

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:  
22-554**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

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**NDA/** 22-554/  
**Sequence Number:** 0000, 0002, 0003, 0004, 0005, 0006, 0007, 0010  
**Drug Name:** XIFAXAN® (rifaximin) 550 mg tablets BID  
**Indication(s):** Maintenance of Remission of Hepatic Encephalopathy  
**Applicant:** Salix Pharmaceuticals, Inc.  
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## **1.0 EXECUTIVE SUMMARY**

### **1.1 Conclusions and Recommendations**

XIFAXAN efficacy results are primarily demonstrated by the single pivotal trial (RFHE3001). Study RFHE3002 provides marginally supportive evidence while studies RFHE9701 and RFHE9901 are too short in duration and targeted an inappropriate patient population (patients with active HE). However, the effectiveness of XIFAXAN is clearly established by Study RFHE3001 as seen by the highly significant results from the primary and secondary analyses as well as from important subgroup and sensitivity analyses.

### **1.2 Brief Overview of Clinical Studies**

In order to establish the clinical efficacy of XIFAXAN for the maintenance of remission of HE, Salix conducted one pivotal clinical trial, RFHE3001, which consequently serves as the principal source for any efficacy claim to be reflected in the labeling of this drug. RFHE3001 is a Phase 3, long term (6 month), randomized, double-blind, placebo-controlled, multicenter study. Salix also conducted a subsequent open-label long term safety trial, RFHE3002, which is still ongoing. This roll-over protocol is comprised of patients who participated in the RFHE3001 study while also enrolling new patients for long-term XIFAXAN use. However, due to the principal objective and subsequent design of this follow-up study, any efficacy results are viewed as marginally supportive. Two further acute treatment phase 3 studies, RFHE9701 and RFHE9901, which each investigate XIFAXAN therapy for up to 15 days in subjects with active HE were also included in the submission to provide supportive evidence, albeit marginal.

### **1.3 Statistical Issues and Findings**

There were no special review concerns regarding the design and subsequent statistical analyses of the efficacy data from the RFHE3001 study per se. The efficacy results themselves are consistently favorable across many different analyses. However, a principle clinical issue regarded the un-validated and controversial neurological endpoint which is a function of Conn score and Asterixis grade. The other major issue is in regard to lactulose usage which questions the originally intended generalizability of study results for stand-alone therapy. The prominence of lactulose use in the patient population should be conveyed in the labeling.

## **2.0 INTRODUCTION**

### **2.1 Background**

XIFAXAN® (rifaximin; 600 mg/day, 200 mg taken three times daily) is currently approved in the U.S. for Travelers' Diarrhea. Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, Salix Pharmaceuticals, Inc. (Salix), on June 24, 2009, submitted an efficacy supplement to the New Drug Application (NDA 21-361) for XIFAXAN tablets regarding the proposed orphan drug indication of the maintenance of remission of HE in patients 18 years of age or older. This supplement was a Type 6 NDA (filed under new NDA number 22-554) which provided data for a new strength (550 mg) of the currently approved (200 mg) oral tablet dosage form. XIFAXAN was granted orphan designation for the treatment of HE on February 10, 1998 which encompassed the proposed indication as confirmed with the Office of Orphan Products Development on November 24, 2008. Consequently, the NDA User Fee has been waived. This application consisted of data from a global clinical development program conducted under IND 59,133. Salix requested and was ultimately granted priority review status for this efficacy supplement by the Division of Gastroenterology Products (DGP), however due to a major amendment to the application during the review cycle, the PDUFA goal date was extended by three months.

HE is a serious, rare, complex, episodic, neuropsychiatric syndrome associated with advanced liver disease. HE is a formidable burden on the patient, his/her family, and the healthcare system. Overt HE episodes are debilitating, can present without warning, render the patient incapable of self-care, and frequently result in hospitalization. Overt, episodic HE is common among patients with liver cirrhosis; however, the condition is rare among individuals in the overall, general population.

XIFAXAN (1100 mg/day; 550 mg taken twice daily) has the potential to provide a safe and effective therapy to maintain patients' remission from HE for which there is no satisfactory alternative therapy. Lactulose is often used for the treatment of HE, but its usefulness is limited by side effects which may exacerbate symptoms of HE. Neomycin is approved as an adjunctive therapy for patients in hepatic coma only; however, neomycin has a well-documented history of systemic side effects, namely, oto- and nephrotoxicity. Outside the U.S., XIFAXAN has been approved for the treatment of multiple GI conditions including travelers' diarrhea, diarrhea in diverticular disease, intestinal infection, and adjunctive therapy for HE or hyperammonemia.

### **2.2 Brief Overview and Summary of Relevant Trials**

In order to establish the clinical efficacy of XIFAXAN for the maintenance of remission of HE, Salix conducted one pivotal clinical trial, RFHE3001, which consequently serves as the principal source for any efficacy claim to be reflected in the labeling of this drug. RFHE3001 is a Phase 3, long term (6 month), randomized, double-blind, placebo-controlled, multicenter study. Salix has also conducted a subsequent open-label long

term safety trial, RFHE3002, which is still ongoing. This roll-over protocol is comprised of patients who participated in the RFHE3001 study while also enrolling new patients for long-term XIFAXAN use. However, since safety is the principal objective of this ongoing follow-up study, any efficacy results are consequently considered exploratory in nature. Two further acute treatment phase 3 studies, RFHE9701 and RFHE9901, which each investigate XIFAXAN therapy for up to 15 days in subjects with active HE were also included in the submission to provide supportive evidence, albeit marginal. Note that the pivotal RFHE3001 study was designed and conducted in accordance to agreements attained at the End of Phase 2 meeting held with DGP on December 14, 2004. Table 1 below contains further summary information for the relevant clinical trials submitted under this application.

**Table 1 – Summary Information for Relevant Trials**

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Subjects	Patient Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	RFHE3001	<i>Primary:</i> Compare the maintenance of remission from previously demonstrated recurrent episodic HE as measured by Conn score and Asterixis grade; <i>Secondary:</i> Safety and tolerability	Multinational, Multicenter, randomized, double-blind, placebo-controlled, parallel groups	XIFAXAN 550mg and matching placebo; BID; 550mg tablets	XIFAXAN: 140 placebo: 159 Total: 299	Patients diagnosed with HE currently in remission	6 months	Complete; Full
Safety	RFHE3002	Long-term safety and tolerability	Multinational, Multicenter, open-label, single-arm	XIFAXAN 550mg; BID; 550mg tablets	RFHE3001:154 New: 126 Total: 280	Patients diagnosed with HE currently in remission	At least 24 months, regulatory approval, or sponsor termination	Ongoing; Interim
Efficacy and Safety	RFHE9701	Efficacy and safety compared with lactitol	Multicenter, randomized, double-blind, double-dummy, active-controlled, parallel groups	XIFAXAN 400mg and lactitol monohydrate 20g; TID; 200mg tablets and 10g sachets respectively	XIFAXAN: 50 lactitol: 53 Total: 103	Adult males and females affected by liver cirrhosis	5-10 days	Complete; Full
Efficacy and Tolerability	RFHE9901	Effectiveness and tolerability compared to placebo in HE patients intolerant to lactulose or lactitol	Multinational, Multicenter, randomized, double-blind, placebo-controlled, parallel groups	XIFAXAN 400mg and matching placebo; TID; 200mg tablets	XIFAXAN: 48 placebo: 45 Total: 93	Mild to moderate HE	14 days	Complete; Full

Source: Table 5.2.1 located in Module 5.2.

## 2.3 Data Sources

Paper and corresponding electronic clinical study reports, by module, were delivered to the assigned reviewers in each respective review discipline. The submitted electronic SAS data sets and labeling information have also been stored in the electronic document room (EDR) within this path location: [\\FDSWA150\NONECTD\N21361\S\\_010\2009-06-24](\\FDSWA150\NONECTD\N21361\S_010\2009-06-24).

## 3.0 STATISTICAL EVALUATION

### 3.1 Study RFHE3001

#### *A. Background Information*

Study RFHE3001 enrolled patients previously diagnosed with recurrent episodic HE who were currently in remission (per Inclusion/Exclusion Criteria defined to be a Conn score of 0 or 1) at screening. Its primary objective was to compare the maintenance of this remission as measured by Conn score and Asterixis grade (both of which are later defined below). Note that both of these neurological instruments are considered un-validated and create a fundamental clinical concern which is beyond the scope of this review. The secondary objective of RFHE3001 was to assess the safety and tolerability of XIFAXAN usage. This was a Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study with patients being administered one 550mg XIFAXAN tablet or corresponding matching placebo to be taken BID.

The number of planned subjects was 250 (125 in each arm) which provides >80% power to demonstrate the superiority of XIFAXAN to placebo. The number of patients enrolled was 381, and 299 were subsequently centrally randomized (1:1) with, ultimately, 140 patients to XIFAXAN and 159 to placebo.

The duration of treatment was to be for 6 months (with bi-weekly visits), and the overall trial lasted roughly two years and eight months with first-patient-first-visit on December 19, 2005 and last-patient-last-visit on August 15, 2008. There were 70 sites in total with 14 in Russia (80 patients), 5 in Canada (14 patients), and 51 in the United States (205 patients). The disposition of all randomized subjects (from the termination CRF page) is presented in Table 2 below.

**Table 2 – Disposition**

	Placebo (N = 159) n (%)	550mg XIFAXAN BID (N = 140) n (%)	Total (N = 299) n (%)
Subjects Treated	159 (100.0%)	140 (100.0%)	299 (100.0%)
Subjects Completed the Study	66 (41.5%)	88 (62.9%)	154 (51.5%)
Subjects Discontinued Early from the Study	93 (58.5%)	52 (37.1%)	145 (48.5%)
Primary Reason for Discontinuation			
Occurrence of an Adverse Event	7 (4.4%)	8 (5.7%)	15 (5.0%)
Development of any Exclusion Criteria	3 (1.9%)	1 (0.7%)	4 (1.3%)
Pregnancy	0	0	0
Subject Request to Withdraw	9 (5.7%)	6 (4.3%)	15 (5.0%)
Breakthrough HE episode	69 (43.4%)	28 (20.0%)	97 (32.4%)
Liver Transplant	1 (0.6%)	0	1 (0.3%)
Death	3 (1.9%)	6 (4.3%)	9 (3.0%)
Other	1 (0.6%)	3 (2.1%)	4 (1.3%)
Subjects Completed Non-Breakthrough Discontinuation Follow Up	19 (11.9%)	17 (12.1%)	36 (12.0%)
Breakthrough HE episode	4 (2.5%)	2 (1.4%)	6 (2.0%)

Source: Table 14.1.1.1a; Section 14 in RFHE3001 CSR located in Module 5.3.5.1.

There is a discrepancy in the number of patients who experienced breakthrough HE, which exists between those that were reported as discontinuations from breakthrough in Table 2 (28 XIFAXAN and 69 placebo) and what was ultimately recorded on the breakthrough HE CRF pages (31 XIFAXAN and 73 placebo) which were loaded into the datasets for the primary and secondary analyses. (Patients were supposed to discontinue from the study due to breakthrough HE hence these numbers should have been reconciled.) Refer to the following summary for final adjudication.

