CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-908

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 30, 2006

FROM: Julie Beitz, MD

SUBJECT: Acting Office Director Memo

TO: NDA 21-908 Amitiza (RU-0211, lubiprostone) capsules; Sucampo Pharmaceuticals, Inc.

Summary
Amitiza (lubiprostone) is a prostaglandin E_1 (PGE_1) metabolite analogue that enhances chloride-rich intestinal fluid secretion thereby increasing motility in the intestine and fecal transit. The proposed dose is 24 mcg administered orally bid. This memo documents my concurrence with the Division of Gastroenterology Product's (DGP's) decision to approve lubiprostone for the treatment of adults with chronic idiopathic constipation.

The submitted studies support the sponsor's claim for efficacy for this indication. Two 4-week randomized, placebo-controlled trials in patients with chronic idiopathic constipation (239 patients on lubiprostone, 240 on placebo) showed that lubiprostone 24 mcg bid was statistically superior to placebo for the primary endpoint, namely, spontaneous bowel movement frequency rate during week 1. In addition, statistical significance for lubiprostone 24 mcg bid relative to placebo was observed for several secondary endpoints including: spontaneous bowel movement frequency rates during weeks 2, 3, and 4 of therapy; percentage of patients experiencing spontaneous bowel movements within the first 24 hours after lubiprostone administration; time to first spontaneous bowel movement; responder rates at each week and all weeks; constipation severity ratings; and signs and symptoms related to stool consistency and straining. Following four weeks of treatment, withdrawal of lubiprostone did not result in a rebound effect. Three open-label long-term safety studies conducted in 871 patients with chronic idiopathic constipation demonstrated that lubiprostone 24 mcg bid decreased abdominal bloating, discomfort and constipation severity over 6-12 month periods.

Despite the preponderance of female patients enrolled in these studies, male patients also had significantly higher spontaneous bowel movement frequency rates during week 1 on lubiprostone compared to placebo. Lubiprostone-treated patients over 65 years were underrepresented in the clinical trials and did not show significantly higher spontaneous bowel movement frequency rates during week 1. However, this patient group did experience higher spontaneous bowel movement frequency rates during weeks 1-4 and symptomatic improvement compared to elderly placebo-treated patients. Product labeling will reflect that lubiprostone has not been adequately studied in patients with hepatic or renal impairment, or pediatric patients.

A total of 1113 patients received lubiprostone 24 mcg bid in phase 2 and 3 clinical trials and were evaluable for safety. The most common adverse events reported were headache and gastrointestinal events (nausea, diarrhea, abdominal distention or pain). Gastrointestinal events were also the most common events leading to product withdrawal. There was no evidence for adverse effects on heart rate, cardiac conduction, cardiac repolarization, or bone mineral density.

Uterine Effects
Prostaglandins have been shown to stimulate uterine contractility. Nonclinical studies evaluating the safety of lubiprostone use in pregnancy have been conducted including 1) *in vitro* pharmacology studies to assess the potency of lubiprostone relative to misoprostol and other prostaglandins with regard to uterine effects, and 2) *in vivo* studies in pregnant rats, guinea pigs, and monkeys. These studies have been reviewed by the DGP pharmacology/toxicology staff, as well as the pharmacology/toxicology team leader in the Division of

Reproductive and Urologic Products, and the Associate Director of Pharmacology/Toxicology assigned to this Office.

The *in vitro* studies suggest that lubiprostone would be much less potent in inducing uterine contractions than misoprostol (a synthetic PGE_1 analogue) and natural prostaglandins. The guinea pig model, chosen because there is a reasonable correlation of uterine effects in guinea pigs and humans, demonstrated a potential for fetal loss after repeated doses of 10 and 25 mcg/kg/day (approximately 2 and 6 times the human dose, respectively) administered on days 40-53 of gestation. The study in pregnant rats was deemed irrelevant due to a lack of sensitivity to prostaglandins in that species, while the study in pregnant monkeys, inherently flawed due to the doses evaluated, did provide evidence that fetal loss did not occur at the doses tested.

There have been no adequate and well-controlled studies of lubiprostone conducted in pregnant women. Four women taking lubiprostone 24 mcg bid became pregnant during clinical trials; per protocol, treatment was discontinued upon pregnancy detection. Three of the four women delivered healthy babies. The fourth woman was monitored for 1 month following discontinuation of study drug, at which time the pregnancy was progressing as expected; the woman was subsequently lost to follow-up.

I agree with the clinical and pharmacology/toxicology review staffs' recommendation for a Pregnancy Category C designation, i.e., that lubiprostone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In addition, I agree with inclusion of a WARNING statement in product labeling to highlight the guinea pig study findings, and to advise women of child-bearing potential to have a negative pregnancy test prior to starting treatment, and use effective contraceptive methods during treatment.

Tradename Review
The tradename "Amitiza" is acceptable.

Phase 4 Studies
The sponsor has committed to conduct Phase 4 studies to assess the need for potential dose adjustment in patients with renal or hepatic impairment. In addition, studies in pediatric patients with chronic idiopathic constipation aged 0 to 17 years will be required under the Pediatric Research Equity Act (PREA).

Julie Beitz, MD
Acting Director,
Office of Drug Evaluation III
CDER, FDA

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/s/

Julie Beitz
1/30/2006 05:07:13 PM
DIRECTOR

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 1/7/2006

FROM: Ruyi He, MD
Medical Team Leader
Division of Gastroenterology Products/ODE III

SUBJECT: GI Team Leader AP Comments
NDA 21-908

APPLICANT: Sucampo Pharmaceuticals, Inc.

DRUG: AMITIZA (lubiprostone)

RECOMMENDATION:

I concur with Dr. Kristen Buck's recommendations that NDA 21-908, oral lubiprostone 48 mcg/day (24 mcg capsules b.i.d.), be approved for the treatment of chronic idiopathic constipation in the adult population. For approval of this application, the sponsor needs to incorporate the Division's recommendations into the lubiprostone drug label and agrees to the required post-marketing commitment studies.

The safety and effectiveness of RU-0211 (lubiprostone) in pediatric patients has not been evaluated. The sponsor requested, and was granted a deferral of pediatric studies in this New Drug Application. I recommend that as a post-marketing study commitment, the sponsor conduct a PK and/or a safety and efficacy study of lubiprostone in the pediatric population.

In addition, the sponsor needs to perform a Phase IV study to assess the need for potential dose adjustment in subjects with renal and hepatic impairments.

I. BACKGROUND:

Factors contributing to the development of constipation include inadequate fiber in the diet, lack of exercise, neurological and systemic disorders and problems with colon, rectum, and/or intestinal function. Chronic constipation is thought to be a disorder of colonic motility that is present for at least twelve weeks (non-consecutively) out of the year. Chronic idiopathic constipation is hallmarked by infrequent bowel movements that are often difficult to evacuate. Regardless of the defining criteria, constipation is more likely to affect females than males and more likely to occur in older patients. The actual occurrence of constipation is likely higher than reported, as many individuals suffer at home without seeking professional care. The term "idiopathic" constipation relates to the fact that there is no known cause for the constipation (i.e., not due to other diseases or drugs).

Lubiprostone (RU-0211) is a prostaglandin E_1 metabolite analogue and is formulated in a soft gelatin capsule with liquid contents of lubiprostone and a medium-chain fatty acid triglyceride. Lubiprostone is classified as a locally acting chloride channel activator that promotes a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine thereby increasing the passage of stool and alleviating symptoms associated with chronic idiopathic constipation.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

Although DDMAC finds the proprietary name, — acceptable from a promotional perspective, DMETS does not recommend use of – as the proprietary name, because — may sound similar or look similar to when spoken or written. The sponsor, Sucampo, submitted a new trade name AMITIZA and a back-up trade name — for review. Both DDMAC and DMETS have concluded that the new trade name AMITIZA is acceptable.

Dr. Khairy Malek, Division of Scientific Investigations, conducted the clinical inspection and concluded that the data submitted from the 4 sites in support of this application appear acceptable.

B. Chemistry and Manufacturing:

Chemistry Review Team concluded that this NDA is approvable pending acceptable manufacturing inspection which is currently ongoing.

The drug substance lubiprostone is a new molecular entity with 4 chiral centers. The drug product was developed as a soft gelatin capsule containing 24 mcg of liquid lubiprostone.

No degradation products were observed in the drug substance under the proposed storage condition — or in the drug product under room temperature. The — impurities are controlled — The shelf life for the drug substance is granted for — based on the current stability data; however, it can be extended when the updated stability data is available. The expiration for the drug product is — — under 25 °C/60%RH based on the stability data. For more information, please see Dr. Zhengfang Ge's review.

C. Pre-Clinical Pharmacology/Toxicology:

Pharmacology Review Team concluded that the sponsor conducted adequate preclinical studies with lubiprostone and the NDA is approvable pending labeling changes. Further nonclinical studies are not recommended. Because lubiprostone caused dose-dependent abortions in guinea pigs, when administered to the pregnant animals, Dr. Chakder recommends that the drug not be used by pregnant women, and have restricted use in women with child-bearing potential. Please see Dr. Sushanta Chakder's review in details.

Pharmacology
lubiprostone (RU-0211) caused a dose-dependent augmentation of acetylcholine-induced contractions of isolated rat ileum. RU-0211 caused a dose-dependent increase in intestinal fluid secretion in rats. RU-0211 had no effects on the serum levels of Na^+, K^+ and Cl^- in rats at oral doses up to 100 μg/kg. The main metabolite of RU-0211, 15-hydroxy-RU-0211 (M3) also caused a dose-dependent increase in the intestinal fluid secretion in rats, with a potency similar to that of the parent compound. RU-0211 had no effects on the respiration rate, heart rate or ECG parameters of anesthetized dogs at intraduodenal doses up to 1000 μg/kg. RU-0211 had no effect on the central nervous system of rats at oral doses up to 1000 μg/kg. RU-0211 did not cause a prolongation of action potentials in canine isolated canine cardiac Purkinje fibers.

Toxicology
In the acute toxicity study in rats, the minimal lethal dose was 60 mg/kg in males and 30 mg/kg in females. In dogs, single oral doses up to 40 mg/kg were non-lethal. Such dose decreased locomotor activity, loose stool/diarrhea, vomiting, lacrimation, salivation and pale buccal mucosa were observed in males and females.

In repeat dose oral toxicity study in rats and mice and dogs, loose stools or diarrhea was observed in all species, which is thought to be related to the pharmacological actions of the drug. Hyperplasia of the zona glomerulosa of the adrenal gland was observed in rats, mice and dogs. In the chronic 39-week oral toxicity study in dogs, atrophy of the seminiferous tubule was observed in males and pyelitis in the kidneys was observed in males and females at a dose of 0.05 mg/kg/day. However, in reproductive toxicology studies, RU-0211 had no effects on the reproductive function of male rats at doses up to 1.0 mg/kg.

RU-0211 was not genotoxic in a battery of genotoxicity assay.

The carcinogenic potential of RU-0211 was assessed in a 104-week oral carcinogenicity study in mice and a 104-week oral carcinogenicity study in rats. In female mice, there was an increase incidence for Harderian gland carcinoma at the high dose (500 μg/kg/day). Male rats receiving RU-0211 had higher incidences of squamous cell papilloma in nonglandular stomach. The incidences of histiocytic sarcoma and benign interstitial cell tumor of the testes were significantly higher in male rats receiving the 400 μg/kg dose. In female rats, treatment with RU-0211 produced hepatocellular adenoma at 400 μg/kg.

In the oral Segment I fertility and general reproductive performance study with RU-0211 in rats, doses up to 0.2 mg/kg/day did not produce any effects on the fertility and reproductive performance of male and female animals. RU-0211 was not teratogenic in rats at oral doses up to 2.0 mg/kg/day. It was not teratogenic in rabbits at oral doses up to 0.10 mg/kg/day. In the Segment III pre- and post-natal developmental toxicity study with RU-0211 in rats, viabilities of pups and mean pup weights from dams receiving the 1.0 mg/kg/day dose were lower than that of controls.

The abortifacient potential of RU-0211 was examined in specific guinea pig and Rhesus monkey models following oral administration. Treatment with RU-0211 was associated with a dose-dependent abortion in guinea pigs. The dose selection for the monkey abortifacient study was based on NOEL in rats, and was not appropriate. For more information, please see Dr. Sushanta Chakder's Review.

D. Biopharmaceutics:

Lubiprostone is not detected in plasma, urine or feces following oral administration of a radiolabeled dose of lubiprostone. Even after administration of a dose that is 3-fold higher than the proposed daily clinical dose, plasma concentrations of lubiprostone are still not detectable. The mean Cmax and AUC values of M3, a detectable active metabolite, increase in a dose-related manner. The findings of a mass balance study demonstrated that a radiolabeled oral dose of lubiprostone is primarily excreted in urine via the kidneys (63% of the administered dose), while around 32% of the radiolabeled dose was excreted in feces. The mean elimination half-life of total radioactivity in plasma was 3 hours. A total of 18 metabolites of lubiprostone were characterized indicating extensive metabolism of lubiprostone following oral administration.

From the view point of Office of Clinical Pharmacology and Biopharmaceutics, the sponsor has provided adequate Clinical Pharmacology and Biopharmaceutics data in support of the sought indication and NDA 21-908 is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor regarding the proposed language in the package insert. Please see Dr. Suliman Al-Fayoumi's review in details.

E. Clinical/Statistical:

Efficacy:

A total of 1688 subjects (1491 subjects with constipation and 197 healthy volunteers) were involved with the clinical development program of RU-0211 (lubiprostone). There were a total of 606 subjects in the Well-Controlled group cohort (WCG) and 878 subjects in the Long-Term-Safety group cohort (LTS). The demographic characteristics of these study populations were relatively consistent yet somewhat limited across all five studies. The overall pooled subject population was predominantly female (89.2% - WCG; 86.1% - LTS) and mostly Caucasian (81.6% - WCG; 86.9% - LTS). The averaged proportion of subjects ≥ 65 years old in the pooled population was 9.7% in the WCG and 18.4% in the LTS.

Following a 2-week baseline/washout period, subjects were randomized to receive 4 weeks of double-blind treatment with either lubiprostone 24 mcg b.i.d. (48 mcg/day) or placebo. The primary endpoint of the studies was SBM frequency for Week 1. An SBM was defined as any BM that did not occur within 24 hours after rescue medication use. The studies demonstrated that subjects treated with lubiprostone had a higher frequency of SBMs during Week 1 than the placebo subjects. In both studies, results similar to those in Week 1 were also observed in Weeks 2, 3 and 4 of therapy, (See Table 1). SBM rate data from the Intent-to-Treat population of Studies SCO131 and SCO232 using the Last-Observation-Carried-Forward imputation method are summarized in the Table 1.

Table 1: SBM Frequency Rates* – from the ITT population using the Last-Observation-Carried-Forward Method

Study	Study Arm		Baseline	Week 1	Week 2	Week 3	Week 4	Change Week 1 from Baseline	Change Week 4 from Baseline
SCO131	Placebo N=122	Mean ± SD	1.58 ± 1.31	3.46 ± 2.29	3.18 ± 2.53	2.84 ± 2.23	2.91 ± 2.36		
		Median	1.50	3.00	3.00	2.00	2.26	1.50	0.76
	48 mcg N=120	Mean ± SD	1.43 ± 0.84	5.69 ± 4.42	5.06 ± 4.08	5.25 ± 4.88	5.30 ± 4.74		
		Median	1.50	5.00	4.00	5.00	4.00	**3.50**	**2.50**
	P-value#		0.3579	**0.0001**	**0.0017**	**0.0002**	**0.0002**		
SCO232	Placebo N=118	Mean ± SD	1.53 ± 0.81	3.99 ± 2.71	3.55 ± 2.67	3.36 ± 2.76	3.46 ± 2.86		
		Median	1.50	3.50	3.00	3.00	3.00	1.50	1.50
	48 mcg N=119	Mean ± SD	1.29 ± 0.90	5.89 ± 4.02	4.96 ± 4.21	5.56 ± 4.56	5.37 ± 4.80		
		Median	1.50	5.00	4.00	5.00	4.29	**3.50**	**2.79**
	P-value#		**0.0174**	**<0.0001**	**0.0487**	**0.0004**	**0.0068**		

*Frequency Rates are calculated as 7x [(Number of SBMs) / (Number of Days Observed for that Week)].
#Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

As noted above in the Table 1, the median baseline spontaneous bowel movement frequency rate was 1.50 for both placebo and RU-0211 subjects in both studies. In both pivotal studies (SC0131 and SC0232), the median SBM frequency rates in the RU-0211 group for Weeks 1, 2, 3, and 4 were higher (range: 4.00-5.00) than that in the placebo group (range: 2.00-3.50). The difference between the two groups was statistically significant at Weeks 1 – 4 in both studies.

When comparing the results before and after treatment, RU-0211 consistently demonstrated a clinically meaningful ≥ 3.5 increase in spontaneous bowel movements at Week 1 (the primary efficacy endpoint) in both studies. By Week 4, RU-0211 showed persistent clinically efficacy of a ≥ 2.5 increase in SBM. After treatment initiation with RU-0211, the median weekly spontaneous bowel movement frequency was increased and maintained to a value of at least 4.0; a value which corresponds to 1 SBM every 1 to 2 days. Of note, the change from baseline analyses did reveal an appreciable placebo effect. Given that the median changes from baseline in the RU-0211 group were significantly greater than the corresponding median changes in the placebo group (3.5 vs. 1.5), clinical evidence still stands to support RU-0211 48 mcg/day as an effective treatment for chronic idiopathic constipation.

The secondary efficacy endpoints included SBM frequency rates during Weeks 2, 3, and 4; SBMs within 24 hours of first RU-0211 dose; Time to first SBM; Responder analyses (at each week and all weeks); Weekly stool consistency; Weekly stool straining; Weekly severity of constipation; Weekly global treatment effectiveness; Weekly abdominal bloating; and Weekly abdominal discomfort. RU-0211 out-performed placebo in all of their secondary efficacy endpoints. The average spontaneous bowel movement response rate within the 24 hours after the first study drug dose was 36.9% for placebo vs. 56.7% for RU-0211 48 mcg ($p=0.0024$) in SC0131; 31.9% for placebo vs. 62.9% for RU-0211 ($p<0.0001$) in SC0232. Treatment with RU-0211 48 mcg also indicated and overall softening of stool with an average median improvement of 1.11 units on the 5-point scoring scale at week 1 and 1.26 units at week 4 when compared to baseline. Comparatively, the placebo group revealed an average median improvement of 0.40 units on the 5-point scoring scale at week1 1 and 0.55 units at week 4.

RU-0211 was analyzed by the primary efficacy variable in four subpopulations; gender (male, female), race (white, non-white), age [($18 \leq$ Age ≤ 50), ($50 \leq$ Age ≤ 65), ($65 \leq$ Age)], and IBS status (IBS, Non-IBS). All subpopulations revealed clinically significant results for the primary efficacy endpoint favoring RU-0211 24 mcg b.i.d over placebo. For detail efficacy evaluation, please see Dr. Kristen Buck's Review.

Safety:

There were a total of 1688 subjects treated in the overall safety population of which 1321 received active drug and 367 received placebo. Of the 1321 subjects who received active

drug, 1119 received RU-0211 48 mcg daily. Four hundred and ninety four subjects remained on lubiprostone 48 mcg daily at 24 weeks trial duration and 221 subjects remained on lubiprostone 48 mcg daily at 48 weeks trial duration.

No subjects died during the treatment period or follow-up period for any of the studies included in this New Drug Application.

The occurrence of serious adverse events in the studied population was relatively low. Four placebo subjects (1.3%) reported 6 serious adverse events (SAEs), with no SAE preferred term being reported by more than one subject. Thirty-two subjects taking RU-0211 48 mcg (2.9%) reported treatment-emergent SAEs. Appendicitis, diverticulitis, syncope, chest pain, and dehydration, all of which were considered unrelated to the study drug by the investigators, were the only SAE preferred terms reported by more than 1 subject. Two SAEs were considered possibly treatment-related: 1 SAE of diarrhea and 1 SAE subject who became pregnant while taking RU-0211 and gave birth to a child with talipes.

Across all active doses of lubiprostone (N=1175) in the well-controlled group and the long-term safety group studies, the most commonly reported adverse event preferred terms were nausea (30.9%), diarrhea (13.2%), headache (13.0%), abdominal distension (6.8%), abdominal pain (6.8%), and flatulence (5.9%). Comparatively for placebo (N=316), the corresponding reports of adverse events in the above preferred terms were; nausea (5.1%), diarrhea (0.9%), headache (6.6%), abdominal distension (2.8%), abdominal pain (2.2%), and flatulence (1.9%). Besides headache, the most commonly reported adverse events in the active drug group were gastrointestinal in nature, which may be representative of the pharmacodynamic effects of lubiprostone.

An analysis of cumulative adverse event incidence rates, time to first adverse events, and a Cox proportional hazard analysis for the occurrence of any adverse event (nausea, diarrhea, abdominal pain, vomiting, headache, dizziness, peripheral edema, fatigue, and dyspnea) indicated that the risk for experiencing those adverse events is greatest within the first few days of treatment and does not increase significantly over time. One exception to the above adverse event incidence rate hazard risk is that of peripheral edema. There was an increase of approximately 10% in the hazard rate for peripheral edema from days 22-28 until days 270-365.

The frequency of withdrawal for RU-0211 48 mcg (24 mcg b.i.d.) subjects in the well-controlled group was significantly higher than for placebo subjects. Overall, 1.1% of placebo subjects and 7.7% of RU-0211 48 mcg subjects withdrew because of gastrointestinal adverse events. The breakdown of gastrointestinal adverse events in the pooled population that led to withdrawal for at least 1% of subjects was nausea (5.2%), diarrhea (1.5%), abdominal pain (1.5%), and flatulence (1.5%). The types and frequencies of the individual AEs that led to withdrawal were generally similar across the long-term studies, and these results were similar to those observed in the well-controlled group.

The clinical and laboratory data presented in this application including biochemistry, hematology, urinalysis, vital signs and physical examination data appeared acceptable and no significant abnormality was noted.

The effects of lubiprostone (RU-0211) on ECG parameters were evaluated. RU-0211 at doses of 24, 48, and 72 mcg per day, for 3 weeks, showed no evidence of effect on heart rate, cardiac conduction, cardiac repolarization, or morphological changes.

Despite the fact that pregnant women were excluded from all clinical trials of RU-0211, and any woman who became pregnant during a study was immediately discontinued from study participation, four pregnancies were reported during the development of RU-0211. Of the four pregnancies, two women had healthy babies, one was lost to follow-up, and one had a baby with bilateral club feet. There was also one ectopic pregnancy reported under IND — that was noted to have "resolved" during short term follow-up.

F. Pediatric Use:

The safety and effectiveness of RU-0211 (lubiprostone) in pediatric patients has not been evaluated. The sponsor requested, and was granted a deferral of pediatric studies in this New Drug Application. I recommend that as a post-marketing study commitment, the sponsor conduct a PK and/or a safety and efficacy study of lubiprostone in the pediatric population. The sponsor has agreed to submit a pediatric development plan within the next several months.

III. Summary Comments:

The studies demonstrated that subjects treated with lubiprostone had a higher frequency of SBMs during Week 1 than the placebo subjects that were both statistically and clinically significant. In both studies, results similar to those in Week 1 were also observed in Weeks 2, 3 and 4 of therapy.

The occurrence of serious adverse events in the studied population was relatively low (1.3% in the placebo group and 2.9% in the RU-0211 48 mcg group). In the well-controlled group and the long-term safety group studies, the most commonly reported adverse event were nausea (30.9%), diarrhea (13.2%), headache (13.0%), abdominal distension (6.8%), abdominal pain (6.8%), and flatulence (5.9%). Comparatively for placebo, the corresponding reports of adverse events in the above preferred terms were; nausea (5.1%), diarrhea (0.9%), headache (6.6%), abdominal distension (2.8%), abdominal pain (2.2%), and flatulence (1.9%). Majority of these side effects were mild and often short-lived.

The safety of lubiprostone in pregnancy has not been evaluated in humans and lubiprostone has been shown to have the potential to cause fetal loss in animal studies. I concurred with the labeling recommendations provided by the Division of Reproductive

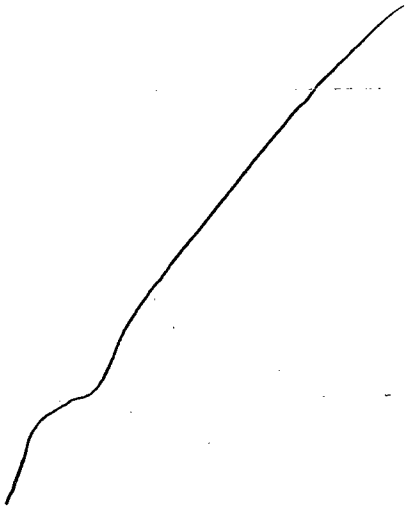
and Urologic Products (DRUP) regarding the use of lubiprostone in pregnant women and women who could become pregnant).

IV. Labeling Recommendations:

I concur with Dr. Kristen Buck's labeling recommendations listed in her review and the labeling recommendations provided by the Division of Reproductive and Urologic Products (DRUP) regarding the use of lubiprostone in pregnant women and women who could become pregnant). The labeling recommendations are summarized as following:

- For the INDICATIONS AND USAGE section, to be consistent with Zelnorm label which was evaluated in similar populations, I recommend the proposed indication ( ) be changed to the treatment of chronic idiopathic constipation. This section should follow the CLINICAL STUDIES section.

