	0.2840	81.9
	16	Midazolam + 14 Days	8.28	93.41	78.47	111.19	0.5139	68.1

[a] Geometric Mean Ratio of midazolam + rifaximin (test) and midazolam alone (reference); expressed as a percent.
[b] p-value for testing difference in natural log-transformed parameter between midazolam + rifaximin (test) and midazolam alone (reference).
[c] Expressed as a percent.

Systemic exposure to a midazolam metabolite, 1'-hydroxymidazolam was higher after 7 days of rifaximin treatment than midazolam alone. Nonetheless, it was lower after 14 days of rifaximin treatment than midazolam alone. Other metabolite 4'-hydroxymidazolam was not measured.

PK parameters of rifaximin after multiple doses of 550 mg rifaximin TID

Days of dosing	Cmax	AUCtau	CL/F
7 days (n=24)	3.61 ± 1.28	13.5 ± 3.58	716 ± 198
14 days (n=20)	3.89 ± 1.27	14.4 ± 4.38	698 ±226

When rifaximin was orally administered at high doses (ie, 550 mg tablet TID) for at least 7 to 14 days, the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of midazolam (a CYP3A4 probe substrate) were reduced by < 25%. While bioequivalence guidelines applied to midazolam exposure suggest that rifaximin was a weak inducer of CYP3A4 in the current study, the minimal effect on mean exposure values indicates that the clinical significance of rifaximin effect on CYP3A4 would be negligible.

Reviewer's comments: *The result of this study is applicable only to patients with normal liver function or in healthy subjects. As the systemic exposure to rifaximin is much higher in patients with a history of hepatic encephalopathy than in healthy subjects, it is unknown if a stronger induction of CYP3A4 by rifaximin in those patients would be observed.*

RFHE9702 A randomised, multi-centre, dose-finding, double-blind, parallel group study comparing three dose levels of rifaximin: 600 mg/day, 1200 mg/day and 2400 mg/day in patients with Grade I, II or III porto-systemic encephalopathy. Treatment was administered for 7 days.

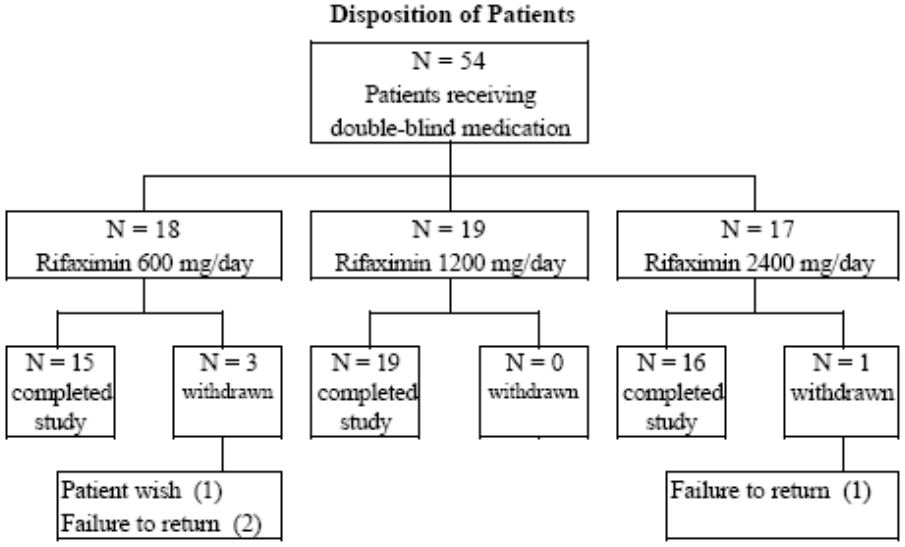
Background
Study RFHE9702 was conducted and sponsored from December 1995 to December 1996 in the United Kingdom by patent holder Alfa-Wasserman, and the final CSR was generated and approved by Alfa-Wasserman in July of 1997. The study was not conducted as part of a US IND, and the CSR and clinical study database were provided to Salix Pharmaceuticals, Inc. (Salix) by Alfa-Wassermann.