As specified in the protocol, subjects were to be withdrawn from the study after experiencing a breakthrough HE episode. As one can see from Table 2, breakthrough HE episode was the primary reason for early study withdrawal for 28 of 140 subjects (20.0%) in the XIFAXAN group and 69 of 159 subjects (43.4%) in the placebo group. Of 48 subjects (24 in each group) who discontinued for reasons other than breakthrough HE episode, 36 subjects (17 and 19 in the XIFAXAN and placebo groups, respectively) were followed to determine if they would still experience a breakthrough HE episode or other outcome (e.g., mortality status). In addition, they were evaluated retrospectively to determine whether there had actually been a breakthrough HE event prior to discontinuing treatment. This evaluation identified 2 additional patients in the XIFAXAN group and 4 additional patients in the placebo group who experienced breakthrough HE prior to or after discontinuing treatment. Furthermore, while on treatment, one other XIFAXAN patient who, through a protocol deviation, continued study treatment despite having experienced a breakthrough HE event.

The sequential summary of all patients who were counted in the datasets as a breakthrough HE episode for the primary efficacy analysis is as follows:

- Results from Table 2 present Breakthrough HE primary reason for discontinuation: 28 XIFAXAN, 69 placebo;
- One additional XIFAXAN subject (764-0002) completed the study although he/she experienced breakthrough HE during the study (a protocol deviation), therefore,  $28 + 1 = 29$ .
- **Two** additional subjects determined retrospectively to have had breakthrough HE (30 XIFAXAN, 70 placebo):
  1. XIFAXAN patient 478-0006 reason for discontinuation = other [cocaine abuse], with breakthrough experienced 36 days before discontinuation
  2. Placebo patient 761-0001 reason for discontinuation = subject request to withdraw, with breakthrough experienced 71 days before discontinuation
- Finally, **four** additional subjects experienced breakthrough HE after discontinuation (31 XIFAXAN, 73 placebo):
  1. XIFAXAN patient 893-0005 reason for discontinuation = occurrence of an AE, with breakthrough experienced 70 days after discontinuation but still within six months of first dose
  2. Placebo patient 106-0003 reason for discontinuation = subject request to withdraw, with breakthrough experienced 52 days after discontinuation but still within six months of first dose
  3. Placebo patient 891-0003 reason for discontinuation = subject request to withdraw, with breakthrough experienced 104 days after discontinuation but still within six months of first dose
  4. Placebo patient 893-0004 reason for discontinuation = subject request to withdraw, with breakthrough experienced 85 days after discontinuation but still within six months of first dose

The demographics and baseline characteristics of all randomized subjects are presented in Table 3 below.

**Table 3 – Demographics and Baseline Characteristics**

	Placebo (N = 159)	550mg XIFAXAN BID (N = 140)	Total (N = 299)
Age (years)			
n	159	140	299
Mean	56.8	55.5	56.2
SD	9.18	9.57	9.38
Median	57.0	55.0	56.0
Min	21	26	21
Max	78	82	82
Age Group – n (%)			
<65	128 (80.5%)	113 (80.7%)	241 (80.6%)
≥65	31 (19.5%)	27 (19.3%)	58 (19.4%)
Gender – n (%)			
Male	107 (67.3%)	75 (53.6%)	182 (60.9%)
Female	52 (32.7%)	65 (46.4%)	117 (39.1%)
Race – n (%)			
American Indian or Alaskan Native	3 (1.9%)	5 (3.6%)	8 (2.7%)
Asian	8 (5.0%)	4 (2.9%)	12 (4.0%)
Black or African American	5 (3.1%)	7 (5.0%)	12 (4.0%)
Native Hawaiian or Other Pacific Islander	1 (0.6%)	2 (1.4%)	3 (1.0%)
White	139 (87.4%)	118 (84.3%)	257 (86.0%)
Other	3 (1.9%)	3 (2.1%)	6 (2.0%)
Missing	0	1 (0.7%)	1 (0.3%)
Ethnicity – n (%)			
Hispanic or Latino	28 (17.6%)	21 (15.0%)	49 (16.4%)
Not Hispanic or Latino	131 (82.4%)	119 (85.0%)	250 (83.6%)
Weight (kg)			
n	159	140	299
Mean	88.04	87.02	87.56
SD	19.108	22.857	20.917
Median	86.60	83.05	85.10
Min	46.1	40.4	40.4
Max	135.7	165.6	165.6
Country – n (%)			
United States	112 (70.4%)	93 (66.4%)	205 (68.6%)
Canada	6 (3.8%)	8 (5.7%)	14 (4.7%)
Russia	41 (25.8%)	39 (27.9%)	80 (26.8%)

Source: Table 14.1.3.1a; Section 14 in RFHE3001 CSR located in Module 5.3.5.1.

## ***B. Statistical Analysis Information***

All information in this section has been pre-specified in the finalized protocol (dated 04Sep2008) and subsequently presented again in the finalized SAP (dated 24Sep2008). The formal definitions of Conn score and Asterixis grade are presented below in Tables 4 and 5 respectively, and the primary and three key secondary efficacy endpoints in the RFHE3001 study subsequently follow.

**Table 4 – Conn Score**

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.

Source: Section 16.1.1 of RFHE3001 CSR located in Module 5.3.5.1.

**Table 5 – Asterixis Grade**

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

Source: Section 16.1.1 of RFHE3001 CSR located in Module 5.3.5.1.

- ***Primary Endpoint***
  - Time to first breakthrough HE Episode defined as an increase in Conn score to  $\geq 2$  (i.e., 0 or 1 to  $\geq 2$ ) or a Conn score and Asterixis grade increase of 1 point each
- ***Key Secondary Endpoints***
  - Time to first HE-Related Hospitalization
    - Hospitalization directly resulting from breakthrough HE or hospitalization later complicated by breakthrough HE
  - Time to any increase from baseline in Conn score
  - Time to any increase from baseline in Asterixis grade

The sponsor designated these three secondary endpoints as most clinically important, and consequently pre-specified the order, as presented, in which they would be analyzed. Unless specified, all analyses were conducted under the Intent-to-Treat (ITT) analysis set (defined as all randomized subjects who ingested at least one dose of study drug).

As stated previously, a total of 250 subjects were planned to be enrolled in this study (approximately 125 each in the XIFAXAN and placebo arms). This sample size is based on an analysis of the relative risk of experiencing breakthrough HE (i.e., Conn score  $\geq 2$ ,

or a Conn score and Asterixis grade increase of 1 each) based upon the Cox proportional hazards regression analysis of time to first breakthrough HE episode. The subsequent null hypothesis of interest is:

$$H_0: \beta_{\text{XIFAXAN}} = 0$$

versus the alternative:

$$H_A: \beta_{\text{XIFAXAN}} \neq 0,$$

where  $\beta_{\text{XIFAXAN}}$  is the coefficient of the treatment arm (XIFAXAN) in a Cox proportional hazards regression model compared to the placebo group. Thus  $\beta_{\text{XIFAXAN}}$  represents the log of the hazard ratio for comparing XIFAXAN to placebo and is equivalent to testing that the hazard ratio for the occurrence of an HE breakthrough event is significantly different from 1.

The sample size for the current study is based upon the following assumptions. It is assumed that approximately 50% of the XIFAXAN subjects and 70% of the placebo subjects will experience breakthrough HE over the course of the six month treatment period. Based upon this assumption, the hazard ratio for XIFAXAN relative to placebo can be estimated as approximately 0.58 ( $\beta_{\text{XIFAXAN}} = -0.54$ ) for comparing time to first breakthrough HE episode in the two treatment groups. Approximately 100 evaluable subjects per treatment group provides >80% power to demonstrate the superiority of XIFAXAN to placebo.

The statistical analysis methodology utilized survival analysis techniques using Kaplan-Meier curve estimation and, as stated previously, Cox proportional hazards modeling. The estimate of the survival function, that is, the probability that breakthrough HE does not occur until the start of a given time point or later, was obtained through Kaplan Meier methods from PROC LIFETEST in SAS. Appropriate figures of these curves were created and are presented below. The hazard ratio estimate (hazard of breakthrough HE in the XIFAXAN group  $\div$  hazard of breakthrough HE in the placebo group) was obtained from the Cox proportional hazards model (using PROC PHREG in SAS) with effect for treatment, stratified/adjusted by analysis region (North America and Russia). The appropriate p-value for treatment effect is based on the Score statistic. The proportional hazards assumption was checked using the graphical method of plotting the curve of the log(-log(Survival Function)) vs. the log(Time to Breakthrough HE) for each treatment group. If the two curves were parallel, then the assumption would be deemed valid.

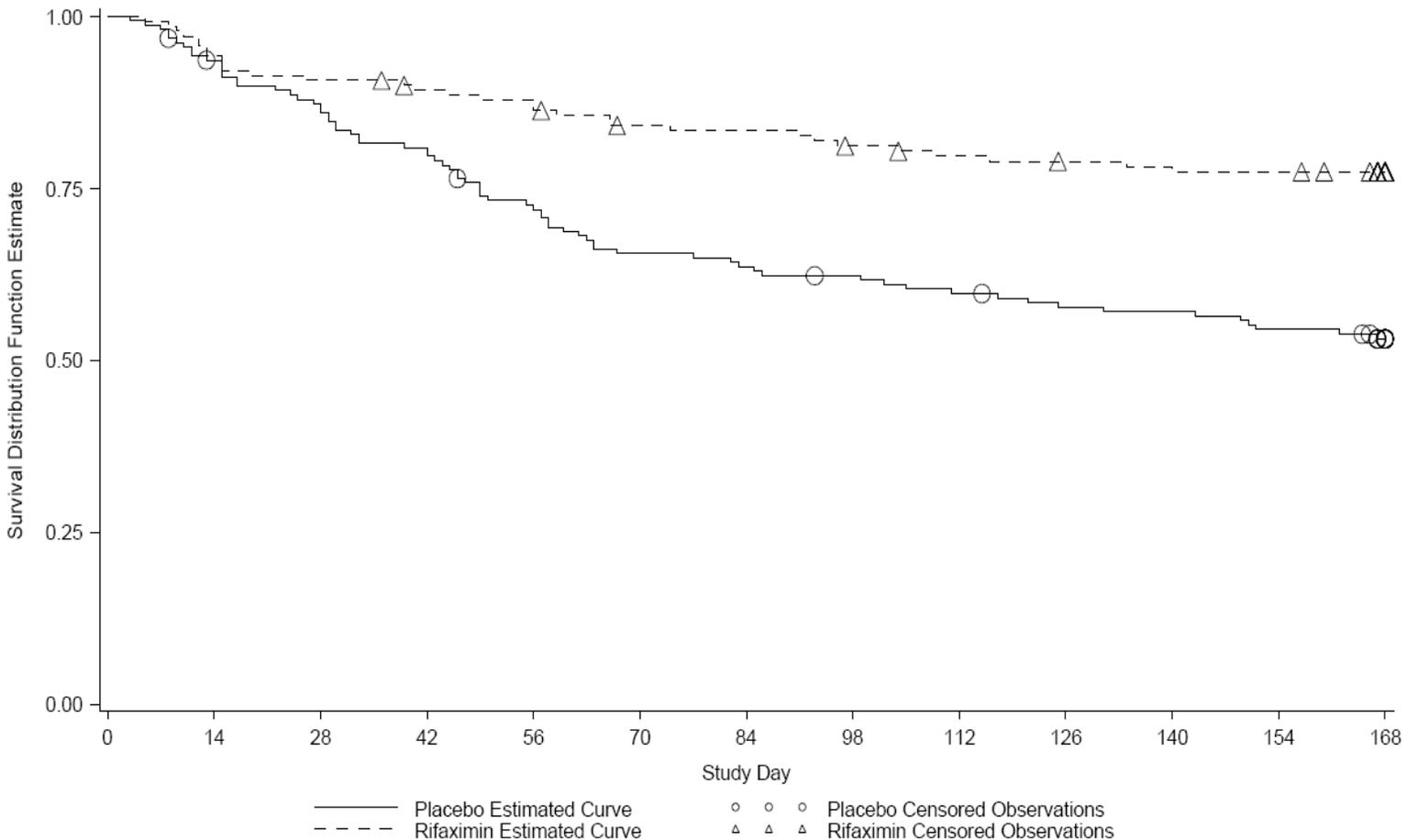
The Missing Data handling strategy is consistent with what is commonly used in survival analysis in that subjects who do not complete the 6 month treatment period and do not experience the event of interest are censored at the time of last available assessment. This may be considered anti-conservative regarding handling missing/censored data in this context, and, consequently, two sensitivity analyses are presented below regarding more conservative missing data assumptions.