- Within the clinical studies section, the should be removed from the label as it provides no additional information or benefit above that which is provided in the text. The should be removed from the label, as this section provides no additional prescribing information or benefit. My recommendations for the clinical studies section are as followings:



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/s/

Ruyi He
1/7/2006 04:04:50 PM
MEDICAL OFFICER

NDA 21-908

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS

Response to Consultation Request

Date December 23, 2005

To Kristen Buck, M.D.
Medical Officer
Division of Gastroenterology Products (DGP)

From Ronald J. Orleans, M.D.
Medical Officer,
Division of Reproductive and Urologic Products (DRUP)

Through Scott Monroe, M.D.
Acting Deputy Director (DRUP)

Daniel Shames, M.D.
Director (DRUP)

Subject Response to Consultation Request from Division of Gastroenterology Products of October 17 2005 regarding the abortifacient potential of Lubiprostone, a prostaglandin metabolite analogue, for the treatment of chronic idiopathic constipation.

Introduction
NDA 21-908 was submitted to the Division of Gastroenterology Products (DGP) seeking approval of lubiprostone, a prostaglandin metabolite analogue, for the treatment of idiopathic chronic constipation. DGP has sent a Request for Consultation to the Division of Reproductive and Urologic Products (DRUP) regarding the Division's opinion on whether the nonclinical studies conducted to date for NDA 21-908 are adequate to determine if lubiprostone is a potential abortifacient in humans, and if so, requesting the Division's advice concerning the adequacy of the clinical trial design to capture abortifacient adverse events, drug labeling, and risk management. The specific clinical questions posed by DGP are summarized below:

1. Can you provide guidance as to the adequacy of the clinical trial design to capture the abortifacient adverse events of concern regarding this drug?
2. Can you provide additional clinical trial requirements for evaluation of the abortifacient safety concerns?
3. Can you provide guidance to increase the probability of safe use in the drug label given the drug's potential as an abortifacient?
4. If pre-clinical data suggests that this drug has abortifacient potential, do you recommend any further clinical study to evaluate this effect? If you do, should these studies be done prior to approval or as Phase 4 commitments?

5. Can you provide guidance with a risk management plan for this drug regarding its abortifacient potential?

Materials Reviewed

No materials for review were submitted with the consultation request. Instead, this reviewer was referred to the entire electronic submission for NDA 21-908 in the EDR. The Clinical Overview (Module 2, Section 2.5) was reviewed in detail. Also reviewed was the memorandum dated November 5, 2005, provided by Lynnda Reid, Ph.D., the Supervisory Pharmacologist in DRUP. Dr. Reid's memorandum is provided as an attachment at the end of the clinical consultation.

Background

Lubiprostone (RU-0211) is a prostaglandin E1 (PGE1) metabolite analogue being developed for the treatment for chronic idiopathic constipation. The recommended therapeutic dose in patients is 24 μg administered b.i.d.. It is known that cyclic fatty acids belonging to the prostaglandin class can promote intestinal fluid secretion which improves fecal transit. In non-clinical testing, it was found that RU-0211 was approximately 100 times more potent than PGE2 in increasing intestinal fluid volume.

Prostaglandins have been shown to have effects on uterine myometrial tissues in women. Misoprostol (a synthetic prostaglandin E1 analogue), because of its capacity to stimulate uterine contractility, is used with mifepristone as part of a medical regimen for termination of an early pregnancy up to 49 days gestation. It is also used off-label to induce cervical ripening in late pregnancy prior to induction of labor. Labeling for misoprostol includes the following Boxed Warning:

WARNINGS

CYTOTEC (MISOPROSTOL) ADMINISTRATION TO WOMEN WHO ARE PREGNANT CAN CAUSE ABORTION, PREMATURE BIRTH, OR BIRTH DEFECTS. UTERINE RUPTURE HAS BEEN REPORTED WHEN CYTOTEC WAS ADMINISTERED IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE EIGHTH WEEK OF PREGNANCY (see also **PRECAUTIONS**, and **LABOR AND DELIVERY**). CYTOTEC SHOULD NOT BE TAKEN BY PREGNANT WOMEN TO REDUCE THE RISK OF ULCERS INDUCED BY NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) (See **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS**).

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

Cytotec should not be used for reducing the risk of NSAID-induced ulcers in women of childbearing potential unless the patient is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, Cytotec may be prescribed if the patient

- has had a negative serum pregnancy test within 2 weeks prior to beginning therapy,
- is capable of complying with effective contraceptive measures,
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake,
- will begin Cytotec only on the second or third day of the next normal menstrual period.

Another prostaglandin approved for marketing in the U.S., dinoprostone (PGE2), is approved for (1) mid-trimester termination of pregnancy (Prostin E_2 Vaginal Suppository) and (2) "initiation and/or continuation of cervical ripening in patients at or near term in whom there is .... indication for induction of labor" (Cervidil).

Non Clinical Studies to Assess the Abortifacient Potential of Lubiprostone
Nonclinical studies submitted by the Applicant on the abortifacient potential of lubiprostone included in vitro pharmacology studies and vivo studies in pregnant rats, guinea pigs, and monkeys.

The in vitro studies were designed to compare the potency of lubiprostone to that of other prostaglandin agonists including misoprostol (a PGE1 analogue), PGE1, PGE2, and PGF2α. The models used were guinea pig ileum smooth muscle (PGE1 and PGE2 receptors), vas deferens smooth muscle (PGE3 receptor) and iris sphincter muscle from dogs (PGF receptor). Although uterine tissues were not evaluated, the results suggest that lubiprostone would be much less potent in inducing uterine contractions than misoprostol and the natural prostaglandins (conclusion of Dr. Reid, DRUP).

Among the non clinical studies, those conducted in pregnant guinea pigs may be the most sensitive animal model to predict possible abortifacient activity in humans. This is because, in pregnant guinea pigs, prostaglandin stimulation of the uterus is possible even in the presence of progesterone. (In pregnant humans and primates, sensitivity of the uterus to prostaglandins increases as gestation progresses.) Dr. Reid considered the findings from the guinea pig study to be suggestive of abortifacient effects. She states in her memorandum that "The PT reviewers in Gastroenterology consider the guinea pig study suggestive of abortifacient effects, the rat study irrelevant due to its lack of sensitivity to prostaglandins, and the monkey study suggestive, but potentially inadequate based on dose selection." Dr. Reid also said that "I concur with the conclusions of the Gastroenterology PT regarding the assessment of the studies in pregnant rats and guinea pigs. While I do agree that the monkey study was inadequate based on the unorthodox method used for dose selection and the lack of any pharmacokinetic data to determine exposures relevant to humans, I do not see evidence suggesting that lubiprostone acts as an abortifacient in monkeys at the doses tested..." Dr. Reed's complete memorandum is included as an attachment to this clinical consultation. Her final conclusion and recommendation are as follows:

> "While lubiprostone may have played a role in the abortions observed in guinea pigs and monkeys, the data is not conclusive. In guinea pigs the abortions could have been related to maternal toxicity, and the single abortion and early deliveries in monkeys are within historical control limits and could have been spontaneous. In vitro pharmacology data would indicate that when compared to natural prostaglandins and misoprostol, lubiprostone has only weak agonist activity in guinea pig ileum smooth muscle. The only definitive study would be a comparison of lubiprostone with a known abortifacient."
>
> "It is my recommendation that all reproductive data generated in the rat, rabbit, guinea pig — be included in labeling, —
> — Other drugs which cause fetal

death but do not cause teratogenicity are generally labeled under Pregnancy Category C, and not recommended for use in pregnant women."

Clinical Studies in NDA 21-908

NDA 21-908 included nine studies designed to evaluate the safety and efficacy of RU-0211. The two primary safety and efficacy trials were double-blind, randomized, multicenter, placebo controlled studies. Study SC0131 had 242 subjects randomized to either active drug or placebo and Study SC0232 had 237 subjects randomized to either active drug or placebo. The duration of treatment in each primary study was four weeks. A follow-up telephone interview took place on Day 43 which was approximately 14 days after the administration of study drug was completed. Information was collected regarding adverse events during the telephone interview but possible pregnancy information was not specifically elicited.

Inclusion criteria required that all female subjects be 18 years of age or older and not be pregnant or breast-feeding. A female of childbearing potential not using adequate contraceptive protection during the trial was an exclusion criteria. Oral contraceptives, Depo Provera® or Norplant® must have been used for at least three months prior to randomization; intrauterine device, sterilization or a double-barrier method or other acceptable methods of birth control were to be used during the trial. Inclusion/exclusion criteria did not specify how long adequate contraception was to be used after study drug completion. Serum pregnancy tests were performed at baseline and at completion of study drug on study Day 29.

None of the clinical trials was designed to assess the abortifacient potential of lubiprostone nor do the data from the two primary trials submitted under this NDA provide any evidence of abortifacient activity associated with lubiprostone in humans. Absence of such evidence, however, cannot be interpreted as implying that there is no risk of an abortifacient potential for lubiprostone.

Specific Questions from DGP

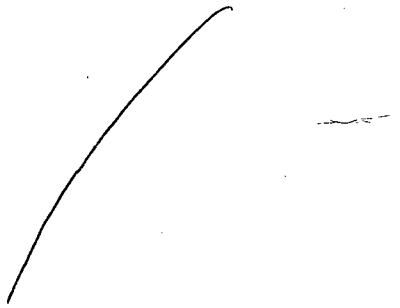
1. Can you provide guidance as to the adequacy of the clinical trial design to capture the abortifacient adverse events of concern regarding this drug?

None of the clinical trials submitted in NDA 21-908 to support the safety and efficacy of lubiprostone were designed to assess the abortifacient potential of the drug. Inclusion criteria excluded women who were at risk for pregnancy if they were not using an acceptable method of contraception.

Four pregnancies were reported during the clinical development of lubiprostone under IND 59,623. Of these, two subjects had healthy babies, one subject had a baby with clubbed feet (according to the investigator possibly related to the study drug), and one subject was lost to follow-up.

The absence of any reports of spontaneous abortion or miscarriage in women in the clinical trials does not imply that lubiprostone is devoid of abortifacient potential.

2. Can you provide additional clinical trial requirements for evaluation of the abortifacient safety concerns?



3. Can you provide guidance to increase the probability of safe use in the drug label given the drug's potential as an abortifacient?

DRUP recommends that the drug not be used in pregnant women. This could be addressed either as a Warning in labeling. The Division of Gastroenterology Products should weigh the benefits of treating chronic constipation in pregnancy with the potential risk that lubiprostone may have abortifacient activity.

Since safety in pregnant women has not been demonstrated by the Applicant, the drug should receive a Pregnancy Category C designation. Drugs where studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women are assigned a Pregnancy Category C and not recommended for use in pregnancy.

DGP will need to decide is the most appropriate designation.

The main safety concern is probably inadvertent exposure to lubiprostone in early pregnancy when the drug might be used by a woman who did not know that she was pregnant. It is difficult to ensure that this will not happen unless there is restricted distribution and very close monitoring of the use a drug such as the program for Accutane. DRUP does not believe that such a program is warranted for lubiprostone based on the information reviewed for this consultation.

Labeling for lubiprostone should include many of the recommendations presently found in the boxed warnings for misoprostol. These include

- a negative pregnancy test within 2 weeks prior to beginning therapy,
- the use of effective contraceptive measures, and
- ensuring that the women receive adequate information about the potential risks of lubiprostone for a pregnancy.

The misoprostol boxed warning also includes a statement that after a negative pregnancy test, women should wait until their next menstrual period before beginning use of the product. This provides some additional assurance that an early pregnancy is not

inadvertently missed but may not be necessary for lubiprostone based on presently available data.

This Division also recommends that all reproductive data generated in the rat, rabbit, guinea pig — studies be included in labeling.

4. If pre-clinical data suggests that this drug has abortifacient potential' do you recommend any further clinical study to evaluate this effect? If you do' should these studies should be done prior to approval or as Phase 4 commitments?

The preclinical data regarding the abortifacient potential of lubiprostone is inconclusive. However, DRUP does not believe that any further preapproval clinical studies are needed in regard to the abortifacient potential of lubiprostone. In our response to Question No. 2, we briefly described a clinical study that might provide useful information and that could be conducted as a Phase 4 commitment. DRUP is not recommending that the Applicant conduct such a study but rather defers this decision to DGP.

5. Can you provide guidance with a risk management plan for this drug regarding its abortifacient potential?

Based on the information reviewed by DRUP for this consultation, adequate risk management could likely be obtained by clear and appropriate labeling of the potential risks associated with the use of lubiprostone in —he physician — components of labeling.

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

/s/

Ronald Orleans
12/23/2005 03:06:36 PM
MEDICAL OFFICER

Scott Monroe
12/23/2005 03:10:01 PM
MEDICAL OFFICER
I concur with the recommendations of Dr. Orleans.

Daniel A. Shames
12/23/2005 03:31:09 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-908
Submission Code	000
Letter Date	31 March 2005
Stamp Date	31 March 2005
PDUFA Goal Date	31 January 2006
Reviewer Name	Kristen K. Buck, M.D.
Review Completion Date	19 December 2005
Established Name	RU-0211 (lubiprostone)
Trade Name	TRADENAME
Therapeutic Class	Prostaglandin metabolite analogue
Applicant	Sucampo Pharmaceuticals, Inc.
Priority Designation	Standard
Formulation	Oral capsule
Dosing Regimen	24 mcg B.I.D
Proposed Indication	— chronic idiopathic constipation —
Intended Population	Adults age 18 years and older

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few days of treatment and does not increase over time to any appreciable degree. One exception to the above adverse event incidence rate hazard risk is that of peripheral edema. There was an increase of approximately 10% in the hazard rate for peripheral edema from days 22-28 until days 270-365, however; the clinical importance of this increase in relation to RU-0211 treatment seems to be minimal.

The frequency of withdrawal for RU-0211 48 mcg (24 mcg b.i.d.) subjects in the well-controlled group was significantly higher than for placebo subjects. Overall, 1.1% of placebo subjects and 7.7% of RU-0211 48 mcg subjects withdrew because of Gastrointestinal adverse events. The breakdown of Gastrointestinal adverse events in the pooled population that led to withdrawal for at least 1% of subjects was nausea (5.2%), diarrhea (1.5%), abdominal pain (1.5%), and flatulence (1.5%). The types and frequencies of the individual AEs that led to withdrawal were generally similar across the long-term studies, and these results were similar to those observed in the well-controlled group. Gastrointestinal disorders were once again the most common System-Order-Class for AEs leading to withdrawal. Adverse events in the pooled group that led to withdrawal for at least 1% of subjects were nausea (7.9%), diarrhea (1.9%), abdominal pain (1.4%), abdominal distension (1.4%), vomiting (1.4%), headache (3.4%), and dyspnea (1.0%).

The clinical and laboratory data presented in this application including biochemistry, hematology, urinalysis, vital signs and physical examination data appeared clinically acceptable for a population of subjects with chronic idiopathic constipation who are otherwise considered generally healthy.

The effects of lubiprostone (RU-0211) on ECG parameters were evaluated in two studies (Phase I and Phase IIb). RU-0211 at doses of 24, 48, and 72 mcg per day, for 3 weeks, showed no evidence of effect on heart rate, cardiac conduction, cardiac repolarization, or morphological changes.

RU-0211 (lubiprostone) was evaluated in special safety study (bilateral hand X-rays at baseline and at final assessment) to determine whether it had a deleterious effect on bone density following long-term exposure. Although formal lumbar and hip bone densitometry analysis would have provided a more accurate reflection of lubiprostone's effect on bone metabolism, lubiprostone did not appear to cause a negative impact on bone density.

To date, no adequate and well-controlled studies of RU-0211 in pregnant or lactating women have been conducted. Despite the fact that pregnant women were excluded from all clinical trials of RU-0211, and any woman who became pregnant during a study was immediately discontinued from study participation, four pregnancies were reported during the development of RU-0211. Of the four pregnancies, two women had healthy babies, one was lost to follow-up, and one had a baby with bilateral club feet. There was also one ectopic pregnancy reported under IND # — that was noted to have "resolved" during short term follow-up. One limitation of this New Drug Application is the sponsor's non-clinical reproductive and developmental toxicity studies in guinea pigs and rhesus monkeys to determine the abortifacient potential of RU-0211. A detailed explanation of these studies will be provided in the Agency's formal pharmacology reviews. Briefly, both maternal death and fetal loss were seen in the sponsor's guinea pig study. The rhesus monkey study revealed one abortion, however; this study

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The medical officer recommends an approval action be taken for oral RU-0211 48 mcg/day (24 mcg capsules b.i.d.) for the treatment of chronic idiopathic constipation in the adult population. Approval of RU-0211 48 mcg/day (24 mcg capsules b.i.d.) for the treatment of chronic idiopathic constipation is contingent upon the sponsor incorporating the Food and Drug Administration's recommended changes to the RU-0211 drug label and adhering to the required Phase IV commitment studies.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

Based upon the pharmacology/toxicology data established in guinea pigs and rhesus monkeys concerning lubiprostone's potential to cause fetal loss in animals, labeling noting the drug's potential adverse effect in pregnant women and those who could become pregnant should be appropriated.

1.2.2 Required Phase 4 Commitments

The medical officer recommends that the sponsor perform a Phase IV commitment study to determine the safety and efficacy of lubiprostone in the pediatric population. This study should be in accordance with the Pediatric Research Equity Act of 2003.

As RU-0211 (lubiprostone) has not been adequately studied in subjects with renal impairment, the medical officer recommends that the sponsor perform a Phase IV study to assess the need for potential dose adjustment in such subjects.

1.2.3 Other Phase 4 Requests

There are no other Phase IV requests in this New Drug Application.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This application includes three comparative efficacy studies; SC9921, SC0131, and SC0232. Study SC9921 was a multi-center, placebo-controlled, double-blind, parallel-group, Phase IIb study which assessed the safety and efficacy of different doses and dose regimens of oral RU-0211 compared to placebo for relief of constipation. Studies SC0131 and SC0232 were multi-

center, parallel-group, double-blind, placebo-controlled, Phase III studies of 4 weeks duration with identical design and were designated as the pivotal studies for this application. These two Phase III pivotal studies assessed the efficacy and safety of oral 48 mcg RU-0211 compared to placebo for the treatment of constipation. The three aforementioned comparative efficacy studies (SC9921, SC0131, and SC0232) were combined for meta-analyses into a grouping called the Well-controlled Group (WCG) cohort. The WCG cohort enrolled a total of 606 patients (273 placebo, 271 48 mcg RU-0211) in 48 centers across the United States.

This application also includes three long-term safety and efficacy studies; SC01S1, SC01S2 [SP2], and SC02S3. These studies were combined for meta-analyses into a grouping called the Long-term Safety Group (LTS) cohort. The LTS studies; SC01S1, SC01S2 [SP2], and SC02S3 were all multi-center, open-label, Phase III studies which assessed the safety of 48 mcg of RU-0211 as the primary endpoint when administered for 24, 48, and 48 weeks, respectively. The secondary objective of the aforementioned studies was to collect additional efficacy data regarding 48 mcg RU-0211. These three long term safety and efficacy studies enrolled a total of 878 patients in 64 centers across the United States.

Additional supportive studies submitted and reviewed in this application included a Phase I QTc study and a 7 week randomized-withdrawal study.

1.3.2 Efficacy

A total of 1688 subjects (1491 subjects with constipation and 197 healthy volunteers) were involved with the clinical development program of RU-0211 (lubiprostone). Two adequate and well-controlled Phase III efficacy studies demonstrated that administration of RU-0211 24 mcg b.i.d. provides relief of chronic idiopathic constipation in the adult population. Statistical significance was attained for the primary efficacy endpoint; the frequency of spontaneous bowel movements (SBMs) at Week 1, for both pivotal studies. Statistical significance for RU-0211 24 mcg b.i.d. over placebo for the treatment of chronic idiopathic constipation was also observed in the following secondary efficacy variables: frequency of SBMs at Weeks 2, 3, and 4; weekly responder rates (at each week and all weeks); percentage of subjects with an SBM within 24 hours after first dose of study drug; time to first SBM; average stool consistency; average degree of straining; constipation severity; and treatment effectiveness.

The primary efficacy analysis was based upon the frequency rate of spontaneous bowel movements during Week 1. An SBM was defined as any BM that did not occur within 24 hours after rescue medication use. Outlined below are the SBM rate data from the Intent-to-Treat population of the Well-Controlled Group using the Last-Observation-Carried-Forward imputation method.

EXECUTIVE SUMMARY Table 1:

Spontaneous Bowel Movement Frequency Rates+ – Lubiprostone 48 mcg vs. Placebo

Study	Study Arm	Baseline	Week 1	Week 2	Week 3	Week 4	Change In SBM Baseline To Week 1	Change In SBM Baseline To Week 4
SCO131	Placebo N=122	1.50	3.00	3.00	2.00	2.26	1.50	0.76
	RU-0211 N=120	1.50	5.00	4.00	5.00	4.00	**3.50**	**2.50**
	P-value~	0.3579	**0.0001**	**0.0017**	**0.0002**	**0.0002**		
SCO232	Placebo N=118	1.50	3.50	3.00	3.00	3.00	1.50	1.50
	RU-0211 N=119	1.50	5.00	4.00	5.00	4.29	**3.50**	**2.79**
	P-value~	**0.0174**	**<0.0001**	**0.0487**	**0.0004**	**0.0068**		
SC9921	Placebo N=33	1.50	3.00	3.00	3.00	*	1.50	*
	RU-0211 N=32	1.29	5.00	4.00	4.20	*	**3.71**	*
	P-value~	0.9662	**0.0203**	**0.0239**	0.0762			
Pooled	Placebo N=273	1.50	3.00	3.00	3.00	3.00	1.50	1.50
	RU-0211 N=271	1.50	5.00	4.00	5.00	4.07	**3.50**	**2.57**
	P-value~	0.0728	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**		

Reviewer's table, modified from Table 2.7.3.3-3, pages 48 of 108, Summary of Clinical Efficacy
+ Frequency Rates are calculated as 7x [(Number of SBMs) / (Number of Days Observed for that Week)].
* Study SC9921 only has time points up to Week 3.
~ Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

As noted above in the Executive Summary Table 1, the median baseline spontaneous bowel movement frequency rate was 1.50 for placebo subjects in each of the individual studies, whereas for RU-0211 subjects, the median baseline SBM frequency rate was 1.29 in SC9921, and 1.50 in both SC0131 and SC0232. In both pivotal studies (SC0131 and SC0232), the median SBM frequency rates in the RU-0211 group for Weeks 1, 2, 3, and 4 were higher (range: 4.00-5.00) than that in the placebo group (range: 2.00-3.50). The difference between the two groups was statistically significant at Weeks 1 – 4 in SC0131 and SC0232, whereas in SC9921, the difference between the two groups was significant at Week 1 ($p=0.0203$) and Week 2 ($p=0.0239$) but not at Week 3 ($p=0.0762$). In the pooled group, the median baseline SBM frequency rate was 1.50 for both the placebo and RU-0211 48 mcg groups. For Weeks 1 through 4, the difference in SBM frequency rate between the two groups was statistically significant ($p<0.0001$ at each time point).

Treatment with RU-0211 48 mcg proved to be a valuable treatment option for subjects suffering from chronic idiopathic constipation. When comparing the results before and after treatment,

RU-0211 demonstrated a clinically meaningful ≥ 3.5 increase in spontaneous bowel movements at Week 1 (the primary efficacy endpoint) in both of the well-controlled studies. By Week 4, RU-0211 showed persistent clinically efficacy of a ≥ 2.5 increase in SBM in the two pivotal studies. After treatment initiation with RU-0211, the median weekly spontaneous bowel movement frequency was increased and maintained to a value of a least 4.00; a value which corresponds to 1 SBM every 1 to 2 days. Of note, the change from baseline analyses did reveal an appreciable placebo effect. Given that the median changes from baseline in the RU-0211 48 mcg group were always at least 50% greater than the corresponding median changes in the placebo group, and that there were significant differences in SBM frequencies across all three well-controlled studies, evidence still stands to support RU-0211 48 mcg/day as an effective treatment for chronic idiopathic constipation.

The secondary efficacy endpoints were many and included SBM frequency rates during Weeks 2, 3, and 4; SBMs within 24 hours of first RU-0211 dose; Time to first SBM; Responder analyses (at each week and all weeks); Weekly stool consistency; Weekly stool straining; Weekly severity of constipation; Weekly global treatment effectiveness; Weekly abdominal bloating; and Weekly abdominal discomfort.

RU-0211 out-performed placebo in all of their secondary efficacy endpoints. These endpoints revealed that RU-0211 is effective in improving the quality of life in subjects diagnosed with chronic idiopathic constipation. Examples of such quality of life improvements include the SBM response rate within 24 hours of first study drug dose and the improvement in overall stool softening with RU-0211. The average spontaneous bowel movement response rate within the 24 hours after the first study drug dose was 36.9% for placebo vs. 56.7% for RU-0211 48 mcg ($p=0.0024$) in SC0131; 31.9% for placebo vs. 62.9% for RU-0211 ($p<0.0001$) in SC0232. Treatment with RU-0211 48 mcg also indicated and overall softening of stool with an average median improvement of 1.11 units on the 5-point scoring scale at week 1 and 1.26 units at week 4 when compared to baseline. Comparatively, the placebo group revealed an average median improvement of 0.40 units on the 5-point scoring scale at week 1 and 0.55 units at week 4.

There were a total of 606 subjects in the Well-Controlled group cohort (WCG) and 878 subjects in the Long-Term-Safety group cohort (LTS). The demographic characteristics of these study populations were relatively consistent yet somewhat limited across all five Phase III studies. The overall pooled subject population was predominantly female (89.2% - WCG; 86.1% - LTS) and mostly Caucasian (81.6% - WCG; 86.9% - LTS). The averaged proportion of subjects ≥ 65 years old in the pooled population was only 9.7% for the WCG and 18.4% for the LTS group. Despite the fact that the literature cites that chronic idiopathic constipation is more prevalent in females and among older patients, a labeled indication for chronic idiopathic constipation will likely achieve a much broader prescription drug market. A more homogeneous patient population would have allowed for a more accurate efficacy analysis by gender and age and perhaps better estimated the true projected patient population. Having noted the limitations in this application's patient population, RU-0211 was analyzed by the primary efficacy variable in four subpopulations; gender (male, female), race (white, non-white), age [(18 ≤ Age ≤ 50), (50 ≤ Age ≤ 65), (65 ≤ Age)], and IBS status (IBS, Non-IBS). All subpopulations with the exception of the (65 ≤ Age) subgroup revealed statistically significant results for the primary efficacy endpoint favoring RU-0211 24 mcg b.i.d over placebo.