The primary efficacy endpoint: PSE index at the end of the treatment
The PSE index which is derived from the evaluation of 5 different test scores:-

1. Mental state score (graded 0-4), weighted x 3
2. EEG (α rhythm) score (graded 0-4), weighted x 1
3. Number Connection Test score (graded 0-4), weighted x 1
4. Asterixis score (graded 0-4), weighted x 1
5. Blood ammonia score (graded 0-4), weighted x 1

The total of the actual weighted scores, the maximum possible of which is 28, is termed the PSE sum, from which is calculated the PSE index:-PSE index = PSE sum/28 x 100%

Number of Patients: 17-19 patients/ dose group



PSE Index

Rifaximin daily dose		PSE Index (%)					Adjusted mean from analysis of covariance	
		N	Mean	St dev	Min	Max	Mean	95% CI
600 mg	Day 1	14	37.8	11.4	25.0	64.3		
	Day 7 or withdrawal	17	31.9	16.9	3.6	67.9	32.4	22.9, 42.7
1200 mg	Day 1	16	38.4	13.8	21.4	75.0		
	Day 7 or withdrawal	18	28.2	18.9	7.1	82.1	30.8	22.7, 39.2
2400 mg	Day 1	16	41.7	8.5	17.9	50.0		
	Day 7 or withdrawal	16	31.0	14.2	7.1	57.1	25.8	18.8, 34.4

The sponsor's conclusion:
There was no difference among dose groups based on the pre-specified primary endpoint i.e. PSE index at the end of the treatment. The preliminary test of the linear component of the dose response showed no significant dose response (p = 0.28). There was no evidence of a difference between the lower doses, 600 mg per day and 1200 mg per day with estimated mean PSE indexes from the analysis of covariance 32.4% and 30.8% respectively, but some indication that the 2400 mg per day dose, with an estimate of 25.8%, might differ from the lower doses.

Reviewer's comments: *Based on this study, Alfa-Wasserman conducted phase 3 trials at 1200 mg daily dose i.e. 400 mg three times daily for 7 days in hepatic encephalopathy patients. Those studies were submitted as supporting studies in this application. Nonetheless, the study population, primary endpoint and dosage regimen are different from the current phase 3 trial RFHE3001. In addition, there was no control group in this dose-ranging study.*

Pharmacoknetic substudy:
In this study, patients with cirrhosis and mild to moderate hepatic encephalopathy (HE) were treated with rifaximin, 600, 1200 or 2400 mg/day in three divided doses for a total of 7 days. Blood samples were taken approximately 3 hours after the first drug dose for estimation of plasma rifaximin concentration using liquid chromatography-mass spectrometry (LC-MS). A 24-hour urine sample was collected, commencing after the first dose on day 7 and the total volume was measured and the rifaximin concentration determined with LC-MS.

PK findings Mean (% CV) Study RFHE 9702

Daily dose	Plasma conc[1]*. (ng/mL)	Urine conc. (ng/mL)	Total amount in urine (mg)	% dose excreted unchanged[2]*
600 mg (200 mg t.i.d)	2.69 (0-13.81) (n=16)	518 (165) (n=13)	0.367 (107) (n=13)	0.061 (0.003-0.229) (n=13)
1200 mg (400 mg t.i.d.)	10.50 (0-57.89) (n=13)	966.9 (93) (n=15)	1.199 (93) (n=15)	0.1 (0.002-0.295) (n=15)
2400 mg (800 mg t.i.d.)	13.47 (0-40.33) (n=14)	1102.4 (106) (n=15)	1.350 (141) (n=15)	0.056 (0.002-0.320) (n=15)

[1] Plasma concentrations were measured 3 hours after the first dose on Day 1
[2] The urine sample was collected over 24 hours after the first dose on Day 7
*(Min-max)

Reviewer's comments: *The bioanalytical assay method was calibrated in a range from 0.5 ng/ml to 50 ng/ml in urine and plasma.*

There was a dose-dependent increase in urinary excretion although it was highly variable. The mean % dose excreted unchanged was notably higher after 1200 mg daily dosing. The plasma concentration of rifaximin at 3 hours after the dose was increased with increase in dose but the typical time to peak plasma concentration is about 1 hour after a dose thus the interpretation of this result is hampered. In this trial, lactulose use was prohibited.

Study XT58-Salix-02-15Mar2008

Evaluation of Rifaximin as a P-glycoprotein Substrate and inhibitor in Caco-2 cells

Experimental design

Cell system:

The monolayer assay was performed on Caco-2 cell monolayers which express human P-gp. Caco-2 cells were cultured in (b) (4) at 37°C in an atmosphere of (b) (4) in cell culture flasks prior to seeding into (b) (4) inserts. Caco-2 cells were grown on the inserts for 21-25 days prior to incubations with rifaximin.