The pre-specified Multiplicity Adjustment strategy for testing the key secondary endpoints used a standard gate-keeping approach (formally testing the next endpoint at  $\alpha = 0.05$  if and only if the result of the test for the current endpoint is found to be significant at  $\alpha = 0.05$ ). It is important to note that the p-values and confidence intervals corresponding to all other analyses are presented with no adjustment for multiplicity. These nominal p-values and confidence intervals are presented as part of the overall exploratory assessment of the efficacy of XIFAXAN and are not viewed as providing formal evidence of efficacy.

### C. Primary Efficacy Analysis

#### 1. Time to First Breakthrough HE Episode (up to Month Six)

**Figure 1 - Kaplan-Meier Plot for Time to First Breakthrough HE Episode (up to Month Six)**



Source: Figure 14.2.1; Section 14 in RFHE3001 CSR located in Module 5.3.5.1.

The Cox Proportional Hazards model, stratified by region, produced a hazard ratio point estimate of 0.421 along with corresponding 95% Confidence Interval (CI) (0.276, 0.641). The p-value corresponding to the test for treatment effect was less than 0.0001. Note that

the proportional hazards assumption was deemed to be valid here as the log(-log(Survival Function)) vs. the log(Time to Breakthrough HE) curves for each treatment group were determined to be parallel. Although there is distinct separation between the two treatment groups at Month Six (shown in Figure 1 above), it appears that this separation was established between the beginning of Month Two and the end of Month Three. These two months are the major contributors to the overall six month results. During the last half of the study, the rate at which patients experienced breakthrough HE events began to converge between the XIFAXAN and placebo groups. Note that the relative behavior of these survival curves which represent both treatment groups is fairly consistent throughout all of the subsequent analyses pertaining to the key secondary endpoints as well.

Table 6 below shows the numbers of breakthrough HE episodes experienced in this study. It is clear that the change in Conn score, rather than Asterixis grade, is responsible for the majority of these episodes.

**Table 6 – Breakthrough HE Episodes by Category**

	Placebo (N = 159) n (%)	550mg XIFAXAN BID (N = 140) n (%)	Total (N = 299) n (%)
Breakthrough HE Episodes	73 (45.9%)	31 (22.1%)	104 (34.8%)
Conn $\geq$ 2	57 (35.8%)	28 (20.0%)	84 (28.1%)
Concurrent Increase in both Conn score and Asterixis grade of 1 each from Baseline	16 (10.1%)	3 (2.1%)	20 (6.7%)

Source: Section 11 in RFHE3001 CSR located in Module 5.3.5.1.

## 2. Sensitivity Analyses

The following sensitivity analyses were conducted:

- Time to first breakthrough HE episode up to last contact (the Intent-to-Treat Analysis which includes data from beyond Month Six)
- Excluded the six patients previously presented who were diagnosed to have experienced breakthrough HE retrospectively or after discontinuation but before Month Six
- Excluding subjects who took prohibited medications
- Whether patients had a concomitant comorbidity at baseline (analgesic use, constipation, infection, and portal shunt surgery)
- Two separate analyses, each corresponding to a different approach to handling the missing/censored data
  1. All non-breakthrough HE subjects who discontinue due to AE, liver transplant, or death prior to the completion of the six month treatment period are categorized as if they experienced a breakthrough HE at that discontinuation time point.

2. Worst case scenario: All non-breakthrough HE subjects who discontinue due to any reason prior to the completion of the six month treatment period are categorized as if they experienced a breakthrough HE at that discontinuation time point.

The principal results of these sensitivity analyses are presented in Table 7 below. Note that the results in this and the following sections pertaining to the primary efficacy analysis are exploratory in nature and hence are not for confirmation of a statistical hypothesis.

**Table 7 – Principal Results for Sensitivity Analyses**

Sensitivity Analysis	Placebo N =	550mg XIFAXAN BID N =	Hazard Ratio Point Estimate	Hazard Ratio 95% CI	Treatment Effect p-value
Time to First Breakthrough HE Episode up to Last Contact (Intent-to-Treat Analysis)	159	140	0.461	(0.307, 0.693)	0.0001
Time to First Breakthrough HE (Exclusion of Six Patients)	159	140	0.419	(0.271, 0.647)	<0.0001
Excluding Subjects who took Prohibited Medications	155	140	0.419	(0.275, 0.640)	<0.0001
Concomitant Comorbidity at Baseline					
Yes	39	30	0.248	(0.108, 0.571)	0.0004
No	120	110	0.512	(0.313, 0.839)	0.0068
Missing Data Strategy I	159	140	0.495	(0.342, 0.715)	0.0001
Missing Data Strategy II/ Worst Case	159	140	0.533	(0.379, 0.749)	0.0002

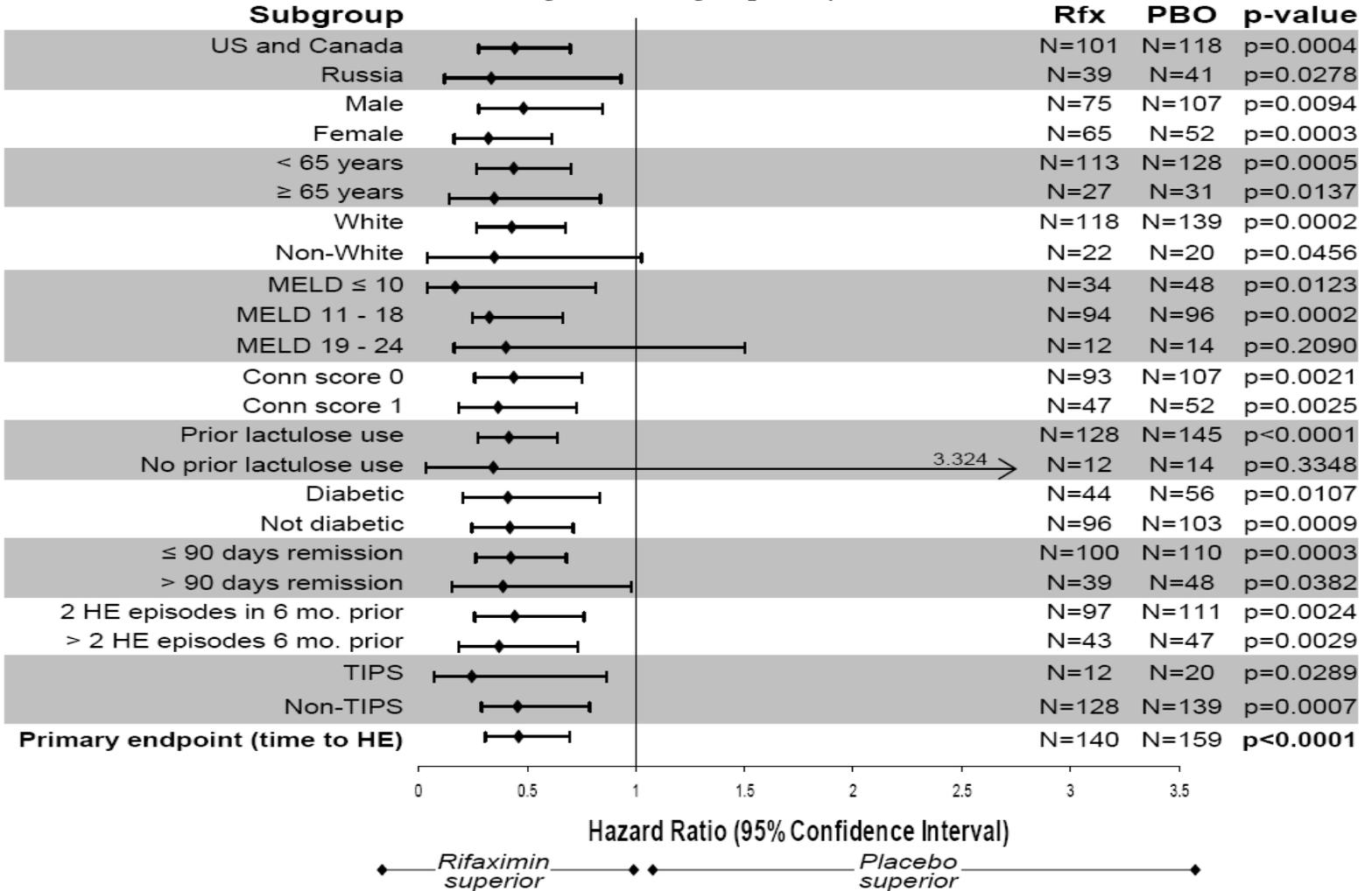
Source: Table 14.2.1b, 14.2.1d, and 14.2.1e; Section 11 in RFHE3001 CSR located in Module 5.3.5.1. Table 2.1 and 2.2; Submission on 17Sep2009 corresponding to Information Request.