The overall efficacy of RU-0211 (lubiprostone) 24 mcg b.i.d. revealed not only improvements in subject regularity with respect to spontaneous bowel movement frequency, but also contributed to several improvements in subjective quality of life assessments. These improvements were true in short-term studies (up to 4 weeks) and long-term studies (up to 48 weeks).

1.3.3 Safety

The clinical trials within this New Drug Application established a favorable safety and tolerability profile for RU-0211 (lubiprostone) 24 mcg b.i.d. in adult patients with chronic idiopathic constipation.

There were a total of 1688 subjects treated in the overall safety population of which 1321 received active drug and 367 received placebo. Of the 1321 subjects who received active drug, 1119 received RU-0211 48 mcg daily. Four hundred and ninety four subjects remained on lubiprostone 48 mcg daily at 24 weeks(6 months) trial duration and 221 subjects remained on lubiprostone 48 mcg daily at 48 weeks (12 months) trial duration.

No subjects died during the treatment period or follow-up period for any of the studies included in this New Drug Application.

The occurrence of serious adverse events in the studied population was relatively low. Four placebo subjects (1.3%) reported 6 serious adverse events (SAEs), with no SAE preferred term being reported by more than one subject. Thirty-two subjects taking RU-0211 48 mcg (2.9%) reported treatment-emergent SAEs. The reported SAE preferred terms were generally rare, with most being reported by only a single subject. Appendicitis, diverticulitis, syncope, chest pain, and dehydration, all of which were considered unrelated to the study drug, were the only SAE preferred terms reported by more than 1 subject. Two SAEs were considered possibly treatment-related: 1 SAE of diarrhea and 1 SAE subject who became pregnant while taking RU-0211 and gave birth to a child with talipes.

Across all active doses of lubiprostone (N=1175) in the well-controlled group and the long-term safety group studies, the most commonly reported adverse event preferred terms were nausea (30.9%), diarrhea (13.2%), headache (13.0%), abdominal distension (6.8%), abdominal pain (6.8%), and flatulence (5.9%). Comparatively for placebo (N=316), the corresponding reports of adverse events in the above preferred terms were; nausea (5.1%), diarrhea (0.9%), headache (6.6%), abdominal distension (2.8%), abdominal pain (2.2%), and flatulence (1.9%). Besides headache, the most commonly reported adverse events in the active drug group were gastrointestinal in nature, which appear to be representative of the pharmacodynamic effects of lubiprostone.

An analysis of cumulative adverse event incidence rates, time to first adverse events, and a Cox proportional hazard analysis for the occurrence of any adverse event (nausea, diarrhea, abdominal pain, vomiting, headache, dizziness, peripheral edema, fatigue, and dyspnea) indicated; that although subjects taking RU-0211 are more likely than placebo subjects to experience most adverse events, the risk for experiencing any of them is greatest within the first

was deemed inadequate by the Agency's pharmacologists as the dose range chosen was based on rats and was underestimated. Given the lack of controlled human pregnancy data from the clinical trials and the non-clinical animal data, the labeling of RU-0211 should contain labeling noting the drug's potential adverse effect in pregnant women or women who could become pregnant.

The addition of RU-0211 (lubiprostone) 24 mcg b.i.d. to the current armamentarium of treatments for constipation would provide treating physicians a viable alternative to the products currently on the market. The results of the clinical studies of RU-0211 24 mcg b.i.d. provide considerable efficacy along with safety and tolerability data up to 48 weeks duration in a population of patients with chronic idiopathic constipation when compared to no treatment at all. RU-0211 (lubiprostone), like most prescription medications, is accompanied by some mild and often short-lived side effects, however; these effects are balanced by the rapid and sustained relief of chronic idiopathic constipation and the associated symptoms therein.

1.3.4 Dosing Regimen and Administration

The sponsor's proposed dose of lubiprostone is 24 mcg p.o. b.i.d. It is this reviewer's opinion that the adequacy of dose finding in this New Drug Application was appropriate. The sponsor's first Phase I study, SC99101 evaluated placebo and single RU-0211 doses ranging from 6 mcg to 96 mcg. An overall clinical assessment of the frequency, characteristics, and symptoms associated with the dose levels evaluated in this study indicated that 96 mcg was the maximum tolerated single dose of RU-0211. The second Phase I study, SC99102, evaluated t.i.d. doses including (24 mcg t.i.d.) 72 mcg, (30 mcg t.i.d.) 90 mcg, and (36 mcg t.i.d.) 108 mcg. The results of this study revealed that there is a saturation of the pharmacodynamics of RU-0211 at the 24 mcg t.i.d. dose level. The final Phase IIb dose finding study SC9921 evaluated dose levels of 24 mcg/day, 48 mcg/day (24 mcg b.i.d.), and 72 mcg/day (24 mcg t.i.d.) over a 3-week treatment period. The results of this study showed that all 3 doses of RU-0211 were more effective than placebo in relieving constipation, however; the RU-0211 24 mcg group did not yield as many statistically significant results as the higher dose groups. Given the aforementioned data, the sponsor chose the 48 mcg/day dose because it was the minimum effective dose with the most desirable safety profile that produced a statistically significant effect in the primary efficacy analysis and most secondary efficacy analyses.

RU-0211 (lubiprostone) has not been adequately tested in subjects with renal or hepatic impairment; therefore recommendations on dose modifications in such special populations cannot be made.

Overall, other than a reduced C_{max} and an associated increase in the time to C_{max} (T_{max}), the effects of food intake on dosing with RU-0211 appeared to be minimal.

1.3.5 Drug-Drug Interactions

RU-0211 was evaluated for its potential to inhibit 8 specific isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP3C19, CYP2D6, CYP2E1, and CYP3A4) of cytochrome P450 enzymes in pooled human liver microsomes. Incubation of RU-0211 in suspensions of human hepatic

microsomes resulted in no significant concentration-dependent inhibition of any of the isoforms tested. Additionally, RU-0211 did not cause any significant (greater than 40%, or at least 0.4-fold) increases in CYP activity and/or immunoreactive protein at the concentrations evaluated. No significant inhibition of 15-hydroxy-RU-0211 formation by any CYP-specific inhibitor, with the possible exception of lauric acid. Biotransformation to 15-hydroxy-RU-0211 was found to take place in human microsomes independent of P450 isozymes.

The three RU-0211 interaction studies with cytochrome P450 isoforms demonstrated that RU-0211 is not expected to interfere with the metabolism of concomitant drugs. Conversely, the metabolism of RU-0211 should not be influenced by the presence of concomitant drugs, and the biotransformation of RU-0211 to its primary metabolite (15-hydroxy-RU-0211) is independent of cytochrome P450 enzymes.

1.3.6 Special Populations

- Safety and effectiveness of RU-0211 (lubiprostone) in pediatric patients has not been established. The sponsor requested, and was granted a deferral of pediatric studies in this New Drug Application.
- The clinical studies for RU-0211 (lubiprostone) included an adequate proportion of subjects aged 65 and older (9.7% - Well-controlled study cohort; 18.4% - Long-term safety cohort). The results for the primary efficacy endpoint between RU-0211 and placebo in this age cohort were not statistically significant. Despite the lack of statistical significance, the actual observed values of effectiveness provide evidence that RU-0211 48 mcg achieved clinical meaningfulness and performed equally well in the 65 and older subgroup. The results of the primary endpoint were clinically relevant as they showed an increase of 4 SBM/week by week 1 and similarly by week 4. The sponsor's responder analysis (responder defined as a subject with $\geq$ 4 SBM per week) also showed that the mean SBM frequency rates were higher for weeks 1 – 4 in subjects older than 65 taking RU-0211 48 mcg than those age-matched subjects taking placebo. The sponsor's all-weeks change-from-baseline responder analysis also indicated that subjects $\geq$ 65 years of age had an increase in SBM by week 4 of 56.5% for RU-0211 vs. 34.5% for placebo.
- RU-0211 has not yet been adequately studied in subjects who have **renal impairment.**
- RU-0211 has not yet been adequately studied in subjects who have **hepatic impairment.**
- There have been no adequate and well-controlled studies of RU-0211 (lubiprostone) in pregnant women.
- The excretion of RU-0211 or its metabolites in the milk of **nursing mothers** has not yet been evaluated.

2 INTRODUCTION AND BACKGROUND

Constipation, generally defined as infrequent and difficult passage of stool, is one of the most common disorders suffered by Americans. It affects between two and twenty-seven percent of the population in Western countries. In the United States, it results in more than 2.5 million visits to physicians and 92,000 hospitalizations annually. Factors contributing to the

development of constipation include inadequate fiber in the diet, lack of exercise, neurological and systemic disorders and problems with colon, rectum, and/or intestinal function. Other contributing factors include side effects from medication, particularly pain medications, antidepressants, antacids, antispasmodics and blood pressure medications. Other contributing factors include side effects from medication, particularly narcotic analgesics, antidepressants, anticholinergics, antispasmodics and antihistamines. Chronic constipation is thought to be a disorder of colonic motility that is present for at least twelve weeks (non-consecutively) out of the year. Chronic idiopathic constipation is hallmarked by infrequent bowel movements that are often difficult to evacuate. Regardless of the defining criteria, constipation is more likely to affect females than males and more likely to occur in older patients, showing an exponential increase after the age of 65. The actual occurrence of constipation is likely higher than reported, as many individuals suffer at home without seeking professional care.

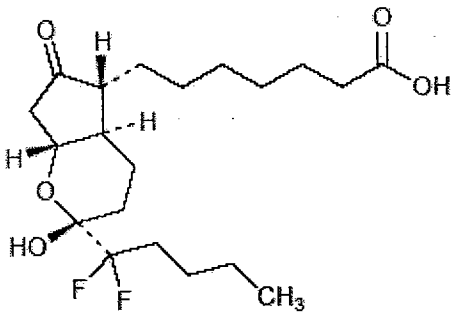
A precise quantitative definition of constipation has been difficult to establish due to the wide range of perceived "normal" bowel habits, as well as the diverse array of symptoms and signs associated with constipation. Currently, the most widely accepted definition of constipation is the one established by the Rome II criteria which include:

> At least 12 weeks, which need not be consecutive, in the preceding 12 months of 2 or more of:
>
> - Straining in more than one quarter of defecations;
> - Lumpy or hard stools in more than one quarter of defecations;
> - Sensation of incomplete evacuation in more than one quarter of defecations;
> - Sensation of anorectal obstruction/blockage in more than one quarter of defecations;
> - Manual maneuvers to facilitate more than one quarter of defecations (e.g., digital evacuation, support of the pelvic floor; ***and/or***
> - Less than 3 defecations per week.
>
> Loose stools are not present, and there are insufficient criteria for irritable bowel syndrome (IBS).

The term "idiopathic" constipation relates to the fact that there is no known cause for the constipation (i.e., not due to other diseases or drugs). The currently available treatments for chronic idiopathic constipation leave considerable room for improvement, in that the milder, better tolerated agents are less effective or have a longer time to onset of relief, while the stronger agents that can produce quicker relief are often generally associated with undesirable side effects. Goals of therapy are to provide a fast-acting alternative which is safe and effective for both short-term and long-term treatment.

2.1 Product Information

Chemical structure of RU-0211



Lubiprostone (RU-0211) is a unique prostaglandin E_1 metabolite analogue with an Agency regulatory history dating back to its original IND submission (#59,623) in December 1999. Lubiprostone's drug substance is a crystalline compound with a molecular weight of 390.46 and a molecular formula of $C_{20}H_{32}O_5F_2$. RU-0211 drug product for oral administration is formulated in a soft gelatin capsule with liquid contents of RU-0211 and a medium-chain fatty acid triglyceride (MCT).

Lubiprostone is classified as a locally acting chloride channel activator that promotes a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating ClC-2, which is a normal constituent of the apical membrane of the human intestine. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine thereby increasing the passage of stool and alleviating symptoms associated with chronic idiopathic constipation.

2.2 Currently Available Treatment for Indications

Currently Approved Over-the-Counter Products

- **Bulk-forming laxatives** generally are considered the safest and most mild treatments but they are not always efficacious in relieving constipation and can interfere with absorption of some medicines. These laxatives, also known as fiber supplements, are taken with water. They absorb water in the intestine and make the stool softer. Brand names which usually are made from bran or psyllium include Metamucil, Citrucel, Konsyl, and Serutan.

- **Stimulants** cause rhythmic muscle contractions in the intestines. Brand names include Correctol, Dulcolax, Purge, and Senokot. Studies suggest that phenolphthalein, an ingredient in some stimulant laxatives, might increase a person's risk for cancer. The Food and Drug Administration has proposed a ban on all over-the-counter products containing phenolphthalein. Most laxative makers have replaced or plan to replace phenolphthalein with a safer ingredient.

- **Stool softeners** provide moisture to the stool. These laxatives are often recommended after childbirth or surgery. Products include Colace and Surfak.
- **Lubricants** grease the stool enabling it to move through the intestine more easily. Mineral oil and glycerin suppositories are the most common examples.
- **Saline laxatives** act like a sponge to draw water into the colon for easier passage of stool. Laxatives in this group include Milk of Magnesia, Citrate of Magnesia and Haley's M-O.
- **Osmotic Agents** draw water into the lumen into the lumen of the bowel and effectively increase the overall stool volume. These agents are made from nonabsorbable inorganic salts or sugars. Agents in this group include Magnesium citrate, Sodium citrate.
- **Enemas** empty the distal colon or rectum of retained solid material through mechanical distention of the bowel. Tap water or other osmotic, stimulant or irritative substances can be used.

Currently Approved Prescription Products

- *Miralax*® is a synthetic polyglycol that acts as an osmotic agent which causes water to be retained within the stool. Miralax thereby softens stool and is indicated for the treatment of occasional constipation. The recommended dose is 17 grams (about 1 heaping tablespoon) of powder per day (or as directed by a physician) in 8 ounces of water, juice, soda, coffee, or tea. Two to four days may be required to produce a bowel movement. Miralax should be used for 2 weeks or less. Prolonged use of Miralax may result in electrolyte imbalance and dependence. Nausea, abdominal bloating, cramping and flatulence may occur. High doses may produce diarrhea.[1]
- *Zelnorm*® is a $5HT_4$ (serotonin type 4) agonist that acts as a promotility agent in the gastrointestinal tract by mimicking the natural effects of serotonin through normalization of impaired gut motility, inhibition of visceral sensitivity, and stimulation of intestinal secretion. Zelnorm is indicated for the treatment of patients less than 65 years of age with chronic idiopathic constipation. The effectiveness of Zelnorm in patients over 65 years of age with chronic idiopathic constipation has not been established. The recommended dose is 6 mg by mouth twice daily. Diarrhea was the most common adverse event in placebo controlled trials and the prescribing information for Zelnorm carries a warning that hypovolemia, hypotension, and syncope may occur as well as ischemic colitis.[2]

2.3 Availability of Proposed Active Ingredient in the United States

RU-0211 is a new molecular entity that is being reviewed for the first time in the United States. RU-0211 has never been reviewed, approved, or marketed in any other country.

2.4 Important Issues with Pharmacologically Related Products

Lubiprostone is a prostaglandin E1 analogue and a new molecular entity. It is the first in a new class of drugs that promotes a chloride-rich intestinal fluid secretion through activation of chloride channels on the apical membrane of the human intestine. The review team has carefully scrutinized the lubiprostone database and the potential for this drug to have similarities to other synthetic prostaglandins (i.e., misoprostol, Cytotec®).

2.5 Pre-submission Regulatory Activity

- The original IND (#59,623) for RU-0211 was submitted to the Agency December 29, 1999.
- On April 11, 2001 an End-of-Phase II meeting was held between the Agency and the sponsor (Sucampo) to discuss plans for Phase III development including primary efficacy analysis, duration of long-term safety exposure, and the number of subjects exposed to long term treatment. The Agency and the sponsor agreed on the recommended Phase III dose of 48 mcg/day, administered as 24 mcg twice daily (b.i.d.).
- The sponsor then conducted two pivotal studies, three long-term safety and efficacy studies, a 7-week randomized withdrawal efficacy and safety study, a Phase I food effect study, and a Phase I definitive QTc study.
- On May 24, 2004 a pre-NDA meeting was held between the Agency and the sponsor which mainly discussed the abortifacient potential of RU-0211 and the possibility of any QT issues with the drug. As recommended by the Agency, the sponsor conducted a guinea pig and a monkey study to evaluate the abortifacient potential of lubiprostone. These study reports are included in this submission.
- The NDA was submitted to the Agency on March 31, 2005.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The drug substance RU-0211 is a new molecular entity with 4 chiral centers. RU-0211 is synthesized

RU-0211 drug substance occurs as white crystals or crystalline powder in solid phase.

RU-0211 is insoluble in water, but soluble in organic solvents such as ethanol and MCT. The drug product was developed as a soft gelatin capsule containing 24 mcg of liquid lubiprostone in MCT.

No degradation products were observed in drug substance under the proposed storage condition — and drug product in room temperature. The — impurities are controlled — — The drug substance is packaged in a — . The shelf life for the drug substance is granted for — based on the current stability data, however; it can be extended provided the updated stability data. The drug product is packaged in HDPE bottle with 100 capsules and — The expiration for the drug product is — under 25 °C/60% RH based on the stability data.

3.2 Animal Pharmacology/Toxicology

RU-0211 has undergone extensive animal testing for general pharmacologic, toxicologic, genotoxic, and antigenic effects in rats, dogs, mice, guinea pigs and rhesus monkeys.

Pharmacology studies revealed that RU-0211 caused no changes in the central nervous system, respiratory system, or circulatory system of anesthetized animals, and had only limited effect on inducing smooth muscle contraction. In addition, unlike prostaglandins, the sponsor noted that RU-0211 had no effect on platelet aggregation.

Single and repeated dose toxicology studies with oral RU-0211 revealed low toxicity in all species. Generally, the effects seen were consistent with the known pharmacological activity of the drug including diarrhea (rats, mice and dogs) and vomiting (dogs; other species indicated a lower food consumption and, together with vomiting, may be reflective of nausea observed in the clinical trials). Additionally, RU-0211 was thought by the sponsor to have no toxicological effects on fertility, *in utero* development, or adverse effects concerning genotoxicity, carcinogenicity, or antigenicity.

Carcinogenicity studies conducted in rodent species indicated hyperplasia and proliferative lesions of the non-glandular stomach, however; there were no tumorigenic effects in mice (up to 0.5 mg/kg/day) or rats (up to 0.4 mg/kg/day). The stomach of the dogs treated with RU-0211 for 39 weeks at doses up to 0.05 mg/kg/day did not indicate any gross or microscopic changes. Reproductive and developmental toxicity studies were conducted in rats at doses that were at or exceeded the maximum tolerated doses for these studies. The results indicated that at doses below the maternally toxic doses, there was no impact on any endpoint. However, at doses that were clearly maternally toxic, there were effects on deliveries, neonatal survival, and *in utero* growth and development. Though the toxicities seen were thought due to exaggerated pharmacologic effects, the severity of the signs in the pregnant animals at the doses used was sufficient to result in adverse effects on the dams and consequently on the offspring. These signs included death, substantially reduced weight gain during pregnancy and/or weight loss, and reduced food consumption. Based on the toxicity studies conducted, the sponsor identified no

toxicities that were considered to be serious or that would limit the use of the drug for the intended indication. Reproductive toxicology will be discussed in detail in section 7.1.14.

In a definitive study to evaluate the abortifacient effect of RU-0211 in guinea pigs two replicates of 12 (for a total of 24) time-mated female guinea pigs were assigned to receive vehicle (MCT) or RU-0211 (0.001, 0.01 or 0.025 mg/kg/day) from days 40 through 53 of presumed gestation. One death occurred in each of the vehicle and 0.001 mg/kg/day dose groups after administration of 2 to 4 doses. These deaths were attributed to trauma from the dosing event. There were 2 abortions in the 0.01 mg/kg/day dose group that occurred after administration of 14 doses of RU-0211 and were presumed to be spontaneous events. In addition, there were several (4) deaths and/or moribund sacrifices in the 0.025 mg/kg/day dose group that occurred after 5 to 11 doses of RU-0211 had been administered; a total of 5 abortions occurred in this group after administration of 8 to 14 doses of RU-0211. Both the deaths and abortions in this group were preceded by reductions in body weights and adverse clinical signs (including un-groomed coat, localized alopecia, cold to touch, red perivaginal substance and decreased motor activity). Seven of the nine deaths, moribund sacrifices and abortions in the 0.025 mg/kg/day dose group were presumably related to RU-0211 administration because they occurred in the highest dose group in the presence of maternal toxicity. Maternal toxicity, as evidenced by significant reductions in body weight and increased numbers of adverse clinical observations that were considered to be test-article-related, occurred only in the 0.025 mg/kg/day group. An increase in the number of deaths and abortions was also seen in this dose group. Lower doses did not significantly increase adverse effects compared to the untreated and treated controls. Based upon the data in this study, the sponsor proposes thatRU-0211 is not an abortifacient, however; when apparent environmental, stress-induced maternal toxicity is noted in this animal model, death, spontaneous abortions, and other clinical findings may become evident.

A study to evaluate the abortifacient effect of RU-0211 when administered orally *via* capsule was conducted in pregnant rhesus monkeys treated during late gestation. Time-mated rhesus monkeys were assigned to one of three treatment groups to receive vehicle medium chain fatty acid triglyceride (MCT) or RU-0211 (0.01 or 0.03 mg/kg/day) from gestation day (GD) 110 through GD 130. No monkeys died, and no abnormalities were observed in clinical signs, food consumption, body weight, or serum progesterone concentrations in any group. Early delivery on GD 149 was observed in 1 monkey in the 0.03 mg/kg/day group and in 1 monkey in the 0.01 mg/kg/day group. The neonates were delivered naturally and alive. No lactation abnormalities were observed in these non-human primates. No abnormalities were observed in body weight, external features or general health condition in these neonates. Accordingly, these deliveries were judged to be normal. An abortion on GD 141 was observed in 1 monkey in the 0.01 mg/kg/day group. This, however; was considered incidental by the sponsor because the incidence of this premature delivery (before GD 150) was within the range of the historical control data of the laboratory (mean: 12.9%) and no abortions occurred in the 0.03 mg/kg/day group. No test-article-related changes were noted in fetal external examination, fetal body weight, placental examination, or placental weight in the 0.01 or 0.03 mg/kg/day groups. Under the conditions of this study, the sponsor concluded that RU-0211 is not an abortifacient.

Medical Officer's Comments

The medical officer does not completely agree with the sponsor's conclusions from these studies. There is further discussion regarding the reproductive toxicology of RU-0211 within this clinical review under the Human Reproductive and Pregnancy Data section (7.1.16). A comprehensive review of the reproductive toxicology of RU-0211 is also contained within the Agency's Clinical Pharmacology formal review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data used in this review are the submitted clinical trials with NDA 21-908 supporting lubiprostone capsules as indicated for the relief of chronic idiopathic constipation

double-blinded, multi-centered, placebo-controlled, pivotal efficacy trials (Studies SC0131 and SC0232) in patients with chronic idiopathic constipation were included and reviewed in this New Drug Application. Three long-term, open-label, safety and efficacy trials (Studies SC01S1, SC01S2, and SC01S3) were also reviewed as well as a Phase IIb dose-finding study, a Phase I food effect study, a Phase I QTc study and a 7-week randomized withdrawal study.