Rifaximin was dissolved in 100% (b) (4)

The apparent membrane permeability was calculated as below.

$$P_{app} = \frac{dQ}{dt}\frac{1}{AC_0}$$

Legend:

dQ: transported amount of test drug

dt: incubation time

A: surface of membrane

C0: initial concentration of the compound in the donor compartment

Efflux ratio is given as the B-A/A-B apparent permeability ratio.

Non-specific binding control: The recovery from the donor compartment after 2 hour incubation in the transwells containing filter without cells was measured. Recovery from the basolateral compartment was about (b) (4) while recovery from the apical compartment was (b) (4)

Efflux Ratio of Rifaximin on Caco-2 Monolayers

Bidirectional transport of rifaximin through Caco-2 cell monolayers was determined. The monolayer was formed on 24-well transwell inserts. Trans-epithelial electric resistance of each well was measured to confirm confluency of the monolayers prior experiments.

Rifaximin was added to the apical or basolateral compartment in (b) (4) at three concentrations (0.5, 5 and 50 µM). Apical to basolateral permeability of (b) (4) were assessed for high and low permeability controls, respectively. Digoxin served as a positive control for P-gp function. Bidirectional permeability of digoxin was determined. After incubation at 37ºC aliquots were taken from the receptor compartments to determine the translocated amount of rifaximin and controls. Samples were taken after 15, 30, 60 and 120 minutes.

Experiments were repeated on two separate days.

Treatment groups in the efflux ratio determination assay	
Monolayer integrity controls	(b) (4) ermeability) and (low permeability) (A-B)
P-gp functionality control	Digoxin (10 µM, A-B, B-A)
TA	Rifaximin (0.5, 5 and 50 µM) (A-B, B-A)
BCS controls	(b) (4) (50 µM), (A-B, B-A) (50 µM), (A-B, B-A) Verapamil (50 µM), (A-B, B-A) Mannitol (0.4 µM), (A-B, B-A)

Results

At 5 and 50 µM, rifaximin showed low PAPP values in the Apical to Basolateral (A-B, absorptive) direction (~1*10-6 cm/sec), but a high permeability in the B-A (excretory) direction (b) (4). These results indicate that one or more transporters are involved in the transport of rifaximin through Caco-2 monolayers. The results obtained at 0.5 µM were difficult to analyze, especially for the A-B experiment, as most of the values were below the limit of quantification (<LOQ). Therefore, no PAPP A-B value was determined at 0.5 µM.

Date:	03-Oct-2008	Experiment:	Efflux Ratio of Rifaximin and BCS controls and Digoxin inhibition	
Compound		P_{app} A-B	P_{app} B-A	ER
Controls	(b) (4)	60.53 ± 2.73	-	NA
		0.25 ± 0.2	-	NA
	Digoxin	2.50 ± 0.73	27.00 ± 2.96	11
Rifaximin	0.5 µM	ND	71.37 ± 7.37	NA
	5 µM	1.19 ± 0.36	52.98 ± 2.85	45
	50 µM	0.89 ± 0.53	35.73 ± 2.51	40
Digoxin	10 µM	2.50 ± 0.73	28.37 ± 2.5	11
	+ 60 µM Verapamil	6.39 ± 0.54	6.67 ± 0.16	1
	+ 0.25 µM GF120918	2.69 ± 0.39	22.58 ± 0.63	8
	+ 50 µM Rifaximin	3.37 ± 0.87	16.05 ± 0.94	5
BCS Controls	Antipyrine (50 µM)	76.79 ± 6.90	66.92 ± 3.83	0.9
	Metoprolol (50 µM)	45.24 ± 3.12	40.34 ± 1.86	0.9
	Verapamil (50 µM)	33.52 ± 1.26	37.05 ± 1.51	1
	Mannitol (50 µM)	2.99 ± 2.31	0.15 ± 0.09	0.05 (± 1)

Efflux Ratio of Rifaximin on Caco-2 Monolayers in the Presence of P-gp Inhibitors

Bidirectional transport of rifaximin was determined through Caco-2 cell monolayers in the absence and presence of the specific P-gp inhibitors verapamil and GF120918 (Elacridar). Rifaximin was applied at a concentration of 5 µM and samples were taken after 120 minutes (linear conditions). Apical to basolateral permeability of antipyrine and (b) (4) were assessed for high and low permeability controls, respectively. Digoxin served as a positive control for P-gp function. Also, the ability of verapamil and GF120918 to inhibit digoxin transport was assessed.