### 3. Subgroup Analysis

A series of subgroup analyses were administered pertaining to region, gender, age, race, baseline Model End Stage Liver Disease (MELD) Score, baseline Conn score, prior lactulose usage, baseline diabetes status, number of days in HE remission prior to study participation, number of HE episodes in the six months prior to study participation, and transjugular intrahepatic portal-systemic shunt (TIPS) procedures ongoing at the time of randomization. The principal results (with comparison to the primary endpoint result on

the last row) are presented respectively in Figure 2 below. The nominal p-values presented are for exploratory purposes only.

**Figure 2 – Subgroup Analyses**



Source: Figure 4; Section 11 in RFHE3001 CSR located in Module 5.3.5.1.

#### 4. Per-Protocol Analysis

All previous primary analyses were then conducted by this reviewer on a Per-Protocol (PP) analysis set of patients defined to be ITT subjects with no major protocol violations (e.g. Inclusion/Exclusion violations). The PP definition often includes a treatment compliance requirement as well (e.g. pill consumption compliance between 80% and 120%), but this was not included for the RFHE3001 PP analysis set. The resulting patient counts were as follows:

- XIFAXAN: 128
- Placebo: 149
- Total: 277

Results from each analysis re-administered under the PP analysis set were consistent with the previous corresponding results under the ITT analysis set. Consequently, reporting the results under the PP analysis set is not necessary, and we will use the ITT analysis set of patients for all remaining analysis presentations.

## 5. Responder Analysis

For all ‘Time to Event’ analyses, in general, a corresponding responder analysis can be determined by defining a responder (or a failure) as a patient who experiences the event of interest before, after or directly at a clinically relevant time point. During the course of the review cycle, DGP requested that the applicant conduct a responder analysis by month. A responder was defined as a patient who had not experienced breakthrough HE by each month sequentially for six months. These analyses and resulting p-values are considered exploratory only.

Two different presentations of this responder analysis are given below in Tables 8 and 9 respectively, and each presentation pertains to how censored patient data are handled. In Table 8 (Responder Analysis I), subjects who discontinued the study due to any reason other than Breakthrough HE were excluded altogether from the analysis for that specified time period. In Table 9 (Responder Analysis II), subjects were classified as non-responders if they discontinued for any reason or had Breakthrough HE. The p-values were calculated using the Cochran-Mantel-Haenszel (CMH) test, adjusted by analysis region. These results further support the reviewer’s earlier observation that XIFAXAN’s separation from placebo primarily occurs between the beginning of Month Two and the end of Month Three.

**Table 8 – Responder Analyses I**

	Placebo (N = 159) n/n' (%)	550mg XIFAXAN BID (N = 140) n/n' (%)	p-value
Responder Throughout Entire 6 Months	80/153 (52.3%)	100/131 (76.3%)	<0.0001
Responder Throughout First 5 Months	87/154 (56.5%)	102/133 (76.7%)	0.0003
Responder Throughout First 4 Months	92/155 (59.4%)	106/134 (79.1%)	0.0003
Responder Throughout First 3 Months	99/156 (63.5%)	113/136 (83.1%)	0.0002
Responder Throughout First 2 Months	112/156 (71.8%)	119/138 (86.2%)	0.0028
Responder Throughout First 1 Month	135/157 (86.0%)	127/140 (90.7%)	0.2230

Note: n' regards the number of patients at risk during the specified time period.  
Source: Table 1.2; Submission on 12Oct2009 corresponding to Information Request.

**Table 9 – Responder Analyses II**

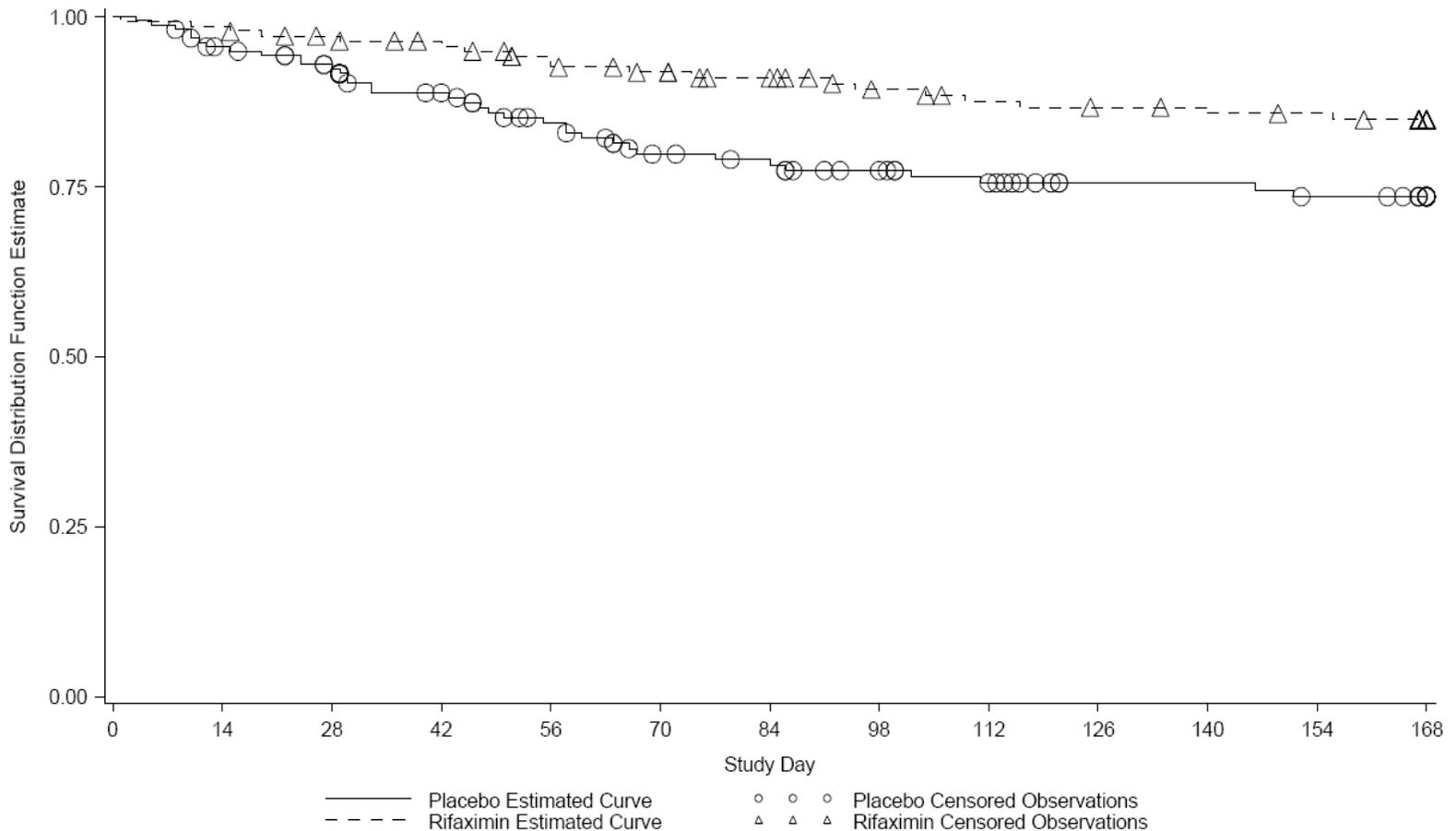
	Placebo (N = 159) n/N (%)	550mg XIFAXAN BID (N = 140) n/N (%)	p-value
Responder Throughout Entire 6 Months	80/159 (50.3%)	100/140 (71.4%)	0.0002
Responder Throughout First 5 Months	87/159 (54.7%)	102/140 (72.9%)	0.0013
Responder Throughout First 4 Months	92/159 (57.9%)	106/140 (75.7%)	0.0012
Responder Throughout First 3 Months	99/159 (62.3%)	113/140 (80.7%)	0.0005
Responder Throughout First 2 Months	112/159 (70.4%)	119/140 (85.0%)	0.0030
Responder Throughout First 1 Month	135/159 (84.9%)	127/140 (90.7%)	0.1414

Source: Table 1.1; Submission on 12Oct2009 corresponding to Information Request.

## D. Secondary Efficacy Analysis

### 1. Time to First HE-Related Hospitalization (up to Month Six)

**Figure 3 - Kaplan-Meier Plot for Time to First HE-Related Hospitalization (up to Month Six)**



Source: Figure 14.2.2; Section 14 in RFHE3001 CSR located in Module 5.3.5.1.

The Cox proportional hazards model, stratified by region, produced a hazard ratio point estimate of 0.500 along with corresponding 95% CI (0.287, 0.873). The p-value corresponding to the test for treatment effect was 0.0129. The formal test for this endpoint was found to be significant at  $\alpha = 0.05$  hence the hypothesis for the next secondary endpoint was formally tested.

The clinical team felt that the time to first HE related hospitalization might be more reflective of clinical benefit than a 1 or 2 point change in Conn score because the need for hospitalization may better reflect the clinical impact of severe HE episodes.

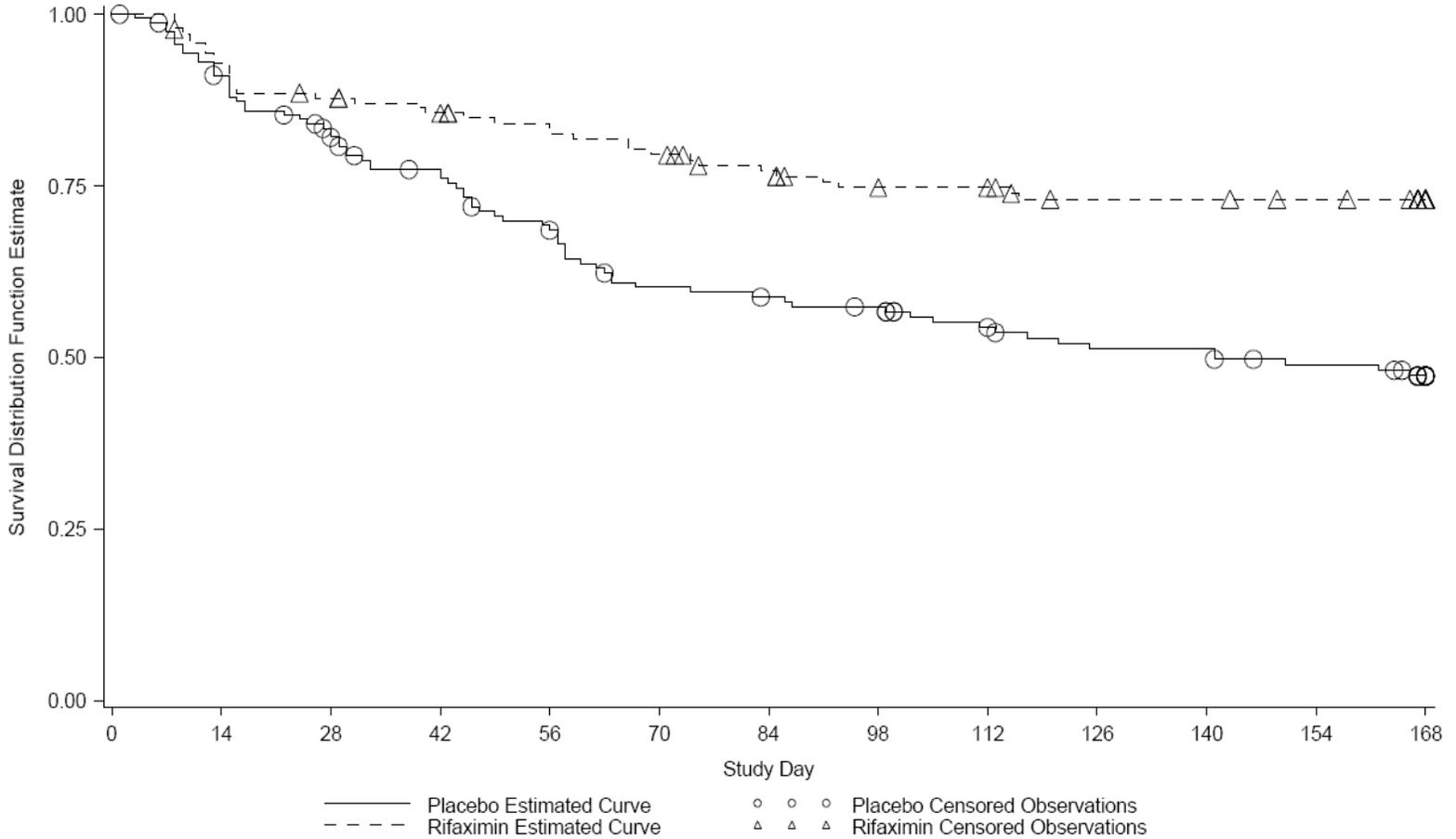
DGP subsequently requested further information from the applicant with analysis of whether the breakthrough-HE episode resulted in any hospitalization (and the duration of this hospitalization) or not. The sponsor replied that data were not collected and hence