4.2 Table of Clinical Studies

Study ID	Number of Study Centers Location(s)	Study Start Enrollment Status, Date Subjects Treated/ Planned	Design Control Type	Study Objective	Study & Control Drugs Dose, Route & Regimen	Number of Subjects Treated/ Completed	Duration	Gender F/M Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
99101	1 Belfast, Northern Ireland	February 1999 Completed; March 1999 17/16[1]	Randomized, rising dose tolerance, leap frog Placebo	Safety, tolerance, pharmacokinetics, pharmacodynamics	**Oral RU-0211** Group 1: Period 1, 6 µg Period 2, 24 µg Period 3, 72 µg Group 2: Period 1, 12 µg Period 2, 48 µg Period 3, 96 µg **Oral Placebo** Group 1 Group 2	 6/6 6/6 6/6 6/6 6/6 6/6 2/2 2/2	3 single doses per subject, separated by a 7-day washout	7/10 mean = 26 years (range = 18-44 years)	Healthy volunteers Males and females aged 18-45 years judged to be in good health	Adverse events, laboratory values
99102	1 Belfast, Northern Ireland	May 1999 Completed; July 1999 26/24[2]	Double-blind, multiple, rising oral dose Placebo	Safety, tolerance, pharmacokinetics, pharmacodynamics	**Oral RU-0211** Group 1: 24 µg t.i.d. Group 2: 30 µg t.i.d. Group 3: 36 µg t.i.d. **Oral Placebo** Group 1 Group 2 Group 3	 6/6 6/6 6/6 2/2 2/2 2/2	7 days (t.i.d. dosing for 6 days with a single dose on Day 7)	13/13 mean = 24 years (range = 18-37 years)	Healthy volunteers Males and females aged 18-45 years judged to be in good health	Adverse events, laboratory values

SC01S1	20 United States[5]	September 2001 Completed; August 2002 242/240	Double-blind, randomized, multicenter Placebo	Efficacy and safety	**Oral RU-0211** 48 µg[7] **Oral Placebo**	120/106 122/118	4 weeks	217/25 48 years (range = 22-80 years)	Constipation On average, < 3 SBMs/ week and 1 associated symptom	SBM frequency during Week 1
SC01S1	22 United States[6]	November 2001 Completed; May 2003 306/300	Open-label, multicenter None	Safety	**Oral RU-0211** 48 µg[7]	305/165	24 weeks	274/32 49 years (range = 19-80 years)	Constipation On average, < 3 SBMs/ week and 1 associated symptom	Adverse events, laboratory values, vital signs, physical exam
SC01S2 (Study Period 1)	8 United States[6]	December 2001 Completed; January 2003 128/120	4-week active treatment (AT); 3-week double-blind, randomized withdrawal (RW); multicenter None during AT; Placebo during RW	Evaluation of post-treatment response	4-week AT **Oral RU-0211** 48 µg[7] 3-week RW **Oral RU-0211** 48 µg[7] **Oral Placebo**	128/87 45/41 42/41	4 weeks 3 weeks	104/24 50 years (range = 20-82 years)	Constipation On average, < 3 SBMs/ week and 1 associated symptom	Relapse, as assessed by responder analyses during RW period of subjects who were responders during AT period
SC01S2 (Study Period 2)	20 United States[6]	December 2001 Completed; October 2003 348/300	Open-label, multicenter None	Safety	**Oral RU-0211** 48 µg[7]	248/127	48 weeks	208/40 51 years (range = 20-85 years)	Constipation On average, < 3 SBMs/ week and 1 associated symptom	Adverse events, laboratory values, vital signs, physical exam
SC02S2	20 United States[5]	October 2002 Completed; September 2003 237/240	Double-blind, randomized, multicenter Placebo	Efficacy and safety	**Oral RU-0211** 48 µg[7] Oral Placebo	119/99 118/107	4 weeks	209/28 46 years (range = 20-81 years)	Constipation On average, < 3 SBMs/ week and 1 associated symptom	SBM frequency during Week 1
SC02S3	22 United States[5]	February 2003 Completed; August 2004 324/309	Open-label, multicenter None	Safety	**Oral RU-0211** 48 µg[7]	324/153	48 weeks	275/49 52 years (range = 21-85 years)	Constipation On average, < 3 SBMs/ week and 1 associated symptom	Adverse events, laboratory values, vital signs, physical exam

Sponsor's table, taken from Summary of Clinical Efficacy for RU-0211, 2.7.3, pages 13-15

Results of the two pivotal studies and three long term safety and efficacy studies will be presented and discussed in detail in the following sections of this review.

4.3 Review Strategy

The medical reviewer thoroughly reviewed the sponsor's two pivotal studies and three long term safety and efficacy studies both individually and as pooled data. The medical reviewer evaluated such studies with equal regard to efficacy and safety. The sponsor's 7-week randomized withdrawal study, a Phase I food effect study, and a Phase I definitive QTc study were also reviewed in the integrated safety and efficacy analyses and highlighted by the medical officer throughout this review.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was consulted by the Agency for this New Drug Application. The Division of Scientific Investigations concluded that Sucampo Pharmaceuticals and their investigators adhered to the applicable statutory requirements and Food and Drug Administration regulations governing the conduct of clinical investigations and the protection of human subjects.

4.5 Compliance with Good Clinical Practices

According to the sponsor, all of the studies were conducted in accordance with U.S. Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), IRBs (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). All studies were also conducted in accordance with U.S. Title 21 CFR on Good Clinical Practices (GCPs) which is consistent with the ethical principles set forth the Declaration of Helsinki, the International Conference on Harmonization, and the Food and Drug Administration.

4.6 Financial Disclosures

The sponsor provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The sponsor also certified that each clinical investigator had no proprietary interest in this product or significant equity in the sponsor as defined by 21 CFR 54.2(b). As defined by 21 CFR 54.2(f), the sponsor certified that no clinical investigator was the recipient of any significant payments of any other sorts.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Pharmacokinetics were thoroughly evaluated in this New Drug Application. ADME studies were performed in mice, rats, rabbits, dogs, and monkeys. The sponsor noted that neither age, race, height, weight, nor gender had any correlations between Cmax and/or AUC_{0-t}.

RU-0211 has a well-defined pharmacokinetic profile. The non-clinical pharmacokinetic (PK) *in vivo* studies have shown that, across species, 34 to >70% of an oral dose of ^{3}H-RU-0211 is absorbed; however, little or no radioactivity is associated with the parent compound. Excretion studies indicate that in animals, 73 to 95% of absorbed radioactivity was excreted by 48 hours. The major route of excretion was *via* the urine in most species, including humans. Approximately 60% of a radiolabeled dose was recovered in the urine by 24 hours post dose and was essentially complete by that time. By 168 hours post dose, radioactivity excreted in urine accounted for a mean of 62.9% of the total dose, which indicated that a minimum of 63% of the administered radioactivity was absorbed. The *in vitro* plasma protein binding of RU-0211 is >90%, and does not appear to be dependent on concentration or gender. The extent of protein binding is not sufficient to cause binding interactions with highly bound drugs that may be concomitantly administered. Tissue distribution after an oral dose of ^{3}H-RU-0211 was primarily detected in the gastrointestinal contents and was largely eliminated within 48 hours after dosing

RU-0211 is rapidly and extensively metabolized within the gastrointestinal tract, which is consistent with the low or undetectable concentrations of unchanged RU-0211 in the plasma after oral administration. The metabolic pathway of RU-0211 is similar across species, including humans. Several metabolites of RU-0211 have been evaluated for the ability to enhance fluid

secretion into the intestine. As mentioned above, only one (15- hydroxy-RU-0211; M3) retains fluid secretion activity similar to that of the parent drug; all others are devoid of this activity at oral doses as high as 10 mcg/kg. Although there is significant metabolism of RU-0211 to 15-hydroxy-RU-0211 (M3) in human microsomes, the process does not appear to be mediated *via* human cytochrome P450; instead it appears to be mediated *via* reductase. Additional studies indicate that RU-0211 does not inhibit, nor does it induce, any of the major human isozymes of cytochrome P450. Thus, RU-0211 is not likely to cause metabolism-based drug interactions.

5.2 Pharmacodynamics

The pharmacodynamic effects of orally administered RU-0211 are local and are due to the highly selective and potent activity on ClC-2, a Cl- channel which is found on the luminal (apical) side of the intestine. RU-0211 is a potent and selective activator of ClC-2. Activation of this chloride channel, which is located on the intestinal epithelial cell, increases chloride transport into the lumen of the intestine, enhances fluid secretion into the bowels and improves fecal transit. Mechanistic studies indicate that this activation of ClC-2 is *via* a protein kinase-A independent mechanism. In addition, several studies have indicated that since the activation of chloride channels by RU-0211 (or it's only known active metabolite, 15-hydroxy RU- 0211; M3) occurs only on the apical (luminal) membrane; there was no effect of either on the basolateral membrane. This indicates that any RU-0211 and/or 15-hydroxy-RU-0211 in the plasma will not cause an effect on the intestine by activating channels located on the basolateral (blood) membrane.

Activation of ClC-2 increases Cl- transport into the lumen, enhances fluid secretion into the bowels and improves fecal transit without altering serum electrolytes. Pharmacodynamic effects of RU-0211 are observed with doses as low as 1 mcg/kg in mice and 0.5 mcg/kg in rats.

RU-0211 has very little activity on prostaglandin E type-1 and prostaglandin F receptors, but does have some activity on prostaglandin E type-2 and prostaglandin E type-3 receptors. Quantitatively, the activity of RU-0211 at the prostaglandin E type-2 and prostaglandin E type-3 receptor sites was approximately 5% and 2% of that of misoprostol, respectively. Thus, overall, the prostaglandin receptor profile of RU-0211 is weak, and RU-0211 is not anticipated to significantly induce activities known to be mediated *via* these receptors.

Several animal models have been used to evaluate the gastrointestinal effects of RU-0211. These studies demonstrated the ability of a single dose of orally administered RU-0211 to increase electrolyte and intestinal fluid secretion without altering serum electrolyte levels. In addition, a single oral dose of RU-0211 was demonstrated to improve fecal transit in an animal model of morphine-induced constipation, without altering the analgesic effects of morphine, and demonstrated significantly more potency than several conventional laxatives tested in the same animal model.
Several metabolites of RU-0211 have been evaluated for intestinal fluid secretion activity. These studies indicate that metabolite M3 has an intestinal fluid secretion activity similar to RU-0211, while the others are devoid of this activity.

RU-0211 also does not inhibit platelet aggregation and has only limited effects on contractions in smooth muscle preparations, including isolated ileum, uterus, and trachea. In safety evaluations, RU-0211 had no remarkable effects in the canine Purkinje fiber assay. In addition, a single dose of RU-0211 has shown no effects on the central nervous system, renal system, respiratory system or circulatory system in anesthetized animals. Furthermore, there were no effects on QTc intervals in dogs that received repeated doses of RU-0211 for up to 39 weeks.

5.3 Exposure-Response Relationships

As RU-0211 was originally planned to be marketed as an orally administered product, all clinical dose-response studies for RU-0211 were evaluated via this route of administration

The **Phase I study 99101** was a first-in-man study which employed a randomized, placebo-controlled, single, rising-dose tolerance, "leap frog" design involving 2 groups of 8 healthy volunteers. The subjects were given oral doses of RU-0211 ranging anywhere from 6 mcg/day to a maximum of 96 mcg/day. The primary objective of this study was to determine the safety and tolerability of oral RU-0211 and to evaluate the pharmacokinetic profile following single doses. Results of this study demonstrated a dose-dependent behavior in the total number of bowel movements in the 24 hours after dosing, the characteristics of the bowel movements, symptoms associated with the bowel movements, and the severity of those symptoms. Results of the study indicated that there was a noticeable increase in pharmacodynamic effects when the RU-0211 was increased from 24 mcg to 48 mcg/day, and the maximum tolerated single dose based on pharmacodynamic results, associated symptoms, and the severity of those symptoms was 96 mcg/day.

The **Phase I study 99102** employed a randomized, placebo-controlled, multiple, rising-dose tolerance design involving 3 groups of 8 healthy volunteers. The subjects took study medication that was either placebo t.i.d. or oral RU-0211 t.i.d. up to a maximum of 108 mcg/day. RU-0211 daily doses included 72 mcg (24 mcg t.i.d.), 90 mcg (30 mcg t.i.d.), and 108 mcg (36 mcg t.i.d.). The primary objective was to determine the maximum tolerated dose of oral RU-0211 when administered t.i.d. for six days as well as to evaluate the pharmacokinetic profile of RU-0211 following single doses. Results of this study demonstrated a lack of additional pharmacodynamic effects at doses above 24 mcg t.i.d. Specifically, the total number of bowel movements and the incidences of loose stools and diarrhea were both highest at the 24 mcg t.i.d. dose level and decreased at the higher dose levels. It was therefore concluded that saturation of the RU-0211 pharmacodynamics occurred at the 24 mcg t.i.d. dose level.

The **Phase IIb study SC9921** employed a multi-center, parallel-group, double-blind, parallel-controlled study design involving 4 groups of approximately 30 subjects suffering from constipation. The data gained from the two previous Phase I studies, led to the proposed dosing levels for the Phase IIb study SC9921 which evaluated dose levels of 24 mcg/day, 48 mcg/day, and 72 mcg/day over a 3-week treatment period. All subjects took study medication t.i.d. that was either provided as placebo t.i.d. or oral RU-0211 24 mcg/day (24 mcg and 2 placebos), 48 mcg/day (2 -24 mcg capsules and one placebo), or 72 mcg/day (24 mcg t.i.d.). The primary objective of determining the safety and tolerability of different doses and dose regimens of oral RU-0211 compared with placebo for constipation relief when administered for 21 days. Results

of this study showed that all 3 doses of RU-0211 were more effective than placebo in relieving constipation, with the 48 mcg and 72 mcg/day doses having similar effects on constipation. The overall tolerability of the 48 mcg (24 mcg b.i.d.) dose was considered better than the 72 mcg/day dose, and revealed better efficacy on more endpoints than the 24 mcg dose. It was therefore chosen for further Phase III development.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication of this New Drug Application is for oral lubiprostone 24 mcg twice daily for — chronic idiopathic constipation —

Medical Officer Comment:
To be consistent with other recently approved drugs which were evaluated in similar populations, the medical officer recommends the proposed indication be changed to the treatment of chronic idiopathic constipation.

6.1.1 Methods

The efficacy evaluation for this New Drug Application was based upon a total of three adequate and well-controlled studies: SC9921, SC0131, and SC0232; and three long-term, open-label safety and efficacy studies: SC01S1, SC01S2 [SP2], and SC02S3.

The two pivotal efficacy studies, SC0131 and SC0232, were multi-center, parallel-group, double-blind, placebo-controlled studies whose primary objective was to evaluate lubiprostone for its proposed indication; — ironic idiopathic constipation — These studies were evaluated both individually and pooled.

Study SC9921 was a Phase IIb multi-center, parallel-group, double-blind, controlled study involving three dose levels of lubiprostone, 24 mcg, 48 mcg and 72 mcg, given in T.I.D. dosing to determine the safety and tolerability of different dose regimens.

The medical officer will perform a detailed, integrated review of the aforementioned studies. The supportive studies submitted with this application will also be reviewed as needed to highlight the proposed indication.

6.1.2 General Discussion of Endpoints

Primary Efficacy Endpoint

- **The frequency rate of spontaneous bowel movements (SBMs) during Week 1.**

An SBM is defined as any bowel movement (BM) that does not occur within 24 hours after rescue medication use. Since rescue was to be disallowed during Week 1, the SBM rate should equal the BM rate. In the case of protocol violators, the analysis will be based on SBMs. In order to adjust for early withdrawals, weekly SBM frequency rates will be calculated as follows:

(Number of SBMs / Number of days) x 7

The number of days in the denominator above is the number of days during the week that the subject was in the study. Weeks will be calculated as 168-hour intervals starting with the exact time of the first intake of study drug. The number of days will generally be 7 unless a subject dropped out during a treatment week. If the number of days is less than 4, then the data will be considered insufficient and the rate will be missing.

Secondary Efficacy Endpoints

- **The frequency rate of spontaneous bowel movements (SBMs) during Weeks 2, 3, and 4.**

Frequency rate of SBMs at Weeks 2, 3, and 4 will be analyzed as discussed above for Week 1 in the Primary Efficacy Endpoint analysis. If the number of days in the week is less than 4 but greater than 0, then the most recent data from days during the previous week will be combined with data from the current week in order to bring the number of days up to 4. This will ensure that data relevant to the given week is not completely discarded and replaced with less relevant data from the previous week.

Other secondary efficacy endpoints included:

- **SBMs within 24 hours of first RU-0211 dose**
- **Time to first SBM**
- **FDA-requested Responder Analyses (A, B, C)**
- **Weekly stool consistency**
- **Weekly stool straining**
- **Weekly severity of constipation**
- **Weekly global treatment of effectiveness**
- **Weekly abdominal bloating**
- **Weekly abdominal discomfort**

6.1.3 Study Design

The two Phase III efficacy studies submitted to support this New Drug Application for the treatment of chronic idiopathic constipation were randomized, double-blind, placebo-controlled studies which included a 2-week baseline/washout period for the confirmation of subject constipation and a 4-week active treatment period. The study populations were well controlled across both studies as both had the same set of inclusion/exclusion criteria. The inclusion criteria

focused primarily on the definition of constipation (< 3 spontaneous bowel movements [SBMs] per week and at least 1 associated symptom at least 25% of the time), while the exclusion criteria dealt mainly with significant chemical or physiological anomalies or conditions that represented potential confounding factors for the planned statistical analyses. Subjects were excluded from the study if they had had documented mechanical obstruction; organic disorders of the bowel (e.g., inflammatory bowel disease, ulcerative colitis, Crohn's Disease); constipation secondary to a documented cause (e.g., surgery, bowel resection); clinically significant cardiovascular, liver, lung, neurologic, or psychiatric disorder; or clinically significant laboratory abnormalities.

For ease of evaluation, two subject populations were created for the evaluation of clinical efficacy.

1. **Well-controlled group (WCG):** This group consisted of the two pivotal, Phase III, double-blind, randomized 4-week trials SC0131 and SC0232, both of which compared RU-0211 to placebo. The primary efficacy endpoint in both pivotal studies was the frequency of spontaneous bowel movements (SBMs) at Week 1. The well-controlled group also included the placebo and 48 mcg arms of the Phase IIb study SC9921.

2. **Long-term safety (LTS) group:** This group consisted of Studies SC01S1, (SC01S2-SP2 portion only), and SC02S3 which were long-term safety and efficacy studies that spanned six months to a year. These trials were all Phase III, open-label, long-term safety studies that were designed to capture safety data during treatment with oral RU-0211 at a dose of 48 mcg/day (24 mcg/b.i.d.), administered for 24 weeks (6 months) [SC01S1] or 48 weeks [SP2 of SC01S2 and SC02S3], as needed. Efficacy data collected in these studies were subjective in nature; however, the same subjective assessments were also performed as part of the well-controlled group, double-blind, randomized, placebo-controlled studies. Therefore, these results contributed to the overall evaluation of RU-0211 efficacy by providing a comparison of results of the same efficacy assessments in both open-label studies and double-blind studies and by demonstrating the persistence of efficacy over time, specifically 6 and 12 months.

Medical officer comments

Overall, the randomization process used in the pivotal studies generated treatment groups that were well balanced with regards to baseline demographic characteristics and past medical histories.

The use of placebo as a comparator in studies SC9921, SC0131, and SC0232 was appropriate as subjects were permitted to administer rescue medication if a significant need for relief existed for their constipation prior to it becoming a possible life-threatening condition.

Although the long-term safety studies did not provide a direct comparison, only a side-by-side contrasting analysis of the efficacy results with the Well-controlled group, they did demonstrate continued efficacy of 48 mcg RU-0211.

The two 4-week pivotal trials were an acceptable duration given that the three long-term safety and efficacy trials provided up to 24 and 48 weeks. As outlined in the Statistical Analysis

Plan, the long-term effectiveness of RU-0211 was to be primarily determined through analysis of studies SC01S1 (24 weeks), SC01S2-SP2 (48 weeks), and SC02S3 (48 weeks). Efficacy measures from these studies was to be analyzed both individually and pooled.
Statistical Analysis:

The **statistical analytic plan** was outlined in each individual study report.

In **Studies SC0131 and SC0232**, the primary and secondary efficacy analyses were performed on Intent-to-Treat (ITT) subjects using the last-observation-carried-forward principle (LOCF). The last-observation-carried-forward technique was used to impute missing values primarily caused by early withdrawal from the study. For a given subject, the most recent non-missing treatment-period data point was carried forward to the subsequent week where data were missing. ITT subjects were subjects who were randomized and took at least one dose of double-blind study drug. If a subject was randomized to one treatment and received the other treatment due to an error, data analysis was based on the original treatment group assignment. Demographic characteristics (age, height, gender, and race) were summarized by treatment group and overall by using descriptive statistics. The comparability between the treatment groups was evaluated by t-tests for age and height, van Elteren tests for ordinal scale baseline disease status variables, and chi-square tests for nominal categorical variables. The comparability of demographic and baseline variables between pooled centers was evaluated by analysis of variance (ANOVA) for continuous variables, Kruskal-Wallis tests for ordinal scale variables, and chi-square tests for nominal categorical variables. For the primary efficacy analysis, a van Elteren's test stratified by center was used instead of a parametric model as far outliers are common in these data. Small centers were pooled when necessary. This procedure tested the null hypothesis of equal SBM frequency rates between Placebo and 48 μg RU-0211 at the end of Week 1 versus the alternate hypothesis of non-equality between the 2 groups. All tests for treatment effects were two-tailed, at a significance level of 5%.

The long-term safety (LTS) group, including **Studies SC01S1, SC01S2 (SP2 portion), and SC02S3** had its primary efficacy analysis performed on the ITT population.

6.1.4 Efficacy Findings

Phase III Pivotal Studies SC0131 and SC0232 (Well Controlled Group – WCG)

Both studies SC0131 and SC0232 evaluated subjects with chronic constipation and compared the efficacy and safety of 48 mcg/day (24 mcg b.i.d.) RU-0211 versus placebo. In both studies, following a 2-week baseline/washout period, subjects received 4 weeks of double-blind medication. No dose escalation was permitted during either study. Each study was powered to detect a difference of 2 spontaneous bowel movements (SBM) between the placebo and RU-0211 48 mcg groups after 1 week of treatment. The studies were comparable with respect to the number of subjects evaluated; 242 subjects in Study SC0131 and 237 in Study SC0232. The two pivotal studies also were similar with regard to the overall mean number of days the subject population was on the study drug; 27.1 for SC0131 and 26.8 for SC0232.

As noted below in Tables 1 and 2, the baseline demographic and disease information was similar throughout the well-controlled group (WCG) population. For the overall pooled group, the mean age was 47.3 years, whereas in the individual studies, the mean age ranged from 45.8 years (Study SC0232) to 48.6 years (Study SC0131). Of the 544 subjects that were treated in the WCG, 314 (57.7%) were less than 50 years of age, 173 (31.8%) were ≥ 50 and < 65 years old, and 57 (10.5%) were ≥ 65 years old. The proportion of subjects ≥ 65 years old was 13.2% in SC0131, 8.4% in SC0232, and 7.7% in SC9921. The subject population in the pooled population was predominantly female, 485/544 (89.2%). This female gender dominance was generally similar across all three trials with 89.7% females in Study SC0131, 88.2% females in Study SC0232, and 90.8% females in Study SC9921. The majority of the well-controlled group's subjects in the pooled population were Caucasian (81.6%). This racial distribution was also seen across all three trials with 86.0% Caucasians in Study SC0131, 75.5% in Study SC0232, and 87.7% in Study SC9921. Of the 479 subjects for whom irritable bowel syndrome status was reported (IBS Status was collected based on subject reporting in SC0131 and SC0232, but not in SC9921), 91 (19.0%) reported having IBS, and 388 (81.0%) did not. Study SC0131 reported 58 (24.0%) subjects with IBS, whereas Study SC0232 only reported 33 subjects, (13.9%) with IBS. Other demographic statistics, such as the mean height and weight, were similar across the three well-controlled studies.

Medical Officer Comments

Although the literature notes that constipation is more likely to affect females and is more prevalent in older patients, the demographic data presented above indicating a pooled female gender predominance of 89.2% and a relatively small percentage of patients ≥ 65 (10.5%) in the well-controlled group, may not reasonably reflect the gender and age distribution of the intended market population for RU-0211. A more homogenous patient population may have allowed for a more accurate efficacy analysis by gender and age and perhaps better estimated the projected patient population.