Results: Rifaximin was incubated in the presence of a P-gp inhibitor, GF120918 (Elacridar, 0.5 μM) and Verapamil (60 μM). Rifaximin concentration (5 μM) and incubation time (120 min) were determined based on the results obtained in part 1 (linear conditions). The BA permeability of rifaximin (b) (4)) decreased slightly yet consistently in the presence of Verapamil while in the presence of GF120918, BA permeability was decreased or did not change in two separate studies. The AB permeability (b) (4) consistently increased to (b) (4) in the presence of both inhibitors. As a result, the efflux ratio (ER) of rifaximin was decreased by 2-12 folds in the presence of P-gp inhibitors.

Inhibition of Rifaximin Transport by P-gp inhibitors

	ER	$ER_{Verapamil}$	$ER_{GF120918}$
Round 1	134.54 ± 0.1	10.89 ± 0.2	16.48 ± 0.17
Round 2	78.53 ± 0.32	11.56 ± 0.28	29.68 ± 0.11

The results indicate that P-gp is only partly involved in the transport of rifaximin through Caco-2 monolayers. Other transporters that probably play a role could be BCRP, MRP2 and / or (basolateral) uptake transporters.

Inhibition of Digoxin Efflux on Caco-2 Monolayers
Bidirectional transport of ^{3}H-digoxin through Caco-2 cell monolayers was determined in the presence and absence of rifaximin. Rifaximin was applied at a high concentration (50 μM). Apical to basolateral permeability of antipyrine and lucifer yellow were assessed for high and low permeability controls, respectively. Digoxin served as a positive control for P-gp function. Verapamil and GF120918 were applied as positive controls for inhibition of digoxin transport. After two hours of incubation at 37^{o}C aliquots were taken from the receptor compartments to determine translocated amount of ^{3}H-digoxin and controls.

Results:
Rifaximin only weakly inhibited digoxin transport. Full inhibition (ER ≈ 1) was not observed at the highest concentration tested (50 μM). Therefore, an IC_{50} determination was not performed. In the presence of rifaximin, the efflux ratio of digoxin decreased from 11-13 to 2-6.

The MDR1 inhibitor verapamil (60 μM) inhibited the transport of digoxin by increasing the permeability of digoxin in the AB direction and decreasing the permeability in the BA direction. An ER of 1 was observed for digoxin in the presence of 60 μM Verapamil. GF120918 (0.25 μM) partially inhibited digoxin transport and a higher concentration of GF120918 (0.5 μM) fully inhibited digoxin transport, reducing the ER of digoxin to ~ 1.

Inhibition of Digoxin Transport in presence of Rifaximin at 50 μM

	ER	$ER_{Rifaximin}$
Round 1	11.35 ± 0.31	4.77 ± 0.27
Round 2	11.74 ± 0.32	1.99 ± 0.44
Round 3	12.32 ± 0.21	6.36 ± 0.28

Reviewer's comments: *A prototype p-gp substrate, digoxin was used as a positive control at 10 μM and the resulted ER was 10-14 and found to be acceptable.*

The sponsor's discussion:
Transport of rifaximin through Caco-2 monolayers was linear up to 50 □M during incubation for two hours. The maximum, theoretical concentration of rifaximin in the lumen is 2.7 mM (Dose/$V_{intestine}$), however, rifaximin is only soluble up to 5 μM. The C_{max} of rifaximin in healthy subjects is 0.005 □M, indicating the drug is very poorly absorbed. The results from this study confirm that one or more efflux transporters are likely involved in the low intestinal absorption of rifaximin at a theoretical lumen concentration of 5 □M, as no saturation of the transport was observed at concentrations up to 50 □M.

At 50 μM, rifaximin inhibited digoxin transport, but not fully. The efflux ratio decreased from 11-13 to 2-6. Rifaximin is thus probably a weak inhibitor of P-gp and accordingly is not likely to cause drug-drug interactions with other substrates of P-gp, hence the drug is only soluble at concentrations up to 5 □M.

***Reviewer's comments**: Although the solubility of rifaximin at pH 4.5 to 7.4 is only up to 5 μM in buffered water, in the presence of surfactant i.e. 0.25% sodium dodecyl sulfate the rifaximin solubility increased to 540 μM. The increased AUC by 2 fold with a concomitant high fat diet is likely attributed to the increased solubility of rifaximin (RFPK1007).*

The extent of decrease in the efflux ratio of digoxin in the presence of 50 M rifaximin did not reach to the unity yet it was greater than 50%. Usually, an in vivo drug interaction study would be warranted with this degree of p-gp inhibitory effect in in vitro. Nonetheless, given the limited solubility of rifaximin, it is unknown if a positive inhibitory effect on digoxin transporter is present with rifaximin at lower concentrations.