not available for duration of breakthrough HE episodes or hospitalizations. They, however, provided the frequency data below regarding breakthrough HE hospitalizations.

- Breakthrough HE hospitalization: Forty-four (15 XIFAXAN, 29 placebo) of the 104 subjects diagnosed with a protocol-defined breakthrough HE episode were hospitalized specifically due to the breakthrough HE episode.
- HE-caused hospitalization: In addition to the 44 patients in bullet 1, there were four patients in the placebo group who were hospitalized with a diagnosis of HE, however, the site investigator felt that they did not meet breakthrough criteria. When those patients were included in the analysis, forty-eight (15 XIFAXAN; 33 placebo) of the 299 subjects had HE-caused hospitalization (i.e., hospitalization directly resulting from breakthrough HE or HE symptoms not meeting breakthrough criteria).
- HE-related hospitalization: In addition to the 44 patients in bullet 1, there were four XIFAXAN patients and 7 placebo patients who were hospitalized for other reasons but subsequently developed HE while in the hospital. Hence fifty-five (19 XIFAXAN; 36 placebo) of the 299 subjects had HE-related hospitalization (i.e., hospitalization directly resulting from HE or hospitalization complicated by HE).
- All-cause hospitalization: One hundred six subjects (46 XIFAXAN; 60 placebo) of the 299 subjects were hospitalized for any reason.

## 2. Time to Any Increase from Baseline in Conn Score (up to Month Six)

**Figure 4 - Kaplan-Meier Plot for Time to Any Increase from Baseline in Conn Score (up to Month Six)**

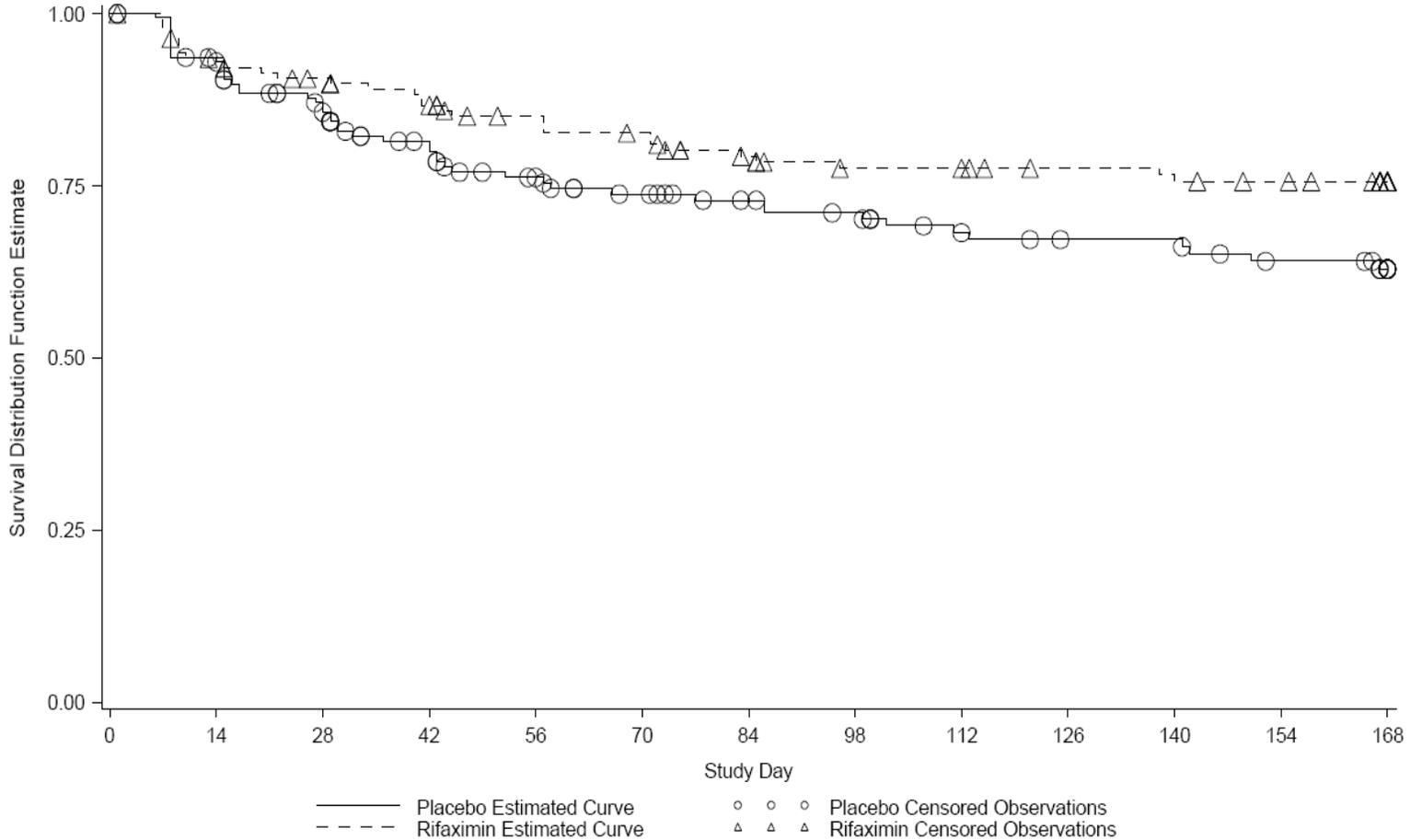


Source: Figure 14.2.3; Section 14 in RFHE3001 CSR located in Module 5.3.5.1.

A hazard ratio point estimate of 0.463 was determined along with corresponding 95% CI (0.312, 0.685). The p-value corresponding to the test for treatment effect was  $<0.0001$ . The formal test for this endpoint was found to be significant at  $\alpha = 0.05$  hence the hypothesis for the next secondary endpoint was formally tested.

### 3. Time to Any Increase from Baseline in Asterixis Grade (up to Month Six)

**Figure 5 - Kaplan-Meier Plot for Time to Any Increase from Baseline in Asterixis Grade (up to Month Six)**



Source: Figure 14.2.4; Section 14 in RFHE3001 CSR located in Module 5.3.5.1.

A hazard ratio point estimate of 0.646 was determined along with corresponding 95% CI (0.414, 1.008). The p-value corresponding to the test for treatment effect was 0.0523. The formal test for this endpoint was not found to be significant at  $\alpha = 0.05$  hence any formal analysis on further efficacy endpoints were halted.

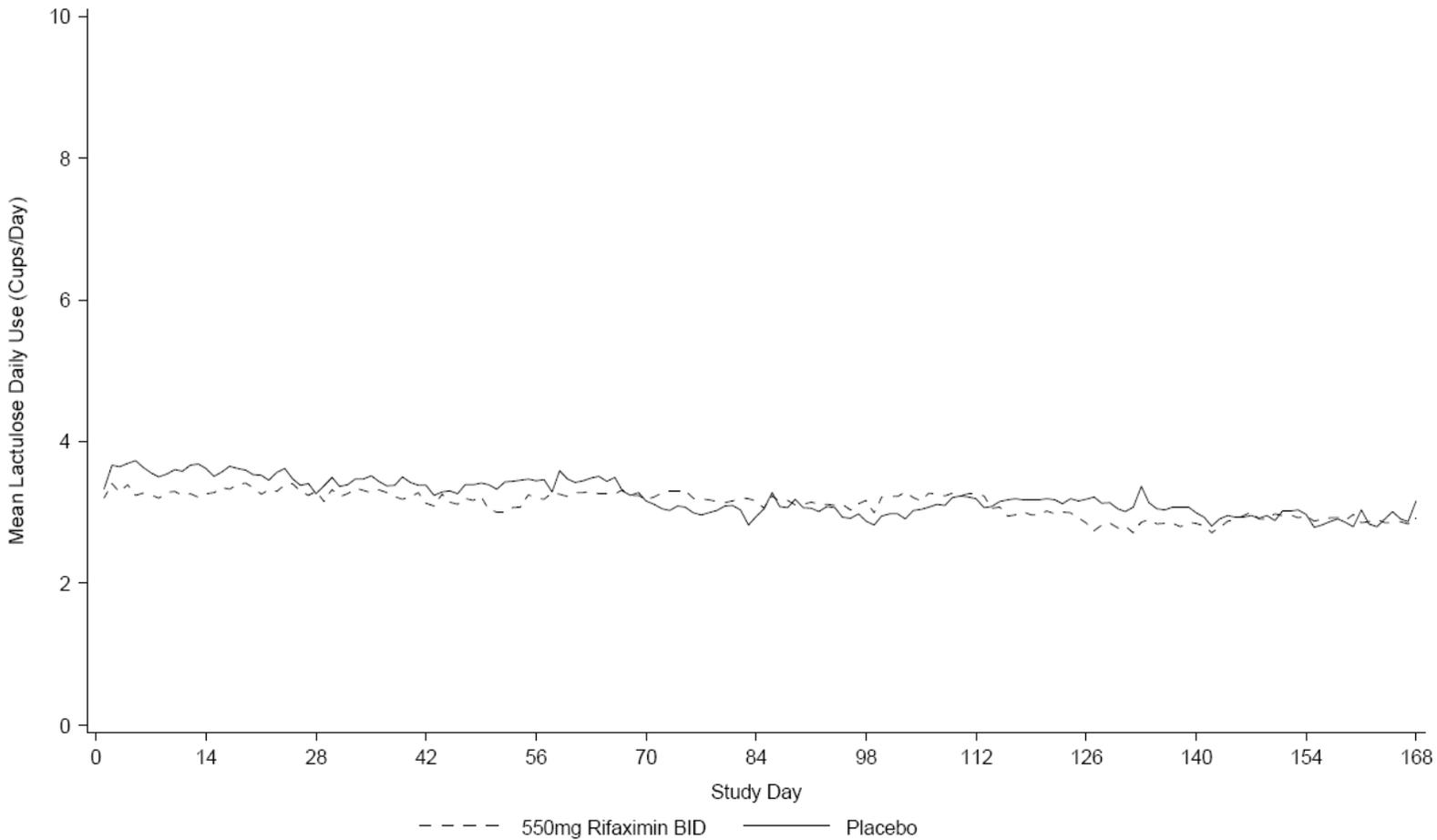
### ***E. Lactulose Usage and its Effect on Interpretability***