Table 1: Demographics for Subjects in the Well Controlled Group- ITT Population

Variable/Statistic		SC0131			SC0232		
Variable	Category	Placebo	RU-0211 48 mcg	Total	Placebo	RU-0211 48 mcg	Total
Subject #	N (%)	122 (100.0)	120 (100.0)	242 (100.0)	118 (100.0)	119 (100.0)	237 (100.0)
Age (years)	Mean	49.1	48.0	48.6	45.4	46.2	45.8
	SD	12.93	12.27	12.60	13.24	12.13	12.68
	Median	48.5	46.0	48.0	46.0	46.0	46.0
	Range	22 - 80	23 - 80	22 - 80	21 - 80	20 - 77	20 – 81
Height (cm)	Mean	165.5	165.1	165.3	165.6	165.3	164.5
	SD	8.72	8.06	8.39	8.69	9.52	9.13
	Median	165.1	165.1	165.1	162.6	163.8	163.8
	Range	132.1-188.0	137.2-182.9	132.1-188.0	134.6-184.4	134.6-195.6	134.6-195.6
Weight (kg)	Mean	71.1	71.5	71.3	71.2	72.4	71.8
	SD	13.94	14.19	14.04	16.26	16.29	16.26
	Median	70.1	68.7	69.4	68.0	68.9	68.0
	Range	46.3-124.3	45.8-115.2	45.8-124.3	44.9-129.3	41.5-128.4	41.5-129.3
Subjects assessed	< 50	66 (54.1)	66 (55.1)	132 (54.5)	78 (66.1)	74 (62.2)	152 (64.1)
	≥ 50 & < 65	37 (30.3)	41 (34.2)	78 (32.2)	30 (25.4)	35 (29.4)	65 (27.4)
	≥ 65	19 (15.6)	13 (10.8)	32 (13.2)	10 (8.5)	10 (8.4)	20 (8.4)
Gender	Male	12 (9.8)	13 (10.8)	25 (10.3)	13 (11.0)	15 (12.6)	28 (11.8)
	Female	110 (90.2)	107 (89.2)	217 (89.7)	105 (89.0)	104 (87.4)	209 (88.2)
Race	Caucasian	103 (84.4)	105 (87.5)	208 (86.0)	89 (75.4)	90 (75.6)	179 (75.5)
	Black	12 (9.8)	9 (7.5)	21 (8.7)	12 (10.2)	13 (10.9)	25 (10.5)
	Asian	2 (1.6)	0 (0.0)	2 (0.8)	1 (0.8)	4 (3.4)	5 (2.1)
	Hispanic	5 (4.1)	5 (4.2)	10 (4.1)	14 (11.9)	11 (9.2)	25 (10.5)
	Other	0 (0.0)	1 (0.8)	1 (0.4)	2 (1.7)	1 (0.8)	3 (1.3)
IBS Status	Yes	26 (21.3)	32 (26.7)	58 (24.0)	20 (16.9)	13 (10.9)	33 (13.9)
	No	96 (78.7)	88 (73.3)	184 (76.0)	98 (83.1)	106 (89.1)	204 (86.1)

Reviewer's table, modified from Table 2.7.3.3-3, pages 39-40 of 108, Summary of Clinical Efficacy

Table 2: Demographics for Subjects in the Well-Controlled Group-ITT Population

Variable/Statistic		SC9921			Pooled Group		
Variable	Category	Placebo	RU-0211 48 mcg	Total	Placebo	RU-0211 48 mcg	Total
Subject #	N (%)	33 (100.0)	32 (100.0)	65 (100.0)	273 (100.0)	271 (100.0)	544 (100.0)
Age (yrs)	Mean	46.8	49.3	48.0	47.2	47.4	47.3
	SD	12.42	12.10	12.23	13.08	12.20	12.63
	Median	48.0	50.5	50.0	48.0	46.0	47.0
	Range	22 - 75	23 - 75	22 - 75	21 - 81	20 - 80	20 – 81
Height (cm)	Mean	164.6	167.2	165.9	164.6	165.4	165.0
	SD	8.24	7.84	8.09	8.66	8.70	8.68
	Median	165.1	166.4	165.1	165.1	165.1	165.1
	Range	149.1-188.0	149.9-185.4	149.9-188.0	132.1-188.0	134.6-195.6	132.1-195.6
Weight (kg)	Mean	69.3	71.0	70.1	71.0	71.9	71.4
	SD	12.84	10.65	11.76	14.83	14.77	14.79
	Median	67.6	72.3	69.4	68.5	69.4	68.9
	Range	46.7-98.9	53.5-87.5	46.7-98.9	44.9-129.3	41.5-128.4	41.5-129.3
Subjects assessed	< 50	17 (51.5)	13 (40.6)	30 (46.2)	161 (59.0)	153 (56.5)	314 (57.7)
	≥ 50 & < 65	14 (42.4)	16 (50.0)	30 (46.2)	81 (29.7)	92 (33.9)	173 (31.8)
	≥ 65	2 (6.1)	3 (9.4)	5 (7.7)	31 (11.4)	26 (9.6)	57 (10.5)
Gender	Male	2 (6.1)	4 (12.5)	6 (9.2)	27 (9.9)	32 (11.8)	59 (10.8)
	Female	31 (93.9)	28 (87.5)	59 (90.8)	246 (90.1)	239 (88.2)	485 (89.2)
Race	Caucasian	28 (84.8)	29 (90.6)	57 (87.7)	220 (80.6)	224 (82.7)	444 (81.6)
	Black	3 (9.1)	2 (6.3)	5 (7.7)	27 (9.9)	24 (8.9)	51 (9.4)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	4 (1.5)	7 (1.3)
	Hispanic	1 (3.0)	0 (0.0)	1 (1.5)	20 (7.3)	16 (5.9)	36 (6.6)
	Other	1 (3.0)	1 (3.1)	2 (3.1)	3 (1.1)	3 (1.1)	6 (1.1)
IBS Status	Yes	-	-	-	46(87.9)	45 (18.8)	91 (19.0)
	No	-	-	-	194 (80.8)	194 (81.2)	388 (81.0)

Reviewer's table, modified from Table 2.7.3.3-3, pages 41-42 of 108, Summary of Clinical Efficacy

PRIMARY EFFICACY VARIABLE:

- FREQUENCY RATE OF SPONTANEOUS BOWEL MOVEMENT DURING WEEK 1

As defined in the sponsor's statistical analytical plan, the primary efficacy analysis is based upon the frequency rate of spontaneous bowel movements during Week 1. An SBM is defined as any BM that does not occur within 24 hours after rescue medication use. Since rescue medication was not allowed during Week 1, the SBM rate should equal that of the BM rate. Outlined below are the SBM rate data from the Intent-to-Treat population of the Well-Controlled Group using the Last-Observation-Carried-Forward imputation method.

Table 3: Spontaneous Bowel Movement Frequency Rates[+] (Well-Controlled Group) (Intent-to-Treat Population with Last-Observation-Carried-Forward Imputation Method)

Study	Study Arm	Statistic	Baseline	Week 1	Week 2	Week 3	Week 4	Change In SBM Baseline To Week 1	Change In SBM Baseline To Week 4
SC0131	Placebo N=122	Median	1.50	3.00	3.00	2.00	2.26	1.50	0.76
	RU-0211 48 mcg N=120	Median **P-value~**	1.50 0.3579	5.00 **0.0001**	4.00 **0.0017**	5.00 **0.0002**	4.00 **0.0002**	**3.50**	**2.50**
SC0232	Placebo N=118	Median	1.50	3.50	3.00	3.00	3.00	1.50	1.50
	RU-0211 48 mcg N=119	Median **P-value~**	1.50 0.0174	5.00 **<0.0001**	4.00 **0.0487**	5.00 **0.0004**	4.29 **0.0068**	**3.50**	**2.79**
SC9921	Placebo N=33	Median	1.50	3.00	3.00	3.00	*	1.50	*
	RU-0211 48 mcg N=32	Median **P-value~**	1.29 0.9662	5.00 **0.0203**	4.00 **0.0239**	4.20 0.0762	*	**3.71**	*
Pooled	Placebo N=273	Median	1.50	3.00	3.00	3.00	3.00	1.50	1.50
	RU-0211 48 mcg N=271	Median **P-value~**	1.50 0.0728	5.00 **<0.0001**	4.00 **<0.0001**	5.00 **<0.0001**	4.07 **<0.0001**	**3.50**	**2.57**

Reviewer's table, modified from Table 2.7.3.3-3, pages 48 of 108, Summary of Clinical Efficacy

+ Frequency Rates are calculated as 7x [(Number of SBMs) / (Number of Days Observed for that Week)].

* Study SC9921 only has time points up to Week 3.

~ Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

As noted above in Table 3, the baseline spontaneous bowel movement frequency rate was 1.50 for placebo subjects in each of the individual studies, whereas for RU-0211 subjects, the median baseline SBM frequency rate was 1.29 in SC9921, and 1.50 in both SC0131 and SC0232. In both pivotal studies (SC0131 and SC0232), the median SBM frequency rates in the RU-0211 group for Weeks 1, 2, 3, and 4 were higher (range: 4.00-5.00) than that in the placebo group (range: 2.00-3.50). The difference between the two groups was statistically significant at Weeks 1 – 4 in SC0131 and SC0232, whereas in SC9921, the difference between the two groups was significant at Week 1 (p=0.0203) and Week 2 (p=0.0239) but not at Week 3 (p=0.0762). In the

pooled group, the median baseline SBM frequency rate was 1.50 for both the placebo and RU-0211 48 mcg groups. For Weeks 1 through 4, the difference in SBM frequency between the two groups was statistically significant ($p<0.0001$ at each time point).

Medical Officer Comments

From a clinical perspective, treatment with RU-0211 48 mcg proved to be a valuable treatment option for subjects suffering from chronic idiopathic constipation. When comparing the results before and after treatment, RU-0211 consistently demonstrated a clinically meaningful ≥ 3.5 increase in spontaneous bowel movements at Week 1 (the primary efficacy endpoint) in all three of the well-controlled treatment arms. By Week 4, RU-0211 showed persistent clinically efficacy of a ≥ 2.5 increase in SBM in all four treatment arms. As noted in table 4, the median baseline weekly spontaneous bowel movement frequency for RU-0211 was 1.50 or 1 SBM every 4 to 5 days (considering a 7 day week). After treatment initiation with RU-0211, the median weekly spontaneous bowel movement frequency was increased and maintained to a value of a least 4.00; a value which corresponds to 1 SBM every 1 to 2 days. Of note, the change from baseline analyses did reveal an appreciable placebo effect. Given that the median changes from baseline in the RU-0211 48 mcg group were always at least 50% greater than the corresponding median changes in the placebo group, and that there were significant differences in SBM frequencies across all three well-controlled studies, evidence still stands to support RU-0211 48 mcg/day as an effective treatment for chronic idiopathic constipation.

In Table 3 above, as well as in the following secondary efficacy tables, it is important to note that the p-values may appear misleadingly small and not truly reflective of the clinical meaningfulness of lubiprostone. The Agency statisticians explained that these relatively small p-values are due to the sponsor's adequate sample size, and the distribution around the medians which allow for detections of small difference.

Figure 1 below graphically depicts the mean SBM frequency rate over time by treatment group for the ITT population with LOCF of the two pivotal studies (SC0131 and SC0232). As noted above, both of the pivotal studies demonstrated statistical significance versus placebo at each of Weeks 1 – 4.

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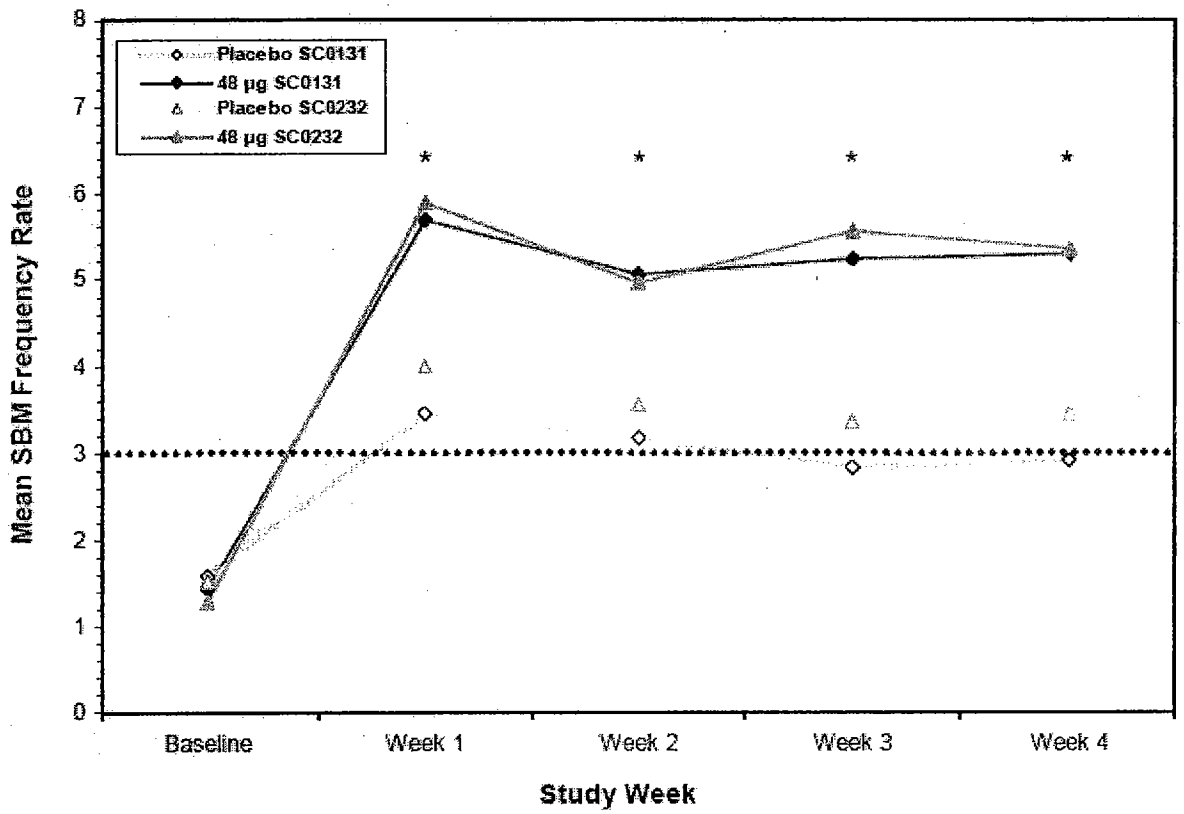
Figure 1: Mean SBM Frequency Rates by Pivotal Study
ITT Population with LOCF
Well-Controlled Group



Sponsor's figure, Figure 2.7.3.3-1, Summary of Clinical Efficacy, page 50 of 108.
Dashed line indicates criteria enrollment; constipation defined as, on average, <3 SBMs per week.
* Statistically significant improvements observed in subjects treated with 48 mcg RU-0211 vs. placebo in both Phase III pivotal studies (SC0131 and SC0232)

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ON ORIGINAL

Table 4: Bowel Movement Frequency Rates+ (Well-Controlled Group) (Intent-to-Treat Population with Last-Observation-Carried-Forward Population)

Study	Study Arm	Statistic	Baseline	Week 1	Week 2	Week 3	Week 4	Change In BM Baseline To Week 1	Change In BM Baseline To Week 4
SC0131	Placebo N=122	Median	2.15	3.00	3.00	3.00	3.00	0.85	0.85
	RU-0211 48 mcg N=120	Median **P-value~**	2.00 0.4458	5.00 **0.0002**	5.00 **<0.0001**	5.00 **0.0001**	5.39 **<0.0001**	**3.00**	**3.39**
SC0232	Placebo N=118	Median	2.00	4.00	4.00	3.10	3.16	2.00	1.16
	RU-0211 48 mcg N=119	Median **P-value~**	2.00 0.3661	5.00 **<0.0001**	4.00 0.0786	5.00 **0.0037**	5.00 **0.0105**	**3.00**	**3.00**
SC9921	Placebo N=33	Median	2.00	3.16	3.00	3.63	*	1.16	*
	RU-0211 48 mcg N=32	Median **P-value~**	2.08 0.4276	6.00 **0.0201**	5.00 **0.0106**	5.58 0.0543	*	**3.92**	*
Pooled	Placebo N=273	Median	2.00	3.16	3.00	3.00	3.00	1.16	1.00
	RU-0211 48 mcg N=271	Median **P-value~**	2.00 0.3127	5.00 **<0.0001**	5.00 **<0.0001**	5.00 **<0.0001**	5.00 **<0.0001**	**3.00**	**3.00**

Reviewer's table, modified from Table 2.7.3.3-6, pages 52 of 108, Summary of Clinical Efficacy
+ Frequency Rates are calculated as 7x [(Number of BMs) / (Number of Days Observed for that Week)].
* Study SC9921 only has time points up to Week 3.
~ Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

As noted above in Table 4, the bowel movement frequency rates for ITT subjects with LOCF are similar to those presented for the spontaneous bowel movements. Bowel movement frequencies are higher than spontaneous bowel movement frequencies, as expected, as bowel movement frequencies are reflective of concomitant rescue medication use. In each of the three studies as well as the pooled population within the well-controlled group, the RU-0211 48 mcg group demonstrated a statistically significant increase in BM, regardless of concomitant rescue medication use compared to placebo at Week 1. Studies SC0131, SC0232, and the pooled population also reached statistical significance versus placebo by Week 4.

Medical Officer Comments

The efficacy of RU-0211 48 mcg is reinforced given that the results of the bowel movement (BM) frequency rates mirror those of the spontaneous bowel movement frequency rates with respect to statistical significance and clinical relevance.

Secondary Efficacy Variables:

The secondary efficacy endpoints in this New Drug Application were as follows:

- SBM frequency rates during Weeks 2, 3, 4
- SBMs within 24 hours of first RU-0211 dose
- Time to first SBM
- FDA-requested Responder Analyses (A, B, C)
- Weekly stool consistency
- Weekly stool straining
- Weekly severity of constipation
- Weekly global treatment effectiveness
- Weekly abdominal bloating
- Weekly abdominal discomfort

Analysis of Spontaneous Bowel Movements within 24 Hours after First Study Drug Dose

The sponsor performed an analysis on the proportion of patients with chronic idiopathic constipation who documented spontaneous bowel movements within 24 hours after receiving their first dose of study drug (lubiprostone or placebo). Table 5 below graphically depicts the sponsor's results for the Intent-to-Treat population for the Well-controlled group.

Table 5: Spontaneous Bowel Movements within 24 Hours after First Study Drug Dose Intent to Treat Population – Well-Controlled Group

	SC0131		SC0232		SC9921		Pooled Group	
Category	Placebo N=122	RU-0211 48 mcg N=120	Placebo N=118	RU-0211 48 mcg N=119	Placebo N=33	RU-0211 48 mcg N=32	Placebo N=273	RU-0211 48 mcg N=271
Subjects N (%)	122/122 (100.0)	120/120 (100.0)	116/118 (98.3)	116/119 (97.5)	33/33 (100.0)	32/32 (100.0)	271/273 (99.3)	268/271 (98.9)
Yes	45/120 (36.9)	68/120 (56.7)	37/116 (31.9)	73/116 (62.9)	11/33 (33.3)	20/32 (62.5)	93/271 (34.3)	161/268 (60.1)
No	77/120 (63.1)	52/120 (43.3)	79/116 (68.1)	43/116 (37.1)	22/33 (66.7)	12/32 (37.5)	178/271 (65.7)	107/268 (39.9)
P-value*	**0.0024**		**<0.0001**		**0.0180**		**<0.0001**	

Reviewer's table, modified from sponsor's table 2.7.3.3-11, page 62 of 108, Summary of Clinical Efficacy

* Tests for differences between groups are based on the CMH test stratified by pooled center for the individual studies and stratified by study for the Pooled Group.

As noted above in Table 5, the proportions of subjects with a spontaneous bowel movement within 24 hours after first study drug dose were 36.9% for placebo vs. 56.7% for RU-0211 48 mcg ($p=0.0024$) in SC0131, 31.9% vs. 62.9% ($p<0.0001$) in SC0232, 33.3% vs. 62.5% ($p=0.0180$) in SC9921, and 34.3% vs. 60.1% ($p<0.0001$) in the pooled group.

Medical Officer Comments

As noted above, there was a statistically significant difference between the RU-0211 group and the placebo group in the analysis of spontaneous bowel movements within 24 hours of first study drug dose. Of note, there was an appreciable placebo effect with an average of 34.0% placebo response rate. The reviewer is uncertain as to the cause of the placebo effect in this analysis, however; historical data suggests this may be an average placebo response for similarly designed trials. Despite the appreciable placebo effect, the average spontaneous bowel movement response rate within the 24 hours after the first study drug dose was on average 26% greater for the RU-0211 group than for the placebo group. Evidence stands to support lubiprostone as an effective treatment with rapid onset after initial administration for relief of chronic idiopathic constipation.

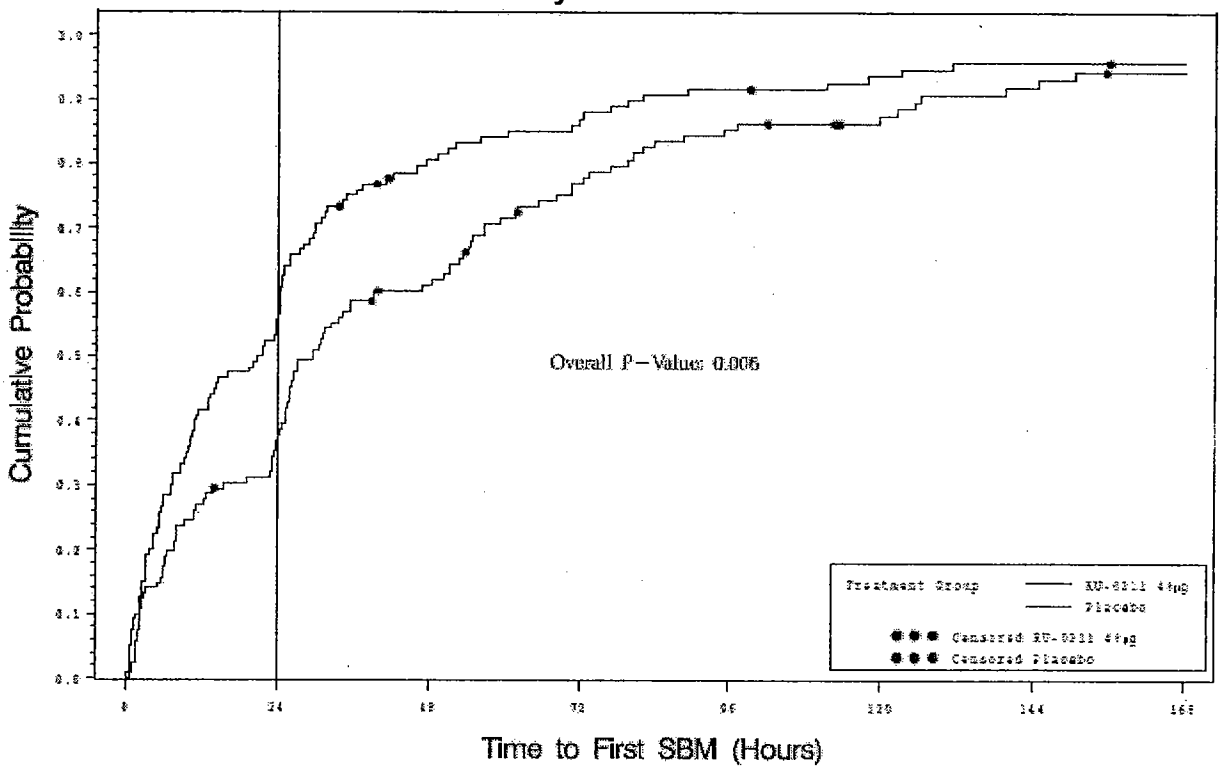
Time to First Spontaneous Bowel Movement

A time-to-event analysis was used to evaluate treatment group differences in the evaluation of the time to subjects' first spontaneous bowel movements. Time to first SBM was defined in the sponsor's statistical analytic plan as the number of hours between the time of the first dose of study medication and the time of the first SBM. Data from subjects who used rescue medication or who dropped out of the study before the first SBM were censored at the time of rescue medication use or early termination. The p-values arise from the Wald test associated with treatment in a Cox Proportional-Hazards Model including center effects. Pooled center and treatment were considered and tested at an alpha level of 0.10 in the saturated model. The number of hours since the most recent BM prior to the start of study drug was used as a covariate. The reverse stepwise modeling process eliminated pooled center at the first step. For the ITT population, the figures below present the cumulative probability comparison between treatment groups graphically with Kaplan-Meier curves.

As noted below in Figures 2, 3, 4 and 5, for each study and the pooled group overall, the upper line in the graph represents the RU-0211 48 mcg group and the lower line represents the placebo group. The vertical line denoting the 24-hour mark is only to illustrate that mark as a point of interest, and is not to be construed as being related to the Cox proportional hazard p-value.

For each study and for the pooled group overall, the time to the first spontaneous bowel movement was significantly shorter ($p \leq 0.022$) for subjects taking RU-0211 48 mcg than for subjects taking placebo.

Figure 2: Kaplan-Meier Curve for Time to First SBM
ITT Population
Study: SC0131



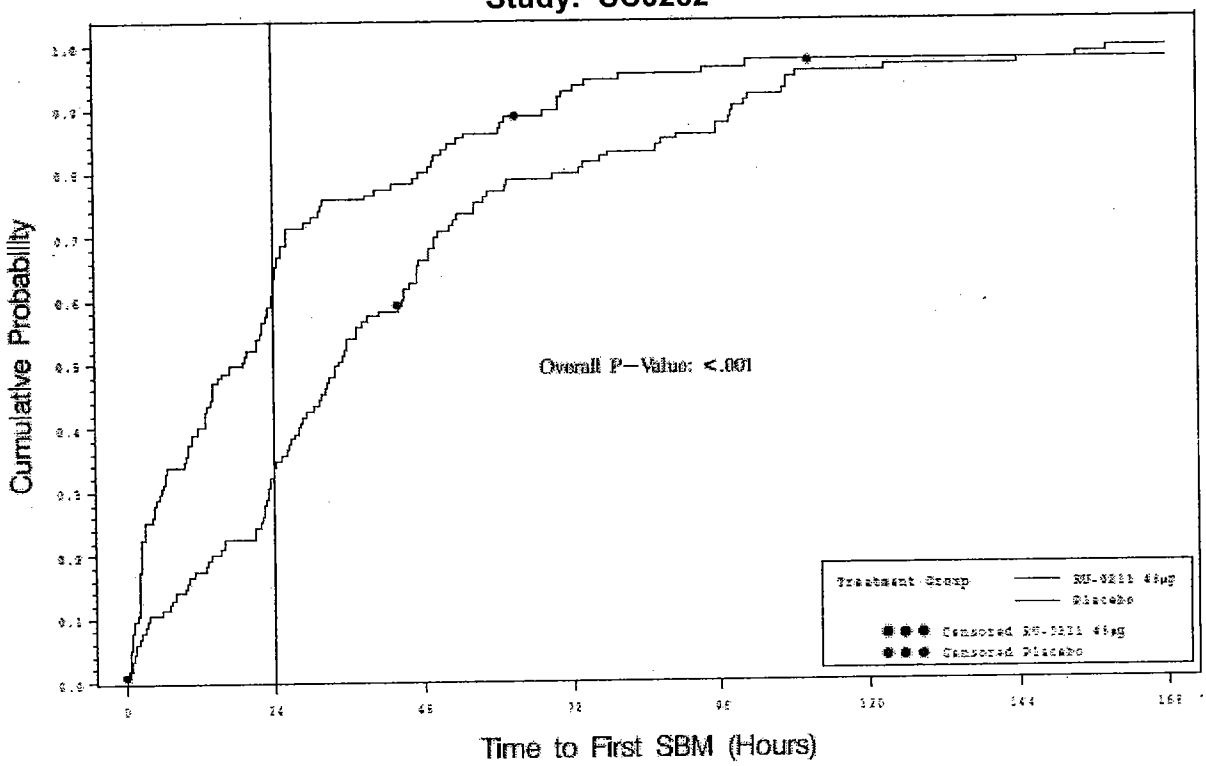
Sponsor's Figure, Figure 2.2.1.1, Integrated Summary of Efficacy, page 344 of 347

APPEARS THIS WAY
ON ORIGINAL

The overall p-value when comparing the RU-0211 48 mcg group versus the placebo group for the time to first spontaneous bowel movement was 0.006.