The effect of concomitant P-gp inhibitors on rifaximin absorption in vivo should be studied. Additional studies at lower concentrations of rifaximin would be useful to determine if an in vivo drug interaction study is necessary.

Study PF09M-0004
In Vivo and In Vitro Plasma Protein Binding Study of Rifaximin by Ultrafiltration

Human plasma samples were selected from Salix study RFHE3002PK, a pharmacokinetic study in subjects with impaired liver function and hepatic encephalopathy secondary to liver cirrhosis, and from Salix study RFPK1007, a phase I study in normal healthy subjects. These plasma samples were subjected to ultrafiltration. The human plasma samples as well as their ultrafiltrate were analyzed for concentration of rifaximin. The protein binding ratios were calculated as below.

$$\% \text{ Plasma Protein Binding} = \frac{C_B}{C_T} \times 100$$

with C_T = Concentration in plasma

C_B = Bound concentration = $(C_T - C_F)$

C_F = Free concentration in ultrafiltrate

Results:
Protein binding values in hepatically-impaired subjects ranged from 55.3% to 68.2%. The average binding ratio in the hepatically-impaired subjects orally dosed with 550 mg rifaximin twice daily was 62.0 % with a coefficient of variation of 7.06%.

Protein binding values in healthy subjects ranged from 62.5% to 72.8%. The average binding ratio in the healthy subjects orally dosed with 550 mg rifaximin was 67.5% with a coefficient of variation of 5.50%.

Non-specific binding to filter was about 11%.

Reviewer's comments: *Based on this result, the free fraction of rifaximin in plasma is expected to be about 9 % higher in hepatic impairment patients than in healthy subjects.*

A blood sample for protein binding was collected 0.5-2 hour post-dose in healthy volunteers and at 2 hours post-dose in 75% patients (9 out of 12). In three patients out of 12 patients, the samples were collected from 4-10 hours post-dose. The plasma concentration of rifaximin when the protein binding was measured ranged from 14 to 52 ng/ml in patients and < 10 ng/ml in healthy subjects.

The observed lower protein binding may be due to a decrease in plasma protein in patients with impaired hepatic function than in healthy subjects.
In RFHE3002PK, plasma albumin level was lower in patients with Child-Pugh B class hepatic impairment than in Child-Pugh A hepatic impairment.

	Child-Pugh A (n =17)	Child-Pugh B (n=7)
Albumin	36.9 (29-44)	29.9 (21-37)

Study RFPK1002

Title: A Two-Way Crossover Scintigraphic Evaluation of the Disintegration of Two Batches of Rifaximin

Study RFPK1002 was an open-label, randomized, single-dose-per-period, 2-way crossover study of 2 batches of rifaximin 200 mg tablets using gamma scintigraphy in 19 healthy male subjects (aged 21 through 58 years). The aim of this study was to determine whether small differences in the *in vitro* dissolution profile of clinical vs commercial batches affected the rate of tablet disintegration or arrival of rifaximin in the colon. Following single 200 mg oral doses, the rifaximin tablets rapidly disintegrated in the stomach (within 6 through 23 minutes), moved through the small intestine within 3.82 through 6.25 h post dose, and through the colon within 3.94 through 7.28 h post dose. The statistical analysis confirmed that there was no difference in the rate of delivery of rifaximin to the colon between the batches (clinical batch 99002 and commercial batch F0982.001).

	$T_{50\%}$ gastric emptying (hours post-dose)	$T_{50\%}$ small intestinal transit (hours post-dose)	$T_{50\%}$ colon arrival (hours post-dose)
Mean	0.34	4.47	4.81
SD	0.19	2.00	1.98
Range	0.06 – 0.62	2.07 – 8.95	2.15 – 9.41
n	18	18	18

$T_{50\%}$: the time when more than 50% of the radiolabel had moved from one anatomical region to the next

The sponsor concluded that overall, the data suggest that the difference in the *in vitro* profile does not affect the *in vivo* performance of the formulation (commercial batch F0982.0010).