According to Section 5.6.2 of the finalized (04SEP2008) RFHE3001 protocol, “Lactulose use is optional for subjects during the study, if lactulose is present at baseline. Lactulose will be available to subjects throughout the study (i.e., from screening through EOS) and, for subjects who use lactulose, it will be titrated to a dose during the 3-to-7-day observation period according to accepted medical practice for this unapproved HE medication. If the subject does not use lactulose then lactulose therapy may not be initiated after baseline unless the subject is withdrawn from the study. Subjects who do not use lactulose prior to screening should not start lactulose during the 3-to-7-day observation period unless the investigator believes there is an immediate need for this concomitant therapy. If lactulose is present at baseline then its use will be permitted as needed throughout the study.”

It was ultimately determined that out of the 299 randomized subjects, 273 of them (128 with XIFAXAN and 145 with placebo) concurrently used lactulose throughout the treatment period. Based on the previously given protocol passage, one could certainly surmise that of the 273 patients (128 with XIFAXAN and 145 with placebo) who had prior lactulose use, that none of them would actually take the option of dropping lactulose before study drug initiation. However, this did indeed occur. Three prior-use subjects (762-0002 [XIFAXAN], 799-0016 [placebo], and 897-0003 [placebo]) declined concurrent use of lactulose during the treatment period. Two of the three, one XIFAXAN subject and one placebo subject, experienced a breakthrough HE event while on study. Furthermore, via a protocol deviation, three non-prior-use subjects (547-0006 [placebo], 882-0003 [placebo], and 905-0002 [XIFAXAN]) had lactulose newly initiated for concurrent usage. These changes offset each other resulting in, as previously indicated, 273 total patients (128 with XIFAXAN and 145 with placebo) who concurrently took lactulose during the trial.

It was also determined that lactulose usage was balanced across the XIFAXAN and placebo groups for this 273 patient subset as evidenced by Figure 6 below. Hence based on these joint findings, pivotal study RFHE3001 was technically an add-on study of XIFAXAN+lactulose vs. placebo+lactulose. (Note that the primary efficacy results using the 26 patients [12 with XIFAXAN and 14 with placebo] who did not partake in concurrent lactulose usage [regardless of the nature of these results; in this case, not compelling] are technically not generalizable due to the relatively small set of patients.) As a consequence, the primary efficacy analysis and all secondary efficacy analyses were re-administered on this 273 patient subset who took lactulose while on study. The principal results of this exploratory analysis are presented in Table 10 below. The only change in results for a re-tested endpoint pertained to the time-to-increase from baseline in Asterixis grade.

**Figure 6 – Average Daily Lactulose Use**



Source: Figure 14.2.5; Section 14 in RFHE3001 CSR located in Module 5.3.5.1.

**Table 10 – Principal Results of Efficacy Endpoint Analyses for Lactulose Users**

Efficacy Endpoint Analysis	Hazard Ratio Point Estimate	Hazard Ratio 95% CI	Treatment Effect p-value
Time to First Breakthrough HE Episode (up to Month Six)	0.417	(0.272, 0.639)	<0.0001
Time to First HE-Related Hospitalization (up to Month Six)	0.501	(0.283, 0.888)	0.0158
Time to Any Increase from Baseline in Conn score (up to Month Six)	0.439	(0.292, 0.660)	<0.0001
Time to Any Increase from Baseline in Asterixis grade (up to Month Six)	0.575	(0.363, 0.909)	0.0166

Source: Reviewer's Table.

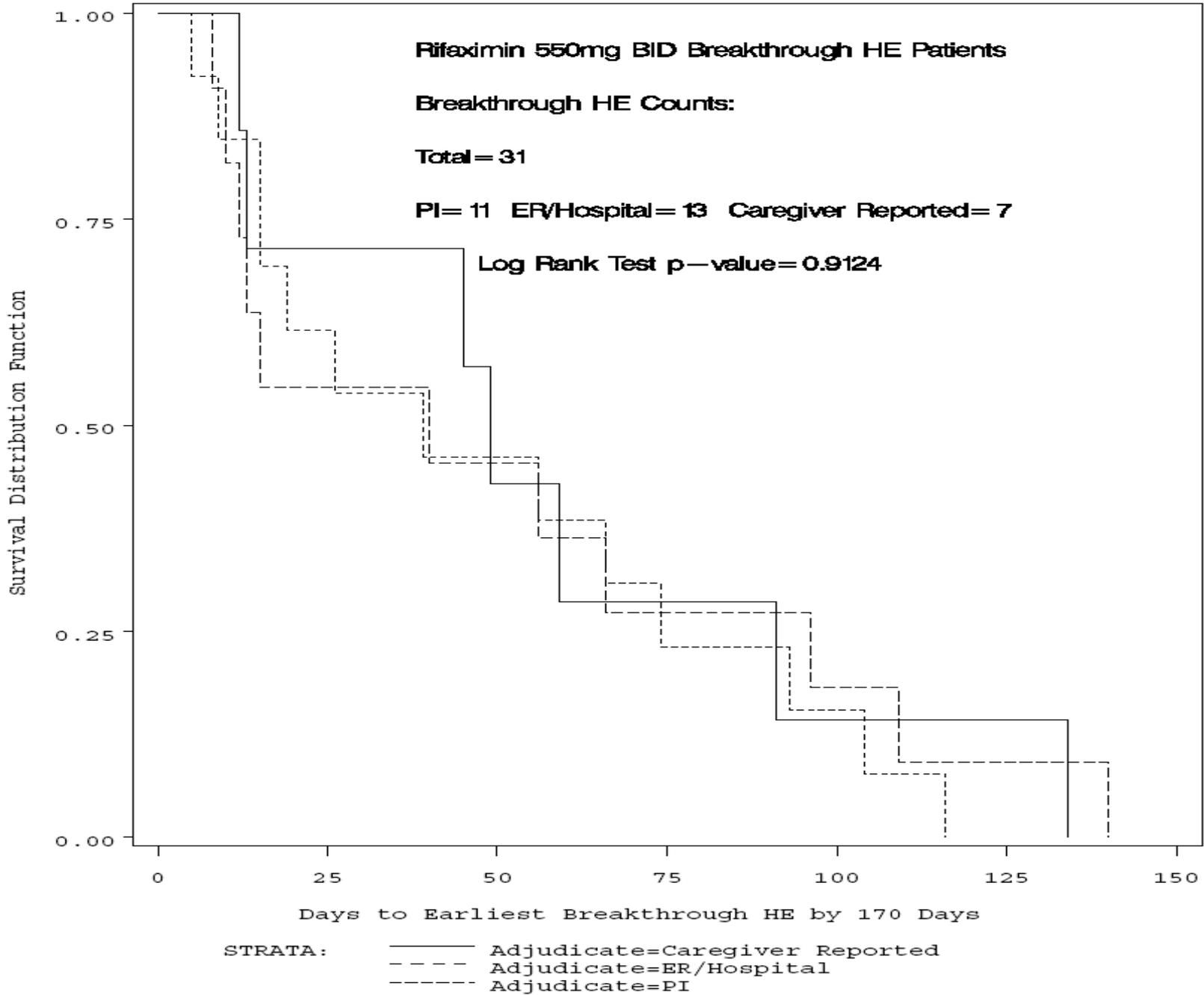
### ***F. Conn Score and Asterixis Grade Assessments***

Breakthrough HE episodes were either evaluated in-person by the principle investigator (PI) or retrospectively reviewed (i.e. not evaluated at a study visit) by the PI through information provided by ER/Hospital records or designated patient caregivers. The evaluation type (i.e., PI, ER/Hospital, or Caregiver Reported) was recorded for the 104 patients in the study who had breakthrough HE episodes by Month Six but was never documented for the other 195 patients who did not have breakthrough HE episodes by Month Six. Of the 104 patients for which these data were accessible, 43 were evaluated directly by the PI (11 XIFAXAN and 32 placebo), 39 were retrospectively reviewed by the PI through information provided by ER/Hospital records (13 XIFAXAN and 26 placebo), and 22 were retrospectively reviewed by the PI through information provided by a designated patient caregiver (7 XIFAXAN and 15 placebo).

An analysis was conducted to show whether detection bias was evident from any of these three evaluation types. This exploratory analysis was executed by re-administering the primary analysis on the breakthrough HE patients, stratified by evaluation type, separately for each treatment group and then overall. If the behavior of the survival curves was found to be significantly different between the breakthrough HE patients from treatment group versus the other, then the presence of detection bias (and possible study un-blinding) might be concluded.