APPEARS THIS WAY
ON ORIGINAL

Figure 3: Kaplan-Meier Curve for Time to First SBM
ITT Population
Study: SC0232



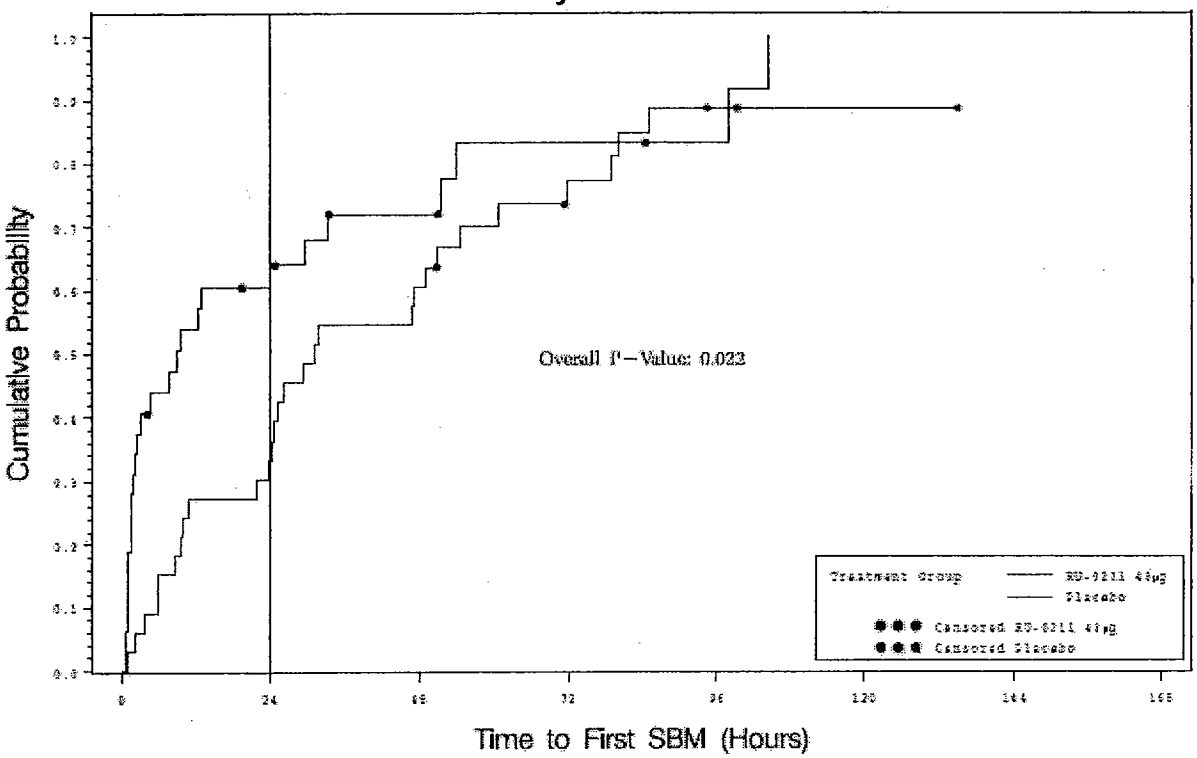
Sponsor's Figure, Figure 2.2.1.2, Integrated Summary of Efficacy, page 345 of 347

APPEARS THIS WAY
ON ORIGINAL

The overall p-value when comparing the RU-0211 48 mcg group versus the placebo group for the time to first spontaneous bowel movement was <0.001.

APPEARS THIS WAY
ON ORIGINAL

Figure 4: Kaplan-Meier Curve for Time to First SBM
ITT Population
Study: SC9921



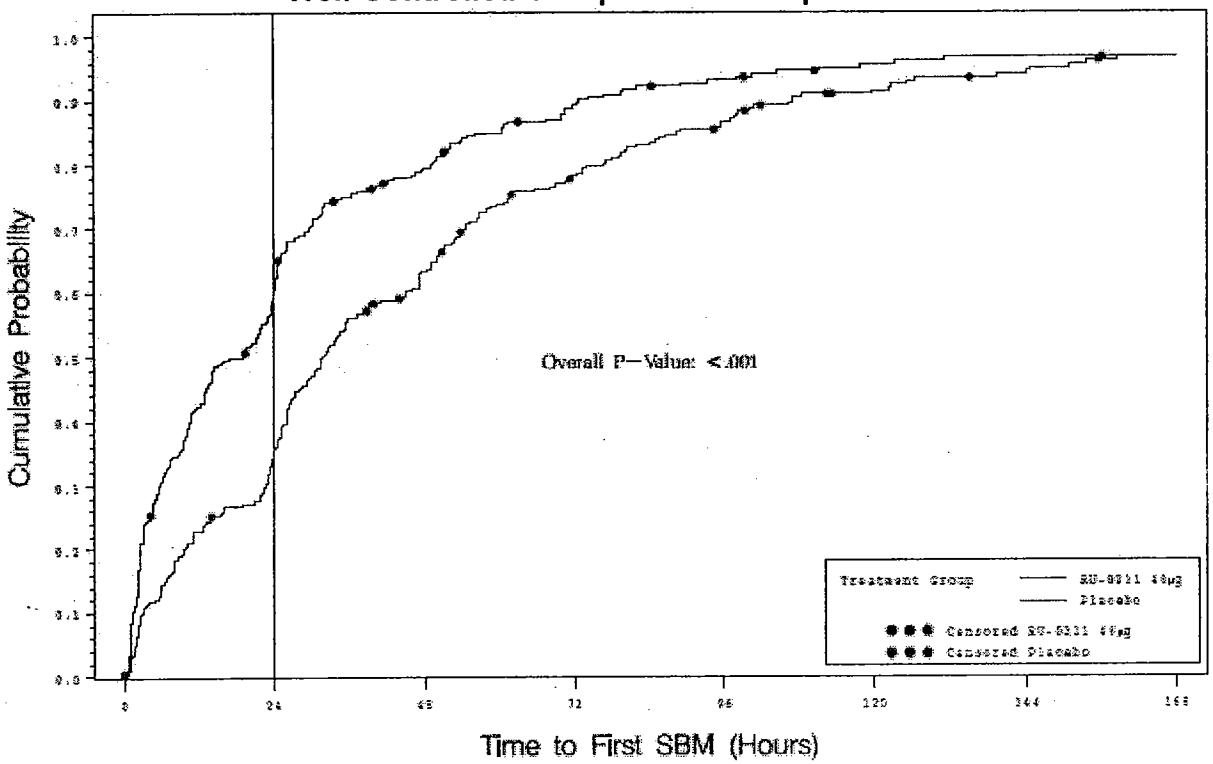
Sponsor's Figure, Figure 2.2.1.3, Integrated Summary of Efficacy, page 346 of 347

APPEARS THIS WAY
ON ORIGINAL

The overall p-value when comparing the RU-0211 48 mcg group versus the placebo group for the time to first spontaneous bowel movement was 0.022.

APPEARS THIS WAY
ON ORIGINAL

Figure 5: Kaplan-Meier Curve for Time to First SBM
ITT Population
Well-Controlled Group – Pooled Population



Sponsor's Figure, Figure 2.2.1.4, Integrated Summary of Efficacy, page 347 of 347

APPEARS THIS WAY
ON ORIGINAL

The overall p-value when comparing the RU-0211 48 mcg group versus the placebo group for the time to first spontaneous bowel movement was <0.001.

Medical Officer Comments

The figures above and the aforementioned time-to-first SBM analysis confirm the results of the primary efficacy endpoint in this study. The statistically significant test of the coefficient of the treatment effect (p<0.023) suggests that an early onset of relief, namely in the form of the first SBM, was much faster in subjects treated with RU-0211 than among placebo subjects.

Responder Analyses

As defined in the sponsor's statistical analytical plan, in order to assess treatment response and to account for study dropout and rescue medication use, a responder analysis was performed for each week. A van Elteren test stratified by pooled center will be used to analyze the responder rates at each week. The sponsor performed responder analyses on the pivotal studies ITT population with LOCF via a weekly responder analysis and an all-weeks responder analysis. The classification was based upon the following responder status definitions: ***full responder***; a responder with ≥ 4 SBMs per week, ***moderate responder***; a responder with ≥ 3 but < 4 SBMs per week, and ***non-responder***; a subject with < 3 SBMs for a given week, who dropped out during the given week due to lack of efficacy, or who used rescue medication during or within 24 hours prior to the given week.

Table 6: Weekly Responder Status Analysis (ITT Population with LOCF) - WCG

Study	Treatment Arm	Responder Status	Week 1	Week 2	Week 3	Week 4	(Δ%) RU-0211 Versus Placebo Full responders
SC0131	Placebo N=122	Subjects assessed	122/122 (100.0)	122/122 (100.0)	122/122 (100.0)	122/122 (100.0)	
		Full Responder	**53/122 (43.4)**	**44/122 (36.1)**	**35/122 (28.7)**	**34/122 (27.9)**	
		Moderate Responder	19/122 (15.6)	17/122 (13.9)	16/122 (13.1)	20/122 (16.4)	
		Non Responder	50/122 (41.0)	61/122 (50.0)	71/122 (58.2)	68/122 (55.7)	**SC0131 Δ% Weeks 1/4 21.3/29.9**
	RU-0211 48 mcg N=120	Subjects assessed	116/120 (96.7)	116/120 (96.7)	116/120 (96.7)	116/120 (96.7)	
		Full Responder	**75/116 (64.7)**	**67/116 (57.8)**	**65/116 (56.0)**	**67/116 (57.8)**	
		Moderate Responder	14/116 (12.1)	10/116 (8.6)	8/116 (6.9)	10/116 (8.6)	
		Non Responder	27/116 (23.3)	39/116 (33.6)	43/116 (37.1)	39/116 (33.6)	
		P-value*	0.0023	0.0037	0.0003	<0.0001	
SC0232	Placebo N=118	Subjects assessed	117/118 (99.2)	117/118 (99.2)	117/118 (99.2)	117/118 (99.2)	
		Full Responder	**57/117 (48.7)**	**50/117 (42.7)**	**42/117 (35.9)**	**45/117 (38.5)**	
		Moderate Responder	14/117 (12.0)	13/117 (11.1)	15/117 (12.8)	17/117 (14.5)	
		Non Responder	46/117 (39.3)	54/117 (46.2)	60/117 (51.3)	55/117 (47.0)	**SC0232 Δ% Weeks 1/4 23.4/21.0**
	RU-0211 48 mcg N=119	Subjects assessed	111/119 (93.3)	111/119 (93.3)	111/119 (93.3)	111/119 (93.3)	
		Full Responder	**80/111 (72.1)**	**64/111 (57.7)**	**68/111 (61.3)**	**66/111 (59.5)**	
		Moderate Responder	16/111 (14.4)	13/111 (11.7)	11/111 (9.9)	13/111 (11.7)	
		Non Responder	15/111 (13.5)	34/111 (30.6)	32/111 (28.8)	32/111 (28.8)	
		P-value*	<0.0001	0.0171	0.0002	0.0022	

Reviewer's table, modified from sponsor's table 2.7.3.3-7, page 55 of 108, Summary of Clinical Efficacy

* Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

Table 7: Weekly Responder Status Analysis Continued

Study	Treatment Arm	Responder Status	Week 1	Week 2	Week 3	Week 4	(Δ%) RU-0211 Versus Placebo Full responders
SC9921 +	Placebo N=33	Subjects assessed	33/33 (100.0)	33/33 (100.0)	33/33 (100.0)	-	
		Full Responder	**13/33 (39.4)**	**10/33 (30.3)**	**11/33 (33.3)**	-	
		Moderate Responder	7/33 (21.2)	7/33 (21.2)	6/33 (18.2)	-	
		Non Responder	13/33 (39.4)	16/33 (48.5)	16/33 (48.5)	-	**SC9921 (Δ%) Weeks 1/3 26.2/23.0**
	RU-0211 48 mcg N=33	Subjects assessed	32/32 (100.0)	32/32 (100.0)	32/32 (100.0)	-	
		Full Responder	**21/32 (65.6)**	**19/32 (59.4)**	**18/32 (56.3)**	-	
		Moderate Responder	1/32 (3.1)	4/32 (12.5)	3/32 (9.4)	-	
		Non Responder	10/32 (31.3)	9/32 (28.1)	11/32 (34.4)	-	
		P-value*	**0.0814**	**0.0412**	**0.1527**	-	
Pooled Group	Placebo N=273	Subjects assessed	272/273 (99.6)	272/273 (99.6)	272/273 (99.6)	139/273 (87.5)	
		Full Responder	**123/272 (48.7)**	**104/272 (42.7)**	**88/272 (35.9)**	**79/239 (33.1)**	
		Moderate Responder	40/272 (12.0)	37/272 (11.1)	37/272 (12.8)	37/239 (15.5)	
		Non Responder	109/272 (39.3)	131/272 (46.2)	147/272 (51.3)	123/239 (51.5)	**Pooled Δ% Weeks 1/4 19.3/25.5**
	RU-0211 48 mcg N=271	Subjects assessed	259/271 (95.6)	259/271 (95.6)	259/271 (95.6)	227/271 (83.8)	
		Full Responder	**176/259 (68.0)**	**150/259 (57.9)**	**151/259 (58.3)**	**133/227 (58.6)**	
		Moderate Responder	31/259 (12.0)	27/259 (10.4)	22/259 (8.5)	23/227 (10.1)	
		Non Responder	52/259 (20.1)	82/259 (31.7)	86/259 (33.2)	71/227 (31.3)	
		P-value*	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	

Reviewer's table, modified from sponsor's table 2.7.3.3-7, page 55 of 108, Summary of Clinical Efficacy
* Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.
+ Study XC9921 only has time points up to Week 3

The aforementioned responder analyses in Tables 6 and 7, revealed that for Studies SC0131, SC0232, and the pooled group analysis, there was a statistically significant difference between the treatment groups in responder status in all post-baseline evaluation time points. For Study SC9921 the difference was significant only at Week 2 (p=0.0412). The statistically significant p-values are highlighted in the above table for ease of identification.

Medical Officer Comments

The proportion of full responders (i.e., those subjects with ≥ 4 SBMs per week) in both well-controlled studies and in the pooled population was much higher in the RU-0211 48 mcg group than in the placebo group at all time points. Specifically, the proportion of full responders in the RU-0211 48 mcg group pooled group was always at least 57% and was always at least 15 percentage points higher than the proportion of full responders in the placebo group. In both treatment groups in all studies including the pooled population, the proportion of full responders was highest for Week 1 (ranges: 39.4% - 48.7% for placebo; 64.7% - 72.1% for RU-0211 48 mcg). Of note, these full responder percentages gradually decreased over time; however, RU-0211, still maintained statistical and clinical significance throughout the four weeks trial duration. Also, the proportion of non-responders was always at least 8 percentage points (in most cases, at least 15 points) higher in the placebo group than in the RU-0211 48 mcg group at all time points. There was a slight increase in non-responder status throughout both the placebo and well controlled studies over time with a small decline noted at week 4.

From a clinical perspective, when comparing RU-0211 versus placebo at Weeks 1 and 4, treatment with RU-0211 revealed an average 23% greater full responder status at Week 1 and an average 25% greater full responder status at Week 4.

All-Weeks Responder Analysis

The sponsor performed three types of all-weeks responder analyses for ITT subjects in the WCG based upon the Agency's request. All three ad-hoc analyses were based on cumulative results up to the given week. The first two analyses require a Spontaneous Bowel Movement rate ≥ 3 at each week, while the third analysis requires a change of ≥ 2 SBMs at each week. In the first analysis (A), subjects who did not meet the responder criteria and dropped out of the study for a reason other than ***lack of efficacy*** were considered missing and were not included in the denominator of the analysis. In the second analysis (B), subjects who dropped out of the study ***for any reason*** and did not meet the responder criteria were considered non-responders and were included in the denominator for that week and thereafter; instead of missing and not being included in the denominator. In the third analysis (C), subjects who dropped out ***and*** who did not meet the responder criteria were considered missing and were not included in the denominator of the analysis. The primary time point for all 3 analyses was Week 4. As the double blind treatment period in SC9921 was only 3 weeks long, this study was not included in these analyses.

All-Weeks Responder Analysis (A):

The results of the first all-weeks responder analysis (A) are summarized in Table 8 below. The sponsor's first all-week responder analysis defined "responders" as subjects who had ≥ 3 SBMs for each week up to the given week and who had not dropped out due to lack of efficacy. Those who dropped out due to reasons other than lack of efficacy were considered missing, were not considered responders for that week, and were not included in the denominator for the responder quotient for that week or thereafter. At Week 4 in Studies SC0131, SC0232 and the pooled population, the proportion of all-weeks responders was significantly higher in the RU-0211 48 mcg group compared with the placebo group ($p=0.0004$), ($p=0.0078$), and ($p<0.0001$), respectively. In SC0131, the proportions of all-weeks responders at Week 4 were 25.8% for placebo, and 49.5% for RU-0211 48 mcg; in SC0232, the proportions were 36.9% and 56.0%; and in the pooled group, the proportions were 31.2% and 52.7%, respectively.

Medical Officer Comments

From a clinical perspective, Table 8 below reveals that treatment with RU-0211 48 mcg provided a greater clinical response at Week 4 than placebo in patients suffering from chronic idiopathic constipation. When comparing RU-0211 versus placebo at Week 4, treatment with RU-0211 demonstrated an average of 21.4% greater responder status. Conversely, by Week 4, the RU-0211 48 mcg group had lower percentages of non responders than the placebo group; 50.5% versus 74.2%, 44.0% versus 63.1 %, and 47.3% versus 68.8% in Studies SC0131, SC0232, and the pooled population, respectively. Reinforcing its durability of response, the RU-0211 48 mcg group demonstrated an average of 21.4% less non-responders than the placebo group across the three studies.

Table 8: All-Week Responder Analysis (A)[1] (ITT Population – Well-controlled Group)[2]

Study	Treatment Arm	Responder Status	Week 1 N (%)	Week 2 N (%)	Week 3 N (%)	Week 4 N (%)	(Δ%) RU-0211 Versus Placebo responders
SC0131	Placebo N=122	Subjects Assessed	122/122 (100.0)	122/122 (100.0)	121/122 (99.2)	120/122 (98.4)	
		Responder	74/122 (60.7)	50/122 (41.0)	37/122 (30.6)	31/120 **(25.8)**	
		Non Responder	48/122 (39.3)	72/122 (59.0)	84/121 (69.4)	89/120 (74.2)	
	RU-0211 48 mcg N=120	Subjects Assessed	120/120 (100.0)	114/120 (95.0)	108/120 (90.0)	105/120 (87.5)	SC0131 Δ% Week 4 **23.7**
		Responder	91/120 (75.8)	66/114 (57.9)	60/108 (55.6)	52/105 **(49.5)**	
		Non Responder	29/120 (24.2)	48/114 (57.9)	48/108 (44.4)	53.105 (50.5)	
		P-value[3]	0.0157	0.0159	0.0002	0.0004	
SC0232	Placebo N=118	Subjects Assessed	118/118 (100.0)	117/118 (99.2)	116/118 (98.3)	111/118 (94.1)	(Δ%) RU-0211 Versus Placebo Responders
		Responder	72/118 (61.0)	53/117 (45.3)	43/116 (37.1)	41/111 **(36.9)**	
		Non Responder	46/118 (39.0)	64/117 (54.7)	73/116 (62.9)	70/111 (63.1)	
	RU-0211 48 mcg N=119	Subjects Assessed	119/119 (100.0)	110/119 (92.4)	100/119 (84.0)	100/119 (84.0)	SC0232 Δ% Week 4 **19.1**
		Responder	97/119 (81.5)	70/110 (63.6)	61/100 (61.0)	56/100 **(56.0)**	
		Non Responder	22/119 (18.5)	40/110 (36.4)	39/100 (39.0)	44/100 (44.0)	
		P-value[3]	0.0005	0.0076	0.0007	0.0078	
Pooled Population	Placebo N=240	Subjects Assessed	240/240 (100.0)	239/240 (99.6)	237/240 (98.8)	231/240 (96.3)	(Δ%) RU-0211 Versus Placebo Responders
		Responder	146/240 (60.8)	103/239 (43.1)	80/237 (33.8)	72/231 **(31.2)**	
		Non Responder	94/240 (39.2)	136/239 (56.9)	157/237 (66.2)	159/231 (68.8)	
	RU-0211 48 mcg N=239	Subjects Assessed	239/239 (100.0)	224/239 (93.7)	208/239 (87.0)	205/239 (85.8)	Pooled population Δ% Week 4 **21.5**
		Responder	188/239 (78.7)	136/224 (60.7)	121/208 (58.2)	108/205 **(52.7)**	
		Non Responder	51/239 (21.3)	88/224 (39.3)	87/208 (41.8)	97/205 (47.3)	
		P-value[3]	<0.0001	0.0002	<0.0001	<0.0001	

Reviewer's table, modified from sponsor's table 2.7.3.3-7, page 58 of 108, Summary of Clinical Efficacy

1 **Responder: Subject has ≥ 3 SBMs for each week up to the given week and does not drop out due to lack of efficacy. Those who drop out due to reasons other than lack of efficacy and are not responders for that week are considered missing, and these subjects are not included in the denominator for that week and subsequent weeks.**

2 The primary time point of this analysis is the Week 4 results. Since SC9921 was a 3-week study, it is not included in this analysis.

3 Tests for differences between groups are based on the CMH test stratified by pooled center for the individual studies and stratified by study for the Pooled population.

All-Weeks Responder Analysis (B):

The results of the sponsor's second all-weeks responder analysis (B) are summarized below in Table 9. The sponsor's second all-week responder analysis defined "responders" as subjects who had ≥ 3 SBMs for each week up to the given week and who had not dropped out due to lack of efficacy. The difference between analysis (B) and the sponsor's first all-week analysis (A) was that in analysis (B) those subjects who dropped out for any reason and had <3 SBMs for that week were considered non-responders and were included in the denominator for the responder quotient for that week and thereafter; instead of missing and not being included in the denominator.

At Week 4 in Studies SC0131 and the pooled population, the proportion of all-weeks responders was significantly higher in the RU-0211 48 mcg group compared with the placebo group (p=0.0051) and (p=0.0006), respectively. In SC0131, the proportions of all-weeks responders at Week 4 were 25.4% for placebo and 43.35% for RU-0211 48 mcg and in the pooled group, the proportions were 30.0% and 45.2%, respectively. In study SC0232, the proportions were 34.7% and 47.1% which trended toward significance but fell shy with p=0.0605.

Medical Officer Comments

Given that non-responders and subjects who dropped out were included in the denominator of the responder quotient, it is expected that the overall responder percentages in this type of analysis be slightly lower than in the all-week responder analysis (A). It is still evident; however, that treatment with RU-0211 48 mcg provided a greater clinical response at Week 4 than did placebo. When comparing RU-0211 versus placebo at Week 4, treatment with RU-0211 demonstrated an average of 15.2% greater responder status. Conversely, the placebo group at Week 4 exhibited higher percentages of non responders than the RU-0211 group; 74.6% versus 56.7%, 65.3% versus 52.9%, and 70.0% versus 54.8% in Studies SC0131, SC0232, and the pooled population, respectively. The RU-0211 48 mcg group demonstrated an average of 17.1% less non-responders than the placebo group across the three studies reinforcing its superiority versus placebo at 4 weeks duration.

Table 9: All-Week Responder Analysis (B)[1] (ITT Population – Well-controlled Group)[2]

Study	Treatment Arm	Responder Status	Week 1 N (%)	Week 2 N (%)	Week 3 N (%)	Week 4 N (%)	(Δ%) RU-0211 Versus Placebo Responders
SC0131	Placebo N=122	Subjects Assessed	122/122 (100.0)	122/122 (100.0)	122/122 (100.0)	122/122 (100.0)	
		Responder	75/122 (61.5)	50/122 (41.0)	37/122 (30.6)	31/120 **(25.4)**	
		Non Responder	47/122 (38.5)	72/122 (59.0)	85/122 (69.7)	91/120 (74.6)	
	RU-0211 48 mcg N=120	Subjects Assessed	120/120 (100.0)	120/120 (100.0)	120/120 (100.0)	120/120 (100.0)	SC0131 Δ% Week 4 **17.9**
		Responder	91/120 (75.8)	66/120 (55.0)	60/120 (50.0)	52/105 **(43.3)**	
		Non Responder	29/120 (24.2)	54/120 (45.0)	60/120 (50.0)	68/120 (56.7)	
		P-value[3]	**0.0220**	**0.0412**	**0.0026**	**0.0051**	
SC0232	Placebo N=118	Subjects Assessed	118/118 (100.0)	118/118 (100.0)	118/118 (100.0)	118/118 (100.0)	(Δ%) RU-0211 Versus Placebo Responders
		Responder	73/118 (61.9)	53/118 (44.9)	43/116 (37.1)	41/118 **(34.7)**	
		Non Responder	45/118 (38.1)	65/118 (55.1)	73/116 (62.9)	77/118 (65.3)	
	RU-0211 48 mcg N=119	Subjects Assessed	119/119 (100.0)	119/119 (100.0)	119/119 (100.0)	119/119 (100.0)	SC0232 Δ% Week 4 **12.4**
		Responder	97/119 (81.5)	70/110 (58.8)	61/119 (51.3)	56/119 **(47.1)**	
		Non Responder	22/119 (18.5)	49/119 (41.2)	58/119 (48.7)	63/119 (52.9)	
		P-value[3]	**0.0007**	**0.0394**	**0.0278**	**0.0605**	
Pooled Population	Placebo N=240	Subjects Assessed	240/240 (100.0)	240/240 (100.0)	240/240 (100.0)	240/240 (100.0)	(Δ%) RU-0211 Versus Placebo Responders
		Responder	148/240 (61.7)	103/240 (42.9)	80/240 (33.3)	72/240 (30.0)	
		Non Responder	92/240 (38.3)	137/240 (57.1)	160/240 (66.7)	168/240 (70.0)	
	RU-0211 48 mcg N=239	Subjects Assessed	239/239 (100.0)	239/239 (100.0)	239/239 (100.0)	239/239 (100.0)	Pooled Population Δ% Week 4 **15.2**
		Responder	188/239 (78.7)	136/239 (56.9)	121/239 (50.6)	108/239 **(45.2)**	
		Non Responder	51/239 (21.3)	103/239 (43.1)	118/239 (49.4)	131/239 (54.8)	
		P-value[3]	**<0.0001**	**0.0023**	**0.0001**	**0.0006**	

Reviewer's table, modified from sponsor's table 2.7.3.3-7, page 59 of 108, Summary of Clinical Efficacy

1 **Responder: Subject has ≥ 3 SBMs for each week up to the given week and does not drop out due to lack of efficacy. Those who drop out for any reason and have <3 SBMs for that week are considered non-responders for that week and all subsequent weeks.**

2 The primary time point of this analysis is the Week 4 results. Since SC9921 was a 3-week study, it is not included in this analysis.