Reviewer's comments: *This study was designed to assess the disintegration and the gastrointestinal transit properties of the two batches of 200 mg rifaximin tablets.* (b) (4) *Because the* (b) (4) *was* (b) (4) *into the formulation, this study does not provide any information on the distribution of rifaximin itself. Based on the intestinal transit time determined in this study, the sponsor supported the twice a day dosing frequency.*

4.4 OCP Filing Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22554**	**Brand Name**	**Xifaxan**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Rifaximin**
Medical Division	**DGP**	**Drug Class**	**Anti-microbial agent**
OCP Reviewer	**Insook Kim, Ph.D.**	**Indication(s)**	**Hepatic Encephalopathy**
OCP Team Leader	**Sue-Chih Lee, Ph.D.**	**Dosage Form**	**Tablet 550 mg**
Pharmacometrics Reviewer		**Dosing Regimen**	**550 mg BID**
Date of Submission	**6/8/2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Salix**
Medical Division Due Date		**Priority Classification**	**P**
PDUFA Due Date	**12/8/2009**	**Type of Submission**	**Type 6 NDA**

Clin. Pharm. and Biopharm. 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.				
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**2**	**2**	
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	**X**	**2**		
multiple dose:	**X**	**1**	**1**	
Patients-				
single dose:	**X**	**2**		
multiple dose:	**X**	**2**	**1**	
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:	**X**	**3**	**1**	
In-vitro:	**X**	**2**	**1**	
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	**X**	**1**		
PD -				
Phase 2:		**1**	**1**	
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**	**1**	
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				
Literature References	**X**	**4**		
Total Number of Studies	**X**	**23**		

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 bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
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 that might affect the pharmacokinetic or pharmacodynamics?			X	
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	
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 __

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Insook Kim, Ph.D.
7/20/2009

Reviewing Clinical Pharmacologist Date

NDA 22-554 Rifaximin 550 mg
(b) (4)

Sue-Chih Lee, Ph.D.
7/20/2009

Team Leader/Supervisor Date

Filing Memo

Rifaximin was approved for traveler's diarrhea for dosage regimen of 200 mg TID for 3 days. In this (b) (4), the sponsor proposes an indication of maintenance of remission of hepatic encephalopathy in patients ≥ 18 years of age for dosage regimen of 550 mg BID.

In support of new dosage regimen and indication, total 20 clinical pharmacology and biopharmaceutics related studies were either additionally submitted or cross-referenced to the original NDA 21-361 which supported the approval of rifaximin for Traveler's diarrhea.

Main new studies to review for 550 mg rifaximin tablet are as bellows:

- **RFPK1007**
  - Part A: single dose PK and food effect
  - Part B: Bioavailability after multiple doses of rifaximin with 550 mg BID and TID dosing regimen
- **RFHE3002PK**: Multiple dose PK in liver-impaired subjects i.e. Child-Pugh A and Child-Pugh B
- **Study XT58-Salix-02**: Evaluation of Rifaximin as a P-glycoprotein Substrate and Inhibitor in Caco-2 cells
- **RFDI1008**: Drug interaction of rifaximin with single dose midazolam (Rifaximin 550 mg TID)
- **RFHE9702**: Dose-comparison of rifaximin in subjects with Grade I, II, or II encephalopathy: 200 mg. 400 mg or 800mg TID for 7 days

Main review issues identified as far are as follows:

What is the effect of severe hepatic impairment on PK and safety? The effect of mild to moderate hepatic impairment on PK was evaluated in patients with a history of HE. It was noted that in Phase 3 trial the most of patients had MELD score 11-18 which corresponds to moderate hepatic impairment and none had MELD score greater than 18. The AUC of rifaximin in patients with moderate hepatic impairment was 50% or 58% greater than in patients with mild hepatic impairment based on Child-Pugh Classification and MELD score, respectively. Nonetheless, there is no information for effect of severe hepatic impairment on PK of rifaximin as well as on safety and efficacy. A subgroup analysis for safety based on a varying degree of hepatic impairment would be helpful yet the lack of information should be adequately reflected in the label.

Induction of CYP3A4 by rifaximin was observed based on decrease in midazolam AUC by ~ 25%. As higher systemic exposure is expected in majority of patient population, the label should have appropriate language about CYP3A4 induction potential of rifaximin.

There was no TQT study conducted.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22554	ORIG-1	SALIX PHARMACEUTICALS INC	XIFAXAN

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

/s/

INSOOK KIM
03/11/2010

SUE CHIH H LEE
03/11/2010