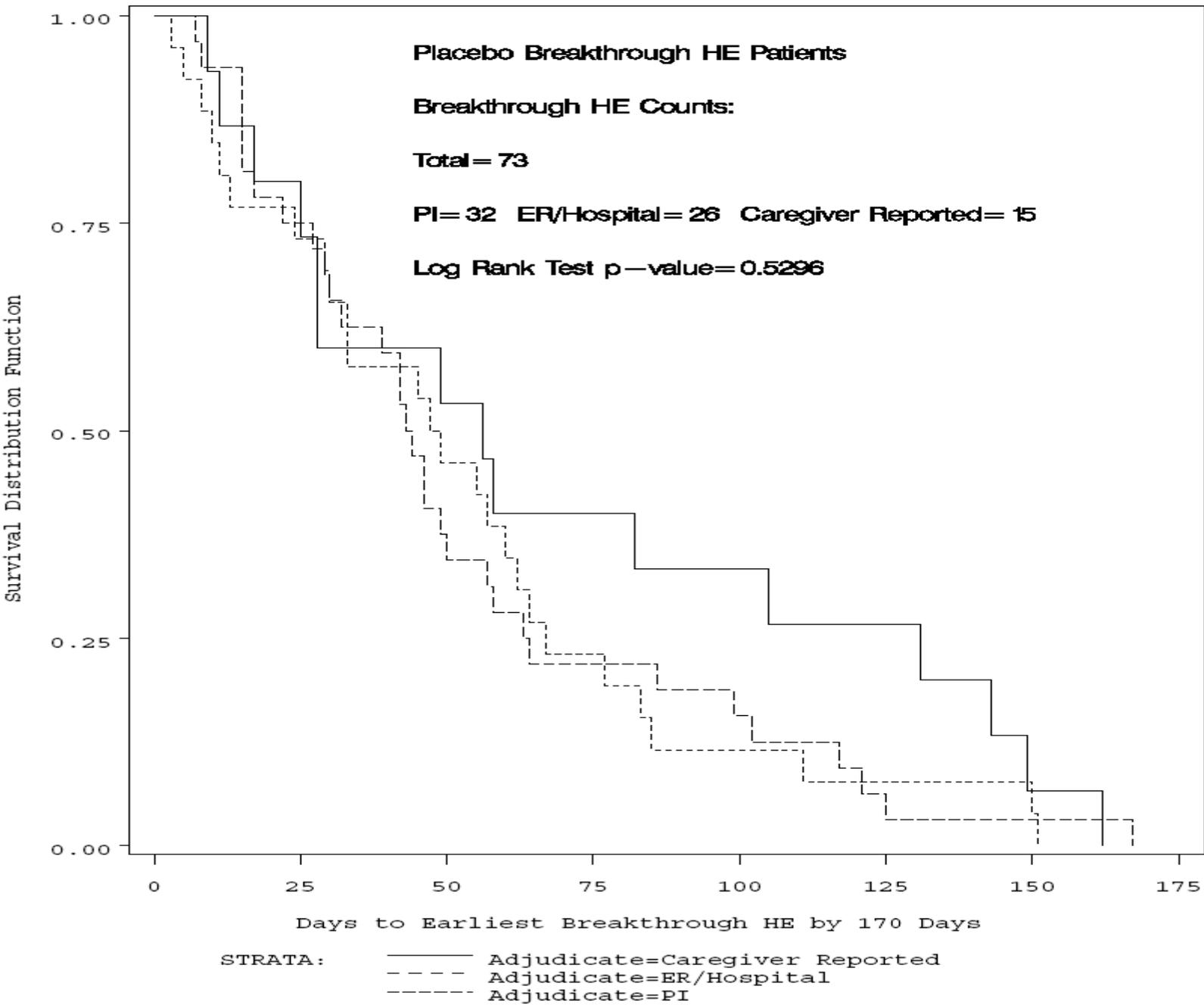
The results of this analysis are shown below in Figures 7, 8, and 9. It is evident that there was no considerable difference in the behavior of these survival curves between the treatment groups and overall. Additionally, as assessed by the log rank test, there was no statistically significant difference between these curves in each of the three groups studied. Hence, based on these results, there does not appear to be a detection bias from any of the three evaluations administered for determining breakthrough HE.

**Figure 7 – Time to Breakthrough HE (up to Month Six) in XIFAXAN Breakthrough HE Patients by Evaluation Type**



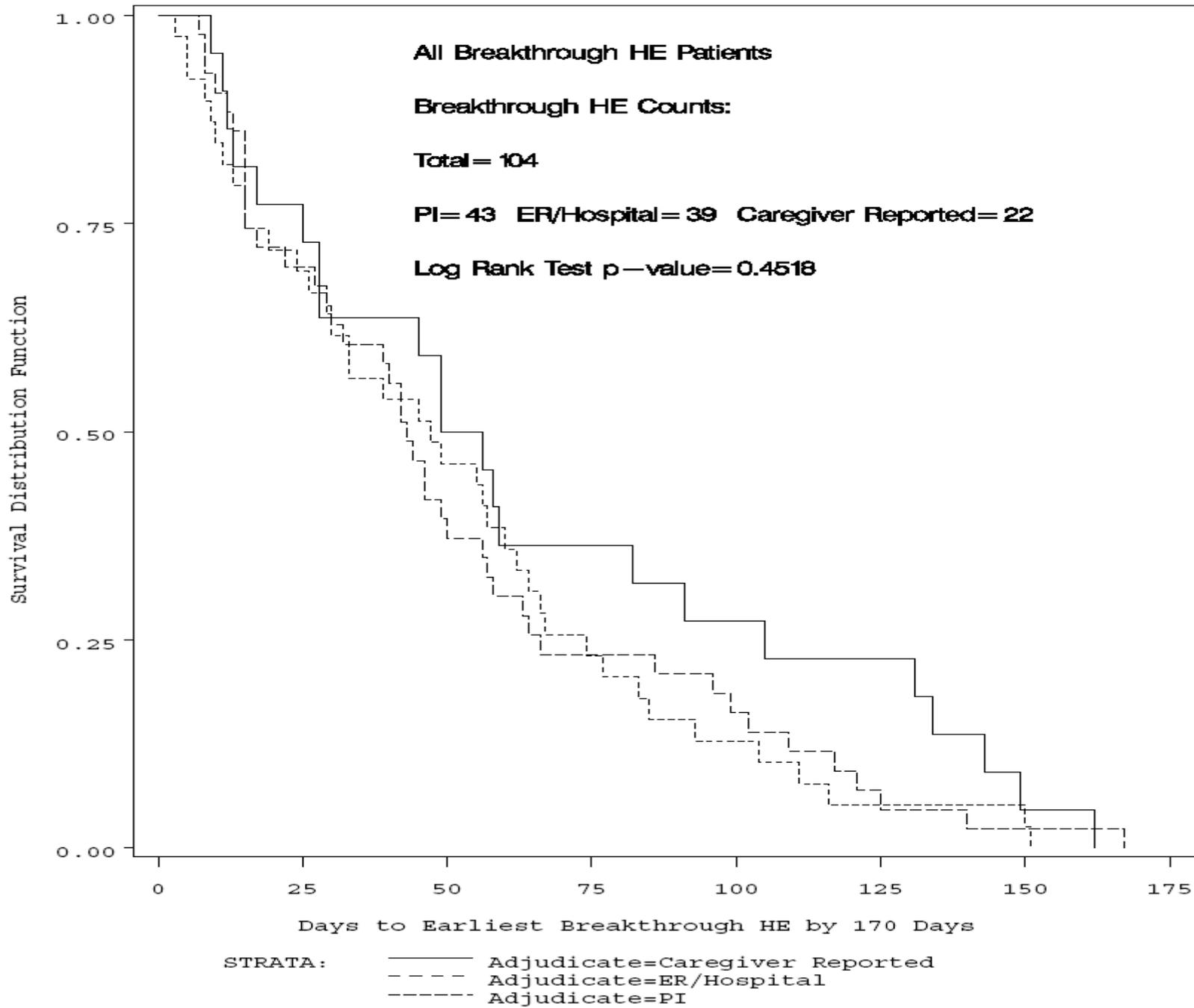
Source: Reviewer's Figure.

**Figure 8 – Time to Breakthrough HE (up to Month Six) in Placebo Breakthrough HE Patients by Evaluation Type**



Source: Reviewer's Figure.

**Figure 9 – Time to Breakthrough HE (up to Month Six) in All Breakthrough HE Patients by Evaluation Type**



Source: Reviewer's Figure.

## **3.2 Study RFHE3002**

### ***A. Background Information***

As shown previously in Table 1, study RFHE3002 enrolled either new patients or those rolled over from protocol RFHE3001 who were previously diagnosed with recurrent episodic HE and holding a Conn score of 0, 1, or 2 at screening. Its primary objective was to serve as a long-term safety and tolerability study. This was a Phase 3, multinational, multicenter, single-arm, open-label study with patients being administered one 550mg XIFAXAN tablet to be taken BID.

The number of patients enrolled was 280 with 208 newly dosing with XIFAXAN (126 new patients and 82 placebo switchover patients from study RFHE3001) and 72 continuing XIFAXAN from the RFHE3001 study.

The duration of treatment was to be for at least 24 months, regulatory approval, or sponsor termination (site visits occurring every 3 months after the first month), and the overall trial is currently ongoing with first-patient-first-visit on March 7, 2007 and the interim clinical data cutoff on September 14, 2009.

### ***B. Statistical Analysis Information***

Since this was an open-label study with a primary objective pertaining to safety, all efficacy analyses are considered exploratory in nature. Nonetheless, the key efficacy parameters of interest in this study were the change from baseline in Conn score and Asterixis grade at all post-baseline visits. Note that for patients newly dosing with XIFAXAN, baseline was defined to be the first dose date of XIFAXAN while in the RFHE3002 study. For patients continuing XIFAXAN therapy, baseline was defined to be the end-of-treatment visit for RFHE3001. There was no formal statistical methodology incorporated into this analysis as only descriptive statistics for the change from baseline in Conn score and Asterixis grade at each post-baseline visit were provided. Since this is still an ongoing trial, safety and efficacy analyses use all available data through the data cutoff date as previously stated.

### ***C. Key Efficacy Analysis***

Due to the principle objective and subsequent design of this study, any efficacy results are viewed as marginally supportive at best. With this in mind, it was generally observed that a reduction from baseline in both Conn score and Asterixis grade did indeed result throughout all post-baseline time points.

### **3.3 Study RFHE9701**

#### ***A. Background Information***

Study RFHE9701 enrolled adult males and females affected by liver cirrhosis. Its primary objective was to study the efficacy and safety of XIFAXAN compared to lactitol. This was a Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group study with patients being administered two 200mg XIFAXAN tablets (along with placebo which matched two 10g sachets of lactitol monohydrate) or two 10g sachets of lactitol monohydrate (along with placebo which matched two 200mg XIFAXAN tablets) to be taken TID.

The number of patients enrolled was 103 with 50 dosing with XIFAXAN and 53 with lactitol. The duration of treatment was to be for 5-10 days with daily site visits.

#### ***B. Statistical Analysis Information***

In this study, the primary endpoint was improvement/reduction from baseline in Conn score at the final post-baseline visit. A chi-squared test was administered to test if there was a difference between the two treatment groups in the number of patients improving/reducing their Conn score at the final post-baseline visit.

#### ***C. Key Efficacy Analysis***

The analysis ultimately showed no significant difference between XIFAXAN and lactitol as the p-value associated with the chi-squared test was nearly equal to 1. This result was further supported by nearly identical changes from baseline in Conn score observed at each post-baseline visit between the two treatment groups.

### **3.4 Study RFHE9901**

#### ***A. Background Information***

Study RFHE9901 enrolled patients diagnosed with mild to moderate HE. Its primary objective was to study the effectiveness and tolerability of XIFAXAN compared to placebo in HE patients intolerant to lactulose or lactitol. This was a Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study with patients being administered two 200mg XIFAXAN tablets or corresponding matching placebo to be taken TID.

The number of patients enrolled was 93 with 48 dosing with XIFAXAN and 45 with placebo. The duration of treatment was to be for 14 days with site visits almost every 3 days.