3 Tests for differences between groups are based on the CMH test stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

All-Weeks Responder Analysis (C):

The results of the first all-weeks responder analysis (C) are summarized in Table 10 below. The sponsor's third all-week analysis defined "responders" as subjects who had a change of ≥ 2 spontaneous bowel movements from baseline to each week up to the given week. Analysis C considered those subjects who dropped out or had missing data as missing, and did not include them in the responder quotient denominator for that week or subsequent weeks.

At Week 4 in Studies SC0131, SC0232 and the pooled population, the proportion of all-weeks responders was significantly higher in the RU-0211 48 mcg group compared with the placebo group ($p=0.0011$), ($p=0.0002$), and ($p<0.0001$), respectively. In SC0131, the proportions of all-weeks responders at Week 4 were 19.5% for placebo, and 39.4% for RU-0211 48 mcg; in SC0232, the proportions were 19.8% and 44.4%; and in the pooled group, the proportions were 19.6% and 41.9%, respectively.

Medical Officer Comments

The sponsor's third all-week responder analysis was designed to explore responder status based upon a change of ≥ 2 spontaneous bowel movements from baseline in each given week. This is somewhat of a weaker "responder" definition and as would be expected, revealed somewhat higher responder percentages compared to the prior two analyses. When comparing RU-0211 versus placebo at Week 4, treatment with RU-0211 demonstrated an average of 22.3% greater responder status. Once again, the placebo group at Week 4 also exhibited higher percentages of non responders than the RU-0211 group; 80.5% versus 60.6%, 80.2% versus 55.6%, and 80.4% versus 58.1% in Studies SC0131, SC0232, and the pooled population, respectively. The placebo group demonstrated an average of 22.3% more non-responders than the RU-0211 48 mcg group across the three studies reinforcing RU-0211's superiority versus placebo at 4 weeks duration.

Table 10: All-Week Responder Analysis (C)[1] (ITT Population – Well-controlled Group)[2]

Study	Treatment Arm	Responder Status	Week 1 N (%)	Week 2 N (%)	Week 3 N (%)	Week 4 N (%)	(Δ%) RU-0211 Versus Placebo Responders
SC0131	Placebo N=122	Subjects Assessed	122/122 (100.0)	120/122 (98.4)	119/122 (97.5)	118/122 (96.7)	
		Responder	57/122 (46.7)	36/120 (30.0)	29/119 (24.4)	23/118 **(19.5)**	
		Non Responder	65/122 (53.3)	84/120 (70.0)	90/119 (75.6)	95/118 (80.5)	
	RU-0211 48 mcg N=120	Subjects Assessed	120/120 (100.0)	120/120 (100.0)	108/120 (90.0)	104/120 (86.7)	**SC0131 Δ% Week 4 19.9**
		Responder	78/120 (65.0)	60/114 (52.6)	52/108 (48.1)	41/104 **(39.4)**	
		Non Responder	42/120 (35.0)	54/114 (47.4)	56/108 (51.9)	63/104 (60.6)	
		P-value[3]	**0.0059**	**0.0006**	**0.0002**	**0.0011**	
SC0232	Placebo N=118	Subjects Assessed	118/118 (100.0)	114/118 (96.6)	112/118 (94.9)	106/118 (89.8)	(Δ%) RU-0211 Versus Placebo Responders
		Responder	57/118 (48.3)	38/114 (33.3)	43/112 (24.1)	41/106 **(19.8)**	
		Non Responder	61/118 (51.7)	76/114 (66.7)	73/112 (75.9)	77/106 (80.2)	
	RU-0211 48 mcg N=119	Subjects Assessed	119/119 (100.0)	110/119 (92.4)	100/119 (84.0)	99/119 (83.2)	**SC0232 Δ% Week 4 24.6**
		Responder	88/119 (73.9)	64/110 (58.2)	51/100 (51.0)	49/99 **(44.4)**	
		Non Responder	31/119 (26.1)	46/110 (41.8)	49/100 (49.0)	55/99 (55.6)	
		P-value[3]	**<0.0001**	**0.0002**	**<0.0001**	**0.0002**	
Pooled Population	Placebo N=240	Subjects Assessed	240/240 (100.0)	234/240 (97.5)	231/240 (96.3)	224/240 (93.3)	(Δ%) RU-0211 Versus Placebo Responders
		Responder	114/240 (47.5)	74/234 (31.6)	80/231 (24.2)	72/224 **(19.6)**	
		Non Responder	126/240 (52.5)	160/234 (68.4)	160/231 (75.8)	168/224 (80.4)	
	RU-0211 48 mcg N=239	Subjects Assessed	239/239 (100.0)	224/239 (93.7)	208/239 (87.0)	203/239 (84.9)	**Pooled Population Δ% Week 4 22.3**
		Responder	166/239 (69.5)	124/224 (55.4)	121/208 (49.5)	108/203 **(41.9)**	
		Non Responder	73/239 (30.5)	100/224 (44.6)	118/208 (50.5)	131/203 (58.1)	
		P-value[3]	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	

Reviewer's table, modified from sponsor's table 2.7.3.3-7, page 60 of 108, Summary of Clinical Efficacy

1 **Responder: Subject has a change of ≥ 2 SBMs from baseline to each week up to the given week. Those who drop out and have missing data are considered missing, and these subjects are not included in the denominator for that week and subsequent weeks.**

2 The primary time point of this analysis is the Week 4 results. Since SC9921 was a 3-week study, it is not included in this analysis.

3 Tests for differences between groups are based on the CMH test stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

Medical Officer Comments: All-Week Responder Analyses Conclusions

The three all-week responder analyses were very subjective as they were based upon individual patient responder status. The analyses therefore, were not heavily influenced by subjects who were outliers with respect to their spontaneous bowel movement behavior. Despite these facts, the analyses did provide clinically meaningful results supporting the efficacy of RU-0211 48 mcg/day. Overall, the three all-week analyses demonstrated an average pooled responder efficacy of 46.6% at 4 weeks which indicates that RU-0211 is generally more effective than placebo in increasing the number of spontaneous bowel movements (whether the endpoint be ≥ 3 SBMs or ≥ 2 SBMs) on a per-subject basis. The sponsor's three all-week analyses also demonstrated that RU-0211 48 mcg/day, when compared to placebo, delivered a combined average of 20.3% less non-responders. This non-responder statistic also supports the efficacy of RU-0211 in relieving patients suffering from chronic idiopathic constipation.

Stool Consistency

A summary of weekly stool consistency for the Intent-to-Treat population with the LOCF is presented below in Table 11. According to the sponsor's statistical analytic plan, the degree of stool consistency score was averaged for each subject and for all SBMs in a given week. Average degree of stool consistency was then analyzed by van Elteren tests, stratified by pooled center, at Weeks 1, 2, 3, and 4. If there were no SBMs during the week or if there were SBMs but all ratings were missing, then the LOCF method was used to impute the average used for the most recent week. In order to assess the change from baseline, Wilcoxon signed-rank tests were performed for each treatment group at the end of each week. The scale used by subjects to evaluate and rate their stool consistency was as follows:

Stool Consistency:
0. Very loose
1. Loose
2. Normal
3. Hard
4. Very Hard

Table 11: Summary of Weekly Stool Consistency+ (ITT Population with LOCF) – Well-controlled Group

Study	Study Arm	Statistic	Baseline	Week 1	Week 2	Week 3	Week 4	Change Baseline To Week 1	Change Baseline To Week 4
SC0131	Placebo N=122	Median	2.90	2.60	2.60	2.67	2.50	0.30	0.40
	RU-0211 48 mcg N=120	Median **P-value~**	3.00 0.0764	2.00 **<0.0001**	1.78 **<0.0001**	1.93 **<0.0001**	1.88 **<0.0001**	1.00	1.88
SC0232	Placebo N=118	Median	3.00	2.50	2.44	2.33	2.33	0.50	0.67
	RU-0211 48 mcg N=119	Median **P-value~**	2.90 0.9374	1.78 **<0.0001**	2.00 **<0.0001**	1.83 **<0.0001**	2.00 **<0.0001**	1.12	0.90
SC9921	Placebo N=33	Median	2.71	2.04	2.00	2.33	*	0.38	*
	RU-0211 48 mcg N=32	Median **P-value~**	2.71 0.8948	1.50 **0.0004**	1.80 **0.0007**	1.67 **0.0006**	*	1.21	*
Pooled	Placebo N=273	Median	2.90	2.50	2.50	2.50	2.33	0.40	0.57
	RU-0211 48 mcg N=271	Median **P-value~**	3.00 0.4514	1.89 **<0.0001**	1.91 **<0.0001**	1.83 **<0.0001**	2.00 **<0.0001**	1.11	1.00
Average change in consistency from baseline to Week 1/ Week 4 RU-0211/Placebo								1.11/0.40	1.26/0.56

Reviewer's table, modified from Table 2.7.3.3-3, pages 66-67 of 108, Summary of Clinical Efficacy
+ Consistency: 0 (Very loose), 1 (Loose), 2 (Normal), 3 (Hard) and 4 (Very hard).
* Study SC9921 only has time points up to Week 3.
~ Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

As noted above, at the study level and for the pooled group, the median baseline stool consistency was similar in both treatment groups. The baseline differences between the groups revealed no statistically significant differences. At all post-baseline evaluation time points for each study and in the pooled population, the median stool consistencies (range 1.50-2.00) reported in the RU-0211 48 mcg group were lower than the values in the placebo group (range 2.00-2.67). The differences at each time point were statistically significant ($p \leq 0.0007$ in each case).

Medical Officer Comments

As noted above, the lower median stool consistency numbers represent an overall softening of stool. Although this secondary efficacy variable is strictly a subjective assessment, the aforementioned table demonstrates that treatment with RU-0211 48 mcg results in an average median improvement of 1.11 units on the 5-point scoring scale at week 1 and 1.26 units at week 4 when compared to baseline. Comparatively the placebo group revealed an average median improvement of 0.40 units on the 5-point scoring scale at week 1 and 0.55 units at week 4. From a clinical perspective, the median improvement exhibited by RU-0211 of 1.11 units on the 5-point scale demonstrates an overall improvement in the quality of life for a patient suffering from chronic idiopathic constipation. A decrease of 1.11 units is clinically relevant in that it may represent the relief of a patient's discomfort by softening stool from a "hard" consistency to a "normal" consistency or from a "very hard" consistency that may lead to obstipation to a "hard" yet still evacuative consistency.

Degree of Straining

A summary of weekly degree of straining for the Intent-to-Treat population with the LOCF is presented below in Table 12. According to the sponsor's statistical analytic plan, the degree of straining score was averaged for each subject and for all days in a given week. Average degree of straining was analyzed by van Elteren tests and stratified by pooled center at Weeks 1, 2, 3, and 4. If there were no SBMs during the week or if there were SBMs but all ratings were missing, then the LOCF method was used to impute the average from the most recent week. In order to assess the change from baseline, Wilcoxon signed-rank tests were performed for each treatment group at the end of each week. The scale used by subjects to evaluate and rate their degree of straining was as follows:

Degree of Straining:
0. Absent
1. Mild
2. Moderate
3. Severe
4. Very Severe

Table 12: Summary of Weekly Degree of Straining+ (ITT Population with LOCF) – Well-controlled Group

Study	Study Arm	Statistic	Baseline	Week 1	Week 2	Week 3	Week 4	Change Baseline To Week 1	Change Baseline To Week 4
SC0131	Placebo N=122	Median	2.40	2.00	2.00	2.00	2.00	0.40	0.40
	RU-0211 48 mcg N=120	Median P-value~	2.50 0.3778	1.67 **<0.0001**	1.42 **<0.0001**	1.50 **<0.0001**	1.50 **<0.0001**	0.83	1.00
SC0232	Placebo N=118	Median	2.40	2.00	2.00	1.82	2.00	0.40	0.40
	RU-0211 48 mcg N=119	Median P-value~	2.33 0.6716	1.56 **0.0017**	1.50 **0.0003**	1.40 **0.0018**	1.40 **0.0002**	0.77	0.93
SC9921	Placebo N=33	Median	2.00	1.54	2.00	2.00	*	0.46	*
	RU-0211 48 mcg N=32	Median P-value~	2.00 0.6756	1.20 0.0905	1.19 **0.0200**	1.33 **0.0055**	*	0.80	*
Pooled	Placebo N=273	Median	2.33	2.00	2.00	2.00	2.00	0.33	0.33
	RU-0211 48 mcg N=271	Median P-value~	2.40 0.4177	1.50 **<0.0001**	1.39 **<0.0001**	1.40 **<0.0001**	1.50 **<0.0001**	0.90	0.90
Average change in degree of straining from baseline to Week 1/ Week 4 RU-0211/Placebo								0.83/0.40	0.94/0.38

Reviewer's table, modified from Table 2.7.3.3-3, pages 68-69 of 108, Summary of Clinical Efficacy
+ Straining: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe) and 4 (Very severe).
* Study SC9921 only has time points up to Week 3.
~ Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

As noted above in Table 12, there were no statistically significant differences in the median baseline degree of straining in both treatment groups and for the pooled group. At all post-baseline evaluation time points for each study and in the pooled group, the median degree of straining (range 1.19 – 1.67) reported in the RU-0211 48 mcg group were lower than the values in the placebo group (range 1.54 – 2.00). The differences at each time point in SC0131, SC0232, Week 2, and Week 3 in SC9921, and at each time point in the pooled group was statistically significant ($p \leq 0.0200$ in each case). At Week 1 in SC9921, median straining was 1.54 for placebo subjects and 1.20 for RU-0211 48 mcg subjects; this difference was not statistically significant (p=0.0905).

Medical Officer Comments

As noted above, the lower median degree of straining numbers represent an overall improvement in patient discomfort. Although this secondary efficacy variable is strictly a subjective assessment, the aforementioned table demonstrates that treatment with RU-0211 48 mcg results in an average median improvement of 0.83 units on the 5-point scoring scale at week 1 and 0.94 units at week 4 when compared to baseline. Comparatively, the placebo group revealed an average median improvement of 0.40 units on the 5-point scoring scale at week 1 and 0.38 units at week 4. From a clinical perspective, the median improvement

exhibited by RU-0211 of 0.94 units on the 5-point scale demonstrates an overall improvement in the quality of life for a patient suffering from chronic idiopathic constipation. A decrease of 0.94 units is clinically relevant in that it may represent relief of patient discomfort by reducing their degree of straining from "severe" straining to a "moderate" straining or from a "very severe" straining; which may lead to complications such as hemorrhoids or Valsalva-induced syncope, to a "severe" yet non-injurious straining.

Severity of Constipation

A summary of weekly constipation severity for the Intent-to-Treat population with the LOCF is presented below in Table 13. The weekly constipation severity score was averaged for each subject and for all days in a given week. Weekly constipation severity was analyzed by van Elteren tests and stratified by pooled center at Weeks 1, 2, 3, and 4. If at Week 2, 3, or 4 the assessment was missing, then the LOCF method was used to impute the score using the most recent score from a previous treatment period week. The scale used by subjects to evaluate and rate their constipation severity was as follows:

Severity of Constipation:
0. Absent
1. Mild
2. Moderate
3. Severe
4. Very Severe

Table 13: Summary of Weekly Severity of Constipation+ (ITT Population with LOCF) – Well-controlled Group

Study	Study Arm	Statistic	Baseline	Week 1	Week 2	Week 3	Week 4	Change Baseline To Week 1	Change Baseline To Week 4
SC0131	Placebo N=122	Median	3.00	3.00	2.00	3.00	3.00	0.00	0.00
	RU-0211 48 mcg N=120	Median **P-value~**	3.00 0.8528	2.00 **0.0003**	2.00 **<0.0001**	2.00 **<0.0001**	2.00 **<0.0001**	1.00	1.00
SC0232	Placebo N=118	Median	2.40	2.00	2.00	2.00	2.00	0.40	0.40
	RU-0211 48 mcg N=119	Median **P-value~**	3.00 0.7766	2.00 **0.0061**	2.00 **0.0243**	2.00 **0.0265**	2.00 **0.0022**	1.00	1.00
SC9921	Placebo N=33	Median	3.00	2.00	2.00	2.00	*	1.00	*
	RU-0211 48 mcg N=32	Median **P-value~**	3.00 0.9558	2.00 0.2599	1.50 0.1597	1.00 **0.0171**	*	1.00	*
Pooled	Placebo N=273	Median	3.00	2.00	2.00	2.00	3.00	1.00	0.00
	RU-0211 48 mcg N=271	Median **P-value~**	3.00 0.7023	2.00 **<0.0001**	2.00 **<0.0001**	2.00 **<0.0001**	2.00 **<0.0001**	1.00	1.00
Average change in weekly severity of constipation from baseline to Week 1/ Week 4 RU-0211/Placebo								1.00/0.60	1.00/0.13

Reviewer's table, modified from Table 2.7.3.3-3, pages 71-72 of 108, Summary of Clinical Efficacy

+ Straining: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe) and 4 (Very severe).

* Study SC9921 only has time points up to Week 3.

~ Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

As noted above in Table 13, there were no statistically significant differences in the median baseline constipation severity in both treatment groups and for the pooled population. The median values in the RU-0211 48 mcg group (range: 1.00-2.00) were similar to or lower than the median values in the placebo group (range: 2.00-3.00); the median value for constipation severity in the RU-0211 48 mcg group was never higher than the median value in the placebo group. The differences at each time point in SC0131, SC0232, and Week 3 in SC9921, and at each time point in the pooled group was statistically significant ($p \leq 0.0265$). At Weeks 1 and 2 in SC9921, median constipation severity was 2.00 for placebo subjects and 2.00 and 1.50, for RU-0211 48 mcg subjects; these differences were not statistically significant ($p=0.2599$ and $p=0.1597$, respectively). The lower scores in the RU-0211 48 mcg group indicate a lessening of constipation severity in subjects taking the study drug.

Medical Officer Comments

As noted above, the lower median weekly constipation severity scores represent an overall improvement in patient discomfort. Although this secondary efficacy variable is strictly a subjective assessment, the aforementioned table demonstrates that treatment with RU-0211 48 mcg results in an average median improvement of 1.00 units on the 5-point scoring scale at week 1 and 1.00 units at week 4 when compared to baseline. Comparatively, the placebo group revealed an average median improvement of 0.60 units on the 5-point scoring scale at week 1 and 0.13 units at week 4. These secondary efficacy findings of constipation severity show that treatment with RU-0211 48 mcg is almost always significantly better than treatment with placebo. Given the above data, the medical officer is inclined to surmise that RU-0211 contributes to overall subject quality of life as evidenced by reduction of constipation severity scores.

Global Assessment of Treatment Effectiveness

A summary of weekly treatment effectiveness for the Intent-to-Treat population with the LOCF is presented below in Table 14. The weekly treatment effectiveness score was averaged for each subject and for all days in a given week. Weekly treatment effectiveness scores were analyzed by van Elteren tests and stratified by pooled center at Weeks 1, 2, 3, and 4. If at Week 2, 3, or 4 the assessment was missing, then the LOCF method was used to impute the score using the most recent score from a previous treatment period week. The scale used by subjects to evaluate and rate their treatment effectiveness was as follows:

Treatment Effectiveness:
0. Not at all Effective
1. A Little Bit Effective
2. Moderately Effective
3. Quite a Bit Effective
4. Extremely Effective

Table 14: Summary of Weekly Treatment Effectiveness+ (ITT Population with LOCF) – Well-controlled Group

Study	Study Arm	Statistic	Week 1	Week 2	Week 3	Week 4	Follow Up
SC0131	Placebo N=122	Median	1.00	0.00	0.00	0.00	0.00
	RU-0211 48 mcg N=120	Median **P-value~**	2.00 **<0.0001**	2.00 **<0.0001**	2.00 **<0.0001**	2.00 **<0.0001**	2.00 **<0.0001**
SC0232	Placebo N=118	Median	1.00	1.00	1.00	1.00	1.00
	RU-0211 48 mcg N=119	Median **P-value~**	2.00 **<0.0001**	2.00 **<0.0001**	2.00 **<0.0001**	2.00 **<0.0001**	2.00 **0.0004**
SC9921	Placebo N=33	Median	1.00	1.00	1.00	*	*
	RU-0211 48 mcg N=32	Median **P-value~**	2.50 0.1155	2.00 **0.0356**	2.00 0.0773	*	*
Pooled	Placebo N=273	Median	1.00	1.00	1.00	1.00	1.00
	RU-0211 48 mcg N=271	Median **P-value~**	2.00 **<0.0001**	2.00 **<0.0001**	2.00 **<0.0001**	2.00 **<0.0001**	2.00 **<0.0001**

Reviewer's table, modified from Table 2.7.3.3-3, pages 74 of 108, Summary of Clinical Efficacy
+ Straining: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe) and 4 (Very severe).
* Study SC9921 only has time points up to Week 3.
~ Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

At all post-baseline evaluation time points including follow-up, the median treatment effectiveness scores for subjects in Studies SC0131, SC0232, and the pooled group, were higher in the RU-0211 48 mcg group than in the placebo group. In each post-baseline evaluation, the difference between the treatment groups was statistically significant ($p \leq 0.0001$). In SC9921, the median treatment effectiveness scores for the RU-0211 48 mcg group were higher than the placebo group at all time points, but the difference was statistically significant only at Week 2 (median: 1.00 vs. 2.00; p=0.0356). In the pooled population, the median treatment effectiveness remained constant for both the RU-0211 48 mcg group (2.00) and for the placebo group (1.00) for the duration of Weeks 1-4 ($p < 0.0001$).

Medical Officer Comments

As noted above in Table 14, higher median treatment effectiveness scores represent the patients' subjective impression of overall improvement. All RU-0211 treatment groups' scores consistently remained at 2.00 which represents "moderately effective" throughout the four week trial. The durability of response over the 4 weeks and follow-up period helps to confirm the overall efficacy of RU-0211 for chronic idiopathic constipation and its effects in relieving patient discomfort.

Abdominal Bloating

A summary of weekly abdominal bloating for the Intent-to-Treat population with the LOCF is presented below in Table 15. The weekly abdominal bloating score was averaged for each subject and for all days in a given week. Weekly abdominal bloating score was analyzed by van Elteren tests and stratified by pooled center at Weeks 1, 2, 3, and 4. If at Week 2, 3, or 4 the assessment was missing, then the LOCF method was used to impute the score using the most recent score from a previous treatment period week. The scale used by subjects to evaluate and rate their abdominal bloating was as follows:

Abdominal Bloating:

0. Absent
1. Mild
2. Moderate
3. Severe
4. Very Severe

Table 15: Summary of Weekly Abdominal Bloating+ (ITT Population with LOCF) – Well-controlled Group

Study	Study Arm	Statistic	Baseline	Week 1	Week 2	Week 3	Week 4	Change Baseline To Week 1	Change Baseline To Week 4
SC0131	Placebo N=122	Median	2.00	2.00	2.00	2.00	2.00	0.00	0.00
	RU-0211 48 mcg N=120	Median P-value~	2.00 0.8660	1.00 0.2928	1.00 **0.0207**	2.00 **0.0310**	1.00 0.0987	1.00	1.00
SC0232	Placebo N=118	Median	2.00	2.00	1.00	2.00	1.50	0.00	0.50
	RU-0211 48 mcg N=119	Median P-value~	2.00 0.4985	1.00 **0.0380**	1.00 0.6274	2.00 0.1788	1.00 0.2800	1.00	1.00
SC9921	Placebo N=33	Median	2.00	2.00	2.00	2.00	*	0.00	*
	RU-0211 48 mcg N=32	Median P-value~	2.00 0.9181	2.00 0.4399	2.00 0.9596	2.00 0.1183	*	0.00	*
Pooled	Placebo N=273	Median	2.00	2.00	2.00	2.00	2.00	0.00	0.00
	RU-0211 48 mcg N=271	Median P-value~	2.00 0.6210	1.00 **0.0092**	1.00 **0.0352**	2.00 **0.0032**	1.00 **0.0279**	1.00	1.00
Average change in weekly abdominal bloating from baseline to Week 1/ Week 4 RU-0211/Placebo								0.75/0.00	1.00/0.16

Reviewer's table, modified from Table 2.7.3.3-3, pages 77-78 of 108, Summary of Clinical Efficacy

+ Straining: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe) and 4 (Very severe).

* Study SC9921 only has time points up to Week 3.

~ Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

As noted above in Table 15, there were no statistically significant differences in the median baseline abdominal bloating scores among both treatment groups and among the pooled population. The median values for the RU-0211 48 mcg group (range: 1.00-2.00) were always similar to or lower than the median value for placebo group (range: 1.00-2.00). Significant differences between the 2 groups were observed at Week 2 (p=0.0207) and Week 3 (p=0.0310) in SC0131, Week 1 (p=0.0380) in SC0232, and Weeks 1-4 of the pooled group analysis ($p \leq 0.0352$). There were no statistically significant differences demonstrated in Study SC9921.

Medical Officer Comments

As noted above, lower median weekly abdominal bloating scores represent an overall lessening of patient discomfort. The aforementioned table demonstrates that treatment with RU-0211 48 mcg results in an average median improvement of 0.75 units on the 5-point scoring scale at week 1 and 1.00 units at week 4 when compared to baseline. Comparatively, the placebo group revealed no average improvement at week 1 and only 0.16 units at week 4. Despite the lack of statistical significance, the actual observed values of effectiveness, provide evidence that RU-0211 shows some clinically relevant benefit in lessening abdominal bloating.

Abdominal Discomfort

A summary of weekly abdominal discomfort for the Intent-to-Treat population with the LOCF is presented below in Table 16. The weekly abdominal discomfort score was averaged for each subject and for all days in a given week. Weekly abdominal discomfort score was analyzed by van Elteren tests and stratified by pooled center at Weeks 1, 2, 3, and 4. If at Week 2, 3, or 4 the assessment was missing, then the LOCF method was used to impute the score using the most recent score from a previous treatment period week. The scale used by subjects to evaluate and rate their abdominal discomfort was as follows:

Abdominal Discomfort:

0. Absent
1. Mild
2. Moderate
3. Severe
4. Very Severe

Table 16: Summary of Weekly Abdominal Discomfort+ (ITT Population with LOCF) – Well-controlled Group

Study	Study Arm	Statistic	Baseline	Week 1	Week 2	Week 3	Week 4	Change Baseline To Week 1	Change Baseline To Week 4
SC0131	Placebo N=122	Median	2.00	1.00	1.00	2.00	2.00	1.00	0.00
	RU-0211 48 mcg N=120	Median P-value~	2.00 0.6635	1.00 0.8005	1.00 **0.0245**	1.00 **0.0169**	1.00 **0.0445**	1.00	1.00
SC0232	Placebo N=118	Median	2.00	1.00	1.00	2.00	1.00	1.00	1.00
	RU-0211 48 mcg N=119	Median P-value~	2.00 0.8589	1.00 0.1514	1.00 0.8716	1.00 0.8060	1.00 0.1383	1.00	1.00
SC9921	Placebo N=33	Median	2.00	2.00	2.00	2.00	*	0.00	*
	RU-0211 48 mcg N=32	Median P-value~	2.00 0.2157	2.00 0.9316	1.50 0.5346	1.00 0.0534	*	0.00	*
Pooled	Placebo N=273	Median	2.00	1.00	1.00	2.00	1.50	1.00	0.50
	RU-0211 48 mcg N=271	Median P-value~	2.00 0.6459	1.00 0.4542	1.00 0.0827	1.00 **0.0098**	1.00 **0.0096**	1.00	1.00
Average change in weekly abdominal discomfort from baseline to Week 1/ Week 4 RU-0211/Placebo								0.75/0.75	1.00/0.50

Reviewer's table, modified from Table 2.7.3.3-3, pages 80-81 of 108, Summary of Clinical Efficacy
+ Straining: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe) and 4 (Very severe).
* Study SC9921 only has time points up to Week 3.
~ Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

As noted above in Table 16, there were no statistically significant differences in the median baseline abdominal discomfort scores among both treatment groups and among the pooled population. The median values for the RU-0211 48 mcg group (range: 1.00-2.00) were always similar to or lower than the median value for placebo group (range: 1.00-2.00). Significant differences between the 2 groups were observed at Week 2 (p=0.0245), Week 3 (p=0.0169), and Week 4 (p=0.0445) in SC0131 and Week 3 (p=0.0098) and Week 4 (p=0.0096) of the pooled group analysis. There were no statistically significant differences demonstrated in Study SC0232 or in Study SC9921.

Medical Officer Comments

As noted above, lower median weekly abdominal discomfort scores represent an overall lessening of patient discomfort. The aforementioned table demonstrates that treatment with RU-0211 48 mcg results in an average median reduction of 0.75 units on the 5-point scoring scale at week 1 and 1.00 units at week 4 when compared to baseline. Comparatively, the placebo group revealed an average median reduction of 0.75 units on the 5-point scoring scale at week 1 and 0.50 units at week 4. Similar to the efficacy outcomes for abdominal bloating,

the results of this secondary efficacy variable reinforce the clinically meaningful benefit of RU-0211 on chronic idiopathic constipation and its related symptoms.

Overall Efficacy Comparison of Pivotal Studies

Studies SC0131 and SC0232 were designed by the sponsor with internal consistency to allow for side-by-side comparison of the pivotal studies. Below is a tabular summary and overall efficacy comparison of the pivotal studies in which an X denotes statistical significance of RU-0211 48 mcg over placebo. The table shows that the results between the pivotal studies were very similar in terms of the statistically significant differences between RU-0211 48 mcg and placebo, in favor of RU-0211 48 mcg.

Table 17: Summary of Statistical Significance of Efficacy Results For Pivotal Studies

Efficacy Variable	Time Point			
	Week 1	Week 2	Week 3	Week 4
SBM Frequency Rate				
SC0131	X	X	X	X
SC0232	X	X	X	X
Protocol-defined Responder Analysis				
SC0131	X	X	X	X
SC0232	X	X	X	X
All-Weeks Responder Analysis A				
SC0131	X	X	X	X
SC0232	X	X	X	X
All-Weeks Responder Analysis B				
SC0131	X	X	X	X
SC0232	X	X	X	**NS**
4-Weeks Responder Analysis C				
SC0131	X	X	X	X
SC0232	X	X	X	X
Weekly Stool Consistency				
SC0131	X	X	X	X
SC0232	X	X	X	X
Weekly Degree of Straining				
SC0131	X	X	X	X
SC0232	X	X	X	X
Weekly Severity of Constipation				
SC0131	X	X	X	X
SC0232	X	X	X	X
Weekly Treatment Effectiveness				
SC0131	X	X	X	X
SC0232	X	X	X	X
Weekly Abdominal Bloating				
SC0131	**NS**	X	X	**NS**
SC0232	X	**NS**	**NS**	**NS**
Weekly Abdominal Discomfort				
SC0131	**NS**	X	X	X
SC0232	**NS**	**NS**	**NS**	**NS**

Reviewer's table, modified from Table 2.7.3.3-19, pages 83 of 108, Summary of Clinical Efficacy

Note: X indicates statistically significant difference ($p<0.05$) between RU-0211 48 µg and placebo, in favor of RU-0211 48 µg.
NS indicates the difference between RU-0211 48 µg and placebo was not significant.

Medical Officer's Comments

As noted above in Table 17, the results of the pivotal studies were nearly identical. They revealed statistically significant ($p<0.05$) results in the primary and most of the secondary efficacy variables. Obvious exceptions were the abdominal symptoms bloating and discomfort. Despite their lack of statistical significance; however, the median decreases from baseline in the abdominal bloating and discomfort symptoms were generally larger for subjects taking RU-0211 48 mcg than placebo, thus trending in the direction of the other efficacy variables. The strong similarity of the results in Study SC0131 and SC0232 effectively eliminated study design bias and allowed for the medical officer to analyze and compare drug efficacy in mutually exclusive patient populations.

Exposure to Rescue Medication

For the pooled population in the Well-controlled group, the proportion of subjects at baseline that reported rescue medication use was higher in the RU-0211 48 mcg group (58%) than in the placebo group (50.9%), however; this was not statistically significant (p=0.0857). A similar result was observed for each of the individual studies. At all post-baseline time points in the pooled group, the proportion of subjects that reported rescue medication use was higher in the placebo group than in the RU-0211 48 mcg group: 13.6% vs. 10.1% during Week 1, 25.4% vs. 21.3% at Week 2, 33.1% vs. 24.5% at Week 3, and 27.2% vs. 19.7% at Week 4. The difference between the groups was significant only at Week 3 (p=0.0351).

Mean rescue medication exposure in the pooled group was the same for placebo and RU-0211 48 mcg subjects at Week 1, higher for RU-0211 48 mcg subjects than placebo subjects at Week 2, and higher for placebo subjects than RU-0211 48 mcg subjects at Weeks 3 and 4.

Medical Officer's Comments

As noted above in the pooled group results, the medical officer would expect to see more rescue medication use in a placebo cohort than in a study drug that is efficacious. The mean rescue medication exposure does not allow for meaningful interpretation.

COMPARISON OF RESULTS IN SUBPOPULATIONS

Primary Efficacy Variable: Analysis by Gender

Overall for the well-controlled studies, 27 males took placebo, 32 males took RU-0211 48 mcg, 246 females took placebo, and 239 females took RU-0211 48 mcg.

As noted below in Table 19, for the male subjects, the difference in baseline SBM frequency between placebo and RU-0211 48 mcg subjects was not statistically significant (p=0.3895). At all post-baseline time points; however, the median SBM frequencies were higher for male subjects taking RU-0211 48 mcg than those taking placebo, and the difference was significant at Week 1 (p=0.0145), Week 2 (p=0.0195), and Week 3 (p=0.0489). For female subjects, the baseline difference in SBM frequency rates was significant (p=0.0355). The median SBM

frequencies were higher for female subjects taking RU-0211 48 mcg than for those taking placebo, and the difference at all post-baseline time points was significant ($p<0.0001$).

Table 18: Summary of SBM Frequency Rates+ by Gender (Well-Controlled Group) (Intent-to-Treat Population with Last-Observation-Carried-Forward Population)

Category	Study Arm	Statistic	Baseline	Week 1	Week 2	Week 3	Week 4	Change In BM Baseline To Week 1	Change In BM Baseline To Week 4
Male	Placebo N=27	Median	1.50	3.00	3.00	2.10	2.00	1.50	0.50
	RU-0211 48 mcg N=32	Median P-value~	1.50 0.3895	5.50 **0.0145**	5.00 **0.0195**	5.50 **0.04891**	4.00 0.0503	**4.00**	**2.50**
Female	Placebo N=246	Median	1.50	3.00	3.00	3.00	3.00	1.50	1.50
	RU-0211 48 mcg N=239	Median P-value~	1.50 0.0355	5.00 **<0.0001**	4.00 **<0.0001**	5.00 **<0.0001**	4.10 **<0.0001**	3.50	2.60

Reviewer's table, modified from Table 1.3.1.1, pages 288 of 347, Integrated Summary of Efficacy
+ Frequency Rates are calculated as 7x [(Number of SBMs or BMs) / (Number of Days Observed for that Week)].
~ Tests for differences between groups are based on van Elteren tests stratified by study.

Medical Officer Comments

Table 18 above demonstrates that the SBM frequency rates analyzed by gender reveal analogous findings to those in the primary efficacy analysis of SBM in Table 4. The gender analysis of RU-0211 illustrated a clinically relevant ≥ 3.5 increase in spontaneous bowel movements at Week 1 (the primary efficacy endpoint) in both gender arms. At Week 4, RU-0211 showed consistent clinical efficacy with a ≥ 2.5 increase in SBM in both males and females. Although at Week 4, the male RU-0211 48 mcg group did not reveal statistical significance versus placebo (p-value = 0.0503), the p-value trended in the general overall direction of efficacy. The smaller male sample size may have contributed to the weaker durability of response at Week 4 in this gender.

Secondary Efficacy Variable: Analysis by Gender

A summary of weekly responder rates by gender are presented below in Table 19. As described in the table, the responder status for male subjects taking RU-0211 48 mcg were significantly better than for placebo at all post-baseline time points; p=0.0281 for Week 1, and p=0.0251, p=0.0139, p=0.0354 for Weeks 2, 3, and 4, respectively. The responder status for female subjects taking RU-0211 48 mcg also revealed statistically significant results when compared to placebo (p<0.0001) in all cases.

Table 19: Summary of Weekly Responder Status by Gender (ITT with LOCF) – WCG

Category	Treatment Arm	Responder Status[1]	Week 1 (%)	Week 2 (%)	Week 3 (%)	Week 4 (%)	(Δ%) RU-0211 Versus Placebo Full responders
Male	Placebo N=27	Subjects assessed	27/27 (100.0)	27/27 (100.0)	27/27 (100.0)	25/27 (92.6)	
		Full Responder	**11/27 (40.7)**	**7/27 (25.9)**	**8/27 (29.6)**	**8/25 (32.0)**	
		Moderate Responder	3/27 (11.1)	7/27 (25.9)	3/27 (11.1)	2/25 (8.0)	
		Non Responder	13/27 (48.1)	13/27 (48.1)	16/27 (59.3)	15/25 (60.0)	
	RU-0211 48 mcg N=32	Subjects assessed	32/32 (100.0)	32/32 (100.0)	32/32 (100.0)	28/32 (87.5)	**Male Δ% Weeks 1/4 24.9/25.9**
		Full Responder	**21/32 (65.6)**	**20/32 (62.5)**	**21/32 (65.6)**	**17/28 (57.8)**	
		Moderate Responder	6/32 (18.8)	2/32 (6.3)	0/32 (0.0)	2/28 (7.1)	
		Non Responder	5/32 (15.6)	10/32 (31.3)	11/32 (34.4)	9/28 (32.1)	
		P-value[2]	0.0281	0.0251	0.0139	0.0354	
Female	Placebo N=246	Subjects assessed	245/246 (99.6)	245/246 (99.6)	245/246 (99.6)	214/246 (87.0)	
		Full Responder	**112/245 (45.7)**	**97/245 (39.6)**	**80/245 (32.7)**	**71/214 (33.2)**	
		Moderate Responder	37/245 (14.1)	30/245 (12.2)	34/245 (13.9)	35/214 (16.4)	
		Non Responder	96/245 (39.2)	118/245 (48.2)	131/245 (53.5)	108/214 (50.5)	
	RU-0211 48 mcg N=239	Subjects assessed	227/239 (95.0)	227/239 (95.0)	227/239 (95.0)	119/239 (83.3)	**Female Δ% Weeks 1/4 22.6/25.1**
		Full Responder	**115/227 (68.3)**	**130/227 (57.3)**	**130/227 (57.3)**	**116/199 (58.3)**	
		Moderate Responder	25/227 (11.0)	25/227 (11.0)	22/227 (9.7)	21/199 (10.6)	
		Non Responder	47/227 (20.7)	72/227 (31.7)	75/227 (33.0)	62/199 (31.2)	
		P-value[2]	<0.0001	<0.0001	<0.0001	<0.0001	

Reviewer's table, modified from sponsor's table 1.3.1.2, page 289 of 347, Integrated Summary of Efficacy

1. Full Responder: defined as a responder with ≥ 4 SBMs per week; Moderate Responder: defined as a responder with ≥ 3 but < 4 SBMs per week; Non-Responder: defined as a subject with < 3 SBMs for a given week, who dropped out during the given week due to lack of efficacy, or any subject who used rescue medication during or within 24 hours prior to the given week.
2. Tests for differences between groups are based on van Elteren tests stratified by study.

Medical Officer Comments

The proportion of full responders (i.e., those subjects with ≥ 4 SBMs per week) in both gender subpopulations was significantly higher in the RU-0211 48 mcg group than in the placebo group at all time points. Specifically, the proportion of full responders in the RU-0211 48 mcg male group was at least 57.8% at all time points and at least 24 percentage points higher than the proportion of full responders in the placebo group. The proportion of full responders in the RU-0211 48 mcg female group was at least 57.3% at all time points and at least 17 percentage points higher than the portion of full responders in the placebo group. In both gender groups in all treatment arms, the proportion of full responders was highest for Week 1 (40.7% for placebo for males; 65.6% for RU-0211 48 mcg for male; 45.7% for placebo for females; 68.36% for RU-0211 48 mcg for females). The percentage difference between male full responders in the RU-0211 48 mcg group versus placebo at Weeks 1 and 4 was 24.9 and 25.9%, respectively. Analogously, the percentage difference between female full responders in the RU-0211 48 mcg group versus placebo at Weeks 1 and 4 was 22.6 and 25.1%.

Overall, the aforementioned gender analyses demonstrate that there are no appreciable differences in the effectiveness of RU-0211 among male and female subjects.

Primary Efficacy Variable: Analysis by Race

Overall, for the well-controlled studies, there were 220 white subjects that took placebo, 224 white subjects that took RU-0211 48 mcg, 53 non-white subjects who took placebo, and 47 non-white subjects who took RU-0211 48 mcg.

As noted below in Table 20, the difference in baseline SBM frequency between placebo and RU-0211 48 mcg for whites and non-whites was not statistically significant (whites; p=0.1611 and non-whites; p=0.1816). At all post-baseline time points, the median SBM frequencies were higher for both white and non-white subjects taking RU-0211 48 mcg than those taking placebo, and the difference was statistically significant at all weeks.

Table 20: Summary of SBM Frequency Rates+ by Race (Well-Controlled Group) (Intent-to-Treat Population with Last-Observation-Carried-Forward Population)

Category	Study Arm	Statistic	Baseline	Week 1	Week 2	Week 3	Week 4	Change In BM Baseline To Week 1	Change In BM Baseline To Week 4
White	Placebo N=220	Median	1.50	3.00	3.00	2.10	3.00	1.50	0.50
	RU-0211 48 mcg N=224	Median P-value~	1.50 0.1611	5.00 **<0.0001**	4.00 **<0.0001**	5.00 **<0.0001**	4.00 **<0.0001**	**3.50**	**2.50**
Non-White	Placebo N=53	Median	1.50	4.00	3.00	3.50	3.25	2.50	1.75
	RU-0211 47 mcg N=239	Median P-value~	1.08 0.1816	5.50 **0.0014**	5.00 **0.0052**	5.00 **0.0076**	6.00 **0.0024**	**4.42**	**4.92**

Reviewer's table, modified from Table 1.3.2.1, pages 293 of 347, Integrated Summary of Efficacy
+ Frequency Rates are calculated as 7x [(Number of SBMs or BMs) / (Number of Days Observed for that Week)].
~ Tests for differences between groups are based on van Elteren tests stratified by study.

Medical Officer's Comments

Table 20 above demonstrates that the SBM frequency rates analyzed by race reveal analogous findings to those in the primary efficacy analysis of SBM in Table 4. The racial analysis of RU-0211 illustrated a clinically relevant ≥ 3.5 increase in spontaneous bowel movements at Week 1 (the primary efficacy endpoint) in both racial arms. By Week 4, RU-0211 showed consistent clinically efficacy of a ≥ 2.5 increase in SBM in both males and females. Of note, over the four week trial, the non-white group's median SBM frequency rate increased to 6.00 SBMs by Week 4 whereas the white group's median SBM frequency rate increased to only 4.00 SBM by Week 4. Although both statistically significant, the non-white subgroup had larger changes from baseline at Weeks 1 and 4 of 4.42 and 4.92 compared to the white subgroup with changes of 3.50 and 2.50, respectively. The reviewer is cautious to draw any conclusions from such data when taken in context with the responder analysis by race as shown below.

Table 21: Summary of Weekly Responder Status by Race (ITT with LOCF) – WCG

Category	Treatment Arm	Responder Status[1]	Week 1 (%)	Week 2 (%)	Week 3 (%)	Week 4 (%)	(Δ%) RU-0211 Versus Placebo Full responders
White	Placebo N=220	Subjects assessed	219/220 (99.5)	219/220 (99.5)	219/220 (99.5)	191/220 (86.8)	
		Full Responder	**96/219 (43.8)**	**84/219 (38.4)**	**64/219 (29.2)**	**59/191 (30.9)**	
		Moderate Responder	33/219 (15.1)	25/219 (11.4)	32/219 (14.6)	28/191 (14.7)	
		Non Responder	90/219 (41.1)	110/219 (50.2)	123/219 (56.2)	104/191 (54.50	**White Δ% Weeks 1/4 22.7/25.0**
	RU-0211 48 mcg N=224	Subjects assessed	215/224 (96.0)	215/224 (96.0)	215/224 (96.0)	186/224 (83.0)	
		Full Responder	**143/215 (66.5)**	**121/215 (56.3)**	**123/215 (57.2)**	**104/186 (55.9)**	
		Moderate Responder	143/215 (11.6)	25/215 (11.6)	18/215 (8.4)	18/186 (9.7)	
		Non Responder	25/215 (21.9)	69/215 (32.1)	74/215 (34.4)	64/186 (34.4)	
		P-value[2]	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	
Non-White	Placebo N=53	Subjects assessed	53/53 (100.0)	53/53 (100.0)	53/53 (100.0)	48/53 (90.6)	
		Full Responder	**27/53 (50.9)**	**20/53 (37.7)**	**24/53 (45.3)**	**20/48 (41.7)**	
		Moderate Responder	7/53 (13.2)	12/53 (22.6)	5/53 (9.4)	9/48 (18.8)	
		Non Responder	19/53 (35.8)	21/53 (39.6)	24/53 (45.3)	19/48 (39.6)	**Non-White Δ% Weeks 1/4 24.1/29.0**
	RU-0211 48 mcg N=47	Subjects assessed	44/47 (93.6)	44/47 (93.6)	44/47 (93.6)	41/47 (87.2)	
		Full Responder	**33/44 (75.0)**	**29/44 (65.9)**	**28/44 (63.6)**	**29/41 (70.7)**	
		Moderate Responder	6/44 (13.6)	2/44 (4.5)	4/44 (9.1)	5/41 (12.2)	
		Non Responder	5/44 (11.4)	13/44 (29.5)	12/44 (27.3)	7/41 (17.1)	
		P-value[2]	**0.0054**	**0.0286**	0.0501	**0.0058**	

Reviewer's table, modified from sponsor's table 1.3.2.2, page 294 of 347, Integrated Summary of Efficacy

1. Full Responder: defined as a responder with ≥ 4 SBMs per week; Moderate Responder: defined as a responder with ≥ 3 but < 4 SBMs per week; Non-Responder: defined as a subject with < 3 SBMs for a given week, who dropped out during the given week due to lack of efficacy, or any subject who used rescue medication during or within 24 hours prior to the given week.
2. Tests for differences between groups are based on van Elteren tests stratified by study

Medical Officer Comments

The proportion of full responders (i.e., those subjects with ≥ 4 SBMs per week) in both racial subpopulations was significantly higher in the RU-0211 48 mcg group than in the placebo group at all time points except Week 3 of the non-white subgroup. Although the difference between placebo and RU-0211 48 mcg was not statistically significant for Week 3 for non-white subjects, the magnitude of the effect of RU-0211 on increasing SBM frequency and improving responder rates was generally similar for both whites and non-white subjects.

Specifically, the proportion of full responders in the RU-0211 48 mcg white subgroup was at least 55.9% at all time points and at least 17 percentage points (at times 25 points) higher than the proportion of full responders in the placebo group. The proportion of full responders in the RU-0211 48 mcg non-white subgroup was at least 63.6% at all time points and at least 18 percentage points (at times 29 points) higher than the portion of full responders in the placebo group. In both racial subgroups, the proportion of full responders was highest for Week 1 (43.8% for placebo for whites; 66.5% for RU-0211 48 mcg for whites; 50.9% for placebo for non-whites; 75.0% for RU-0211 48 mcg for non-whites). The percentage difference between white full responders in the RU-0211 48 mcg group versus placebo at Weeks 1 and 4 was 22.7 and 25.0%, respectively. Analogously, the percentage difference between non-white full responders in the RU-0211 48 mcg group versus placebo at Weeks 1 and 4 was 24.1 and 29.0%.

The aforementioned racial analyses demonstrate that there are no appreciable differences in the effectiveness of RU-0211 among white and non-white subjects.

Primary Efficacy Variable: Analysis by Age

For the well-controlled studies, the numbers of subjects (n) were analyzed in three different age groups. The age groups were classified as followed:

Table 22: Analysis by Age; Age Group Designation

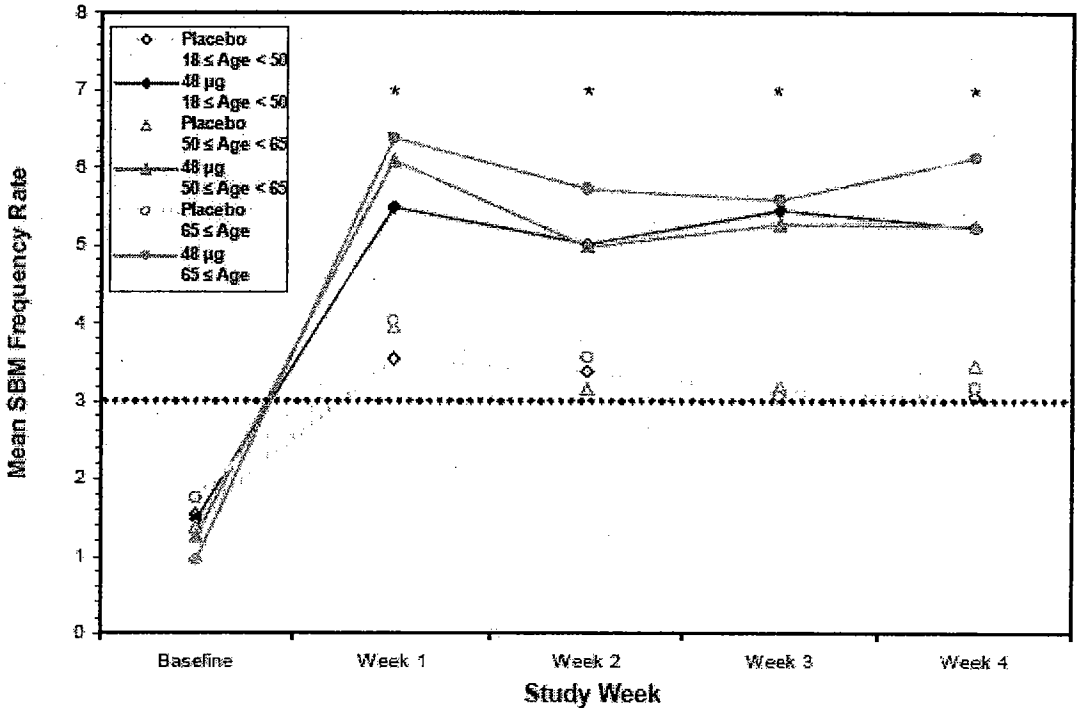
Age Group	