## ***B. Statistical Analysis Information***

In this study, the primary endpoint was improvement/reduction from baseline in Conn score at the final post-baseline visit. A chi-squared test was administered to test if there was a difference between the two treatment groups in the number of patients having no change or improving/reducing their Conn score at the final post-baseline visit. A CMH test was also administered in order to further adjust the analysis for region (Europe and USA).

## ***C. Key Efficacy Analysis***

The analysis showed no significant difference between XIFAXAN and placebo as the p-values associated with the chi-squared and CMH tests were equal to 0.623 and 0.504 respectively. Note that reduction from baseline in Conn score was observed at every post-baseline visit within each treatment group and that this reduction was greater in the XIFAXAN arm relative to placebo (albeit not significantly greater).

## **4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

Age, gender and race subgroup comparisons are presented in Section 3, specifically Figure 2 in Section 3.1.C.3. Examination of age and gender subgroups did not identify differences in response to XIFAXAN among these subgroups. The number of non-Caucasian patients in study RFHE3001 was too small to assess adequately any difference in effects by race.

A special subpopulation was identified that pertained to the patients using lactulose in study RFHE3001, and this analysis is presented in Section 3.1.E. The number of non-lactulose using patients in this pivotal study was also too small to assess adequately any difference in effects by lactulose usage.

## **5.0 SUMMARY AND CONCLUSIONS**

There were no special review concerns regarding the design and subsequent statistical analyses of the efficacy data from the RFHE3001 study per se. The efficacy results themselves are consistently favorable across many different analyses. However, a principle clinical issue regarded the un-validated and controversial neurological endpoint which is a function of Conn score and Asterixis grade. The other major issue is in regard to lactulose usage which questions the originally intended generalizability of study results for stand-alone therapy. The prominence of lactulose use in the patient population should be conveyed in the labeling.

XIFAXAN efficacy results are primarily demonstrated by the single pivotal trial (RFHE3001). Study RFHE3002 provides marginally supportive evidence while studies RFHE9701 and RFHE9901 are too short in duration and targeted an inappropriate patient population (patients with active HE). However, the effectiveness of XIFAXAN is clearly established by Study RFHE3001 as seen by the highly significant results from the primary and secondary analyses as well as from important subgroup and sensitivity analyses.

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

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

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/s/

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BEHRANG D VALI  
03/17/2010

MICHAEL E WELCH  
03/18/2010  
Concur with review.

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

<b>NDA/BLA Number: 22-554</b>	<b>Applicant: Salix Pharmaceuticals, Inc.</b>	<b>Stamp Date: 24JUN2009</b>
<b>Drug Name: Xifaxan® (Rifaximin)</b>	<b>NDA/BLA Type: Type 6 NDA; 505(b)(1)</b>	<b>Indication: Remission of Hepatic Encephalopathy</b>

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

	<b>Content Parameter for RTF</b>	Yes	No	NA	Comments
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.	<b>X</b>			
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.			<b>X</b>	This was a missed paper submission with electronic data sets. The data sets were created and subsequently submitted with satisfactory quality.
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	<b>X</b>			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups (if applicable).	<b>X</b>			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	<b>X</b>			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES**

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

**N/A**

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	<b>X</b>			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	<b>X</b>			Note that the primary endpoint in the pivotal study is not validated hence an Advisory Committee meeting is imminent.
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			<b>X</b>	There were no interim analyses with regard to efficacy in any of the pivotal or supportive studies. DSMB meetings were conducted to monitor safety only.
Appropriate references for novel statistical methodology (if present) are included.	<b>X</b>			References for statistical methodology were presented (although the methodology was not novel per se).
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	<b>X</b>			Safety datasets were submitted for each study individually, however this data can be integrated. Resulting ISS datasets were also submitted which is very helpful.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			<b>X</b>	A time-to-event response was used as the primary endpoint in the pivotal study. Standard strategies were proposed by the sponsor for handling censored patients, however not enough sensitivity analyses were presented for different scenarios regarding handling these censored patients.

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please communicate below any additional requests to the Applicant for the 74-day letter.

- (1) A Per-Protocol (PP) population was not included in the RFHE3001 SAP and thus should be defined (this most likely will require defining protocol violations as well because a standard PP definition is based on whether a patient has committed any protocol violations and also their compliance to treatment). Subsequently all primary analysis tables and figures should be repeated with this PP population to show the robustness of the primary efficacy data.
- (2) A well defined Responder Analysis should be included for the RFHE3001 study. Define a responder based on some clinically meaningful amount of time that a patient stays in HE remission.
- (3) Two further sensitivity analyses should be conducted for the primary efficacy endpoint in the RFHE3001 study. The first pertains to the following: along with all subjects who discontinued due to experiencing a breakthrough HE, all other subjects that discontinue due to any other reason prior to the completion of the six month treatment period should also be categorized as if they experienced a breakthrough HE (i.e. failure) at that discontinuation time point. The second pertains to the following: along with all subjects who discontinued due to experiencing a breakthrough HE, all other subjects that discontinue due to AE, liver transplant, or death prior to the completion of the six month treatment period should also be categorized as if they experienced a breakthrough HE (i.e. failure) at that discontinuation time point.
- (4) For the RFHE3001 study, please separately provide all data on every patient who failed screening and subsequently did not participate in the trial.
- (5) For the RFHE3001 study, please provide the SAS programs corresponding to all efficacy outputs presented (all section 14.2 tables and figures).
- (6) There were peculiar issues/anomalies in the RFHE3001 data sets which imply that the clinical (and subsequently analysis) database may not be 100% clean. Examples include missing randomization numbers in the RAND domain (214 out of 299 patients had missing randomization numbers), and some patients in the AE analysis data set show more adverse events than what they show in the corresponding AE raw data set. These issues/anomalies should be explained and corrected.

## Background

Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, Salix Pharmaceuticals, Inc. (Salix) is submitting an efficacy supplement to the New Drug Application (NDA 21-361) for XIFAXAN® (Rifaximin) tablets for the proposed orphan drug indication of the maintenance of remission of hepatic encephalopathy (HE) in patients 18 years of age and older. This supplement is a Type 6 NDA (filed under new NDA number 22-554) which provides data for a new strength (550 mg) of the currently approved (200 mg) oral tablet dosage form. Rifaximin was granted orphan designation for the treatment of HE on February 10, 1998 which encompasses the proposed indication as confirmed with the Office of Orphan Products Development on November 24, 2008.

Salix requests priority review of this efficacy supplement. Rifaximin (1100 mg/day; 550 mg twice daily) has the potential to provide a safe and effective therapy to maintain patients' remission from HE for which there is no satisfactory alternative therapy. Lactulose is often used for the treatment of HE, but its usefulness is limited by side effects which may exacerbate symptoms of HE. Neomycin is approved as adjunctive therapy for patients in hepatic coma only;

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

however, neomycin has a well-documented history of systemic side effects, namely, oto- and nephrotoxicity.

HE is a serious, rare, complex, episodic, neuropsychiatric syndrome associated with advanced liver disease. HE is a formidable burden on the patient, his/her family, and the healthcare system. Overt HE episodes are debilitating, can present without warning, render the patient incapable of self-care, and frequently result in hospitalization. Overt, episodic HE is common among patients with liver cirrhosis; however, the condition is rare among individuals in the overall, general population.

The use of Rifaximin is well established in the treatment of multiple GI conditions and has been approved in 24 countries worldwide for indications including travelers' diarrhea, diarrhea in diverticular disease, intestinal infection, and adjunctive therapy for HE or hyperammonemia.

Paper study reports, by module, were delivered to the assigned reviewers in each respective review discipline. The submitted electronic data sets and labeling information have been stored in the electronic document room (EDR) at this path location:

[\\FDSWA150\NONECTD\N21361\S\\_010\2009-06-24](\\FDSWA150\NONECTD\N21361\S_010\2009-06-24).

This application consists of data from a global clinical development program conducted under IND 59,133. Due to obtaining orphan designation from the Agency, the NDA User Fee has been waived.

### **Brief Overview and Summary of Relevant Trials**

Rifaximin has been studied by Salix for the maintenance of remission of HE and for the interventional treatment of active HE. The clinical efficacy of Rifaximin for the maintenance of remission of HE was established with a phase 3, long term (6 month), randomized, double-blind, placebo-controlled, multicenter study RFHE3001, additional data from the ongoing and open-label long term safety study RFHE3002, dose ranging study RFHE9702 (demonstrating a dose response at 1200mg/day), and acute treatment phase 3 studies RFHE9701 and RFHE9901 which investigate Rifaximin therapy for up to 15 days in subjects with active HE. The pivotal RFHE3001 study was designed and conducted in accordance to agreements attained at the End of Phase 2 meeting held with the Division of Gastroenterology Products on December 14, 2004.

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

The following table contains information on the relevant trials contained in this submission.

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Subjects	Patient Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	RFHE3001	<i>Primary:</i> compare the maintenance of remission from previously demonstrated recurrent episodic HE as measured by Conn score and Asterixis grade; <i>Secondary:</i> safety and tolerability	Multinational, Multicenter, randomized, double-blind, placebo-controlled, parallel groups	Rifaximin 550mg and matching placebo; BID; 550mg tablets	Rifaximin: 140 Placebo: 159 Total: 299	Patients diagnosed with HE currently in remission	6 months	Complete; Full
Safety	RFHE3002	Long-term safety and tolerability	Multinational, Multicenter, open-label	Rifaximin 550mg; BID; 550mg tablets	RFHE3001:152 New: 115 Total: 267	Patients diagnosed with HE currently in remission	At least 24 months, regulatory approval, or sponsor termination	Ongoing; Interim
Dose-Response	RFHE9702	Dose comparison of Rifaximin in subjects with Grade I, II, or III encephalopathy	Multicenter, randomized, double-blind, parallel groups	Rifaximin 200mg, 400mg, or 800mg; TID; 200mg tablets	Rifaximin 200mg: 18 400mg: 19 800mg: 17 Total: 54	Adult males and females with porto-systemic encephalopathy	7 days	Complete; Full
Efficacy and Safety	RFHE9701	Efficacy and safety compared with lactitol	Multicenter, randomized, double-blind, double dummy, active-controlled, parallel groups	Rifaximin 400mg and lactitol monohydrate 20g; TID; 200mg tablets and 10g sachets respectively	Rifaximin: 50 Lactitol: 53 Total: 103	Adult males and females affected by liver cirrhosis	5-10 days	Complete; Full
Efficacy and Tolerability	RFHE9901 [RIF/HE/INT/99]	Effectiveness and tolerability compared to placebo in HE patients intolerant to lactulose or lactitol	Multinational, Multicenter, randomized, double-blind, placebo-controlled, parallel groups	Rifaximin 400mg and matching placebo; TID; 200mg tablets	Rifaximin: 48 Placebo: 45 Total: 93	Mild to moderate HE	14 days	Complete; Full

### Review Issues

All review issues have been captured above in the additional requests to the Applicant for the 74-day letter.

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/s/  
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BEHRANG D VALI  
08/14/2009

MICHAEL E WELCH  
08/14/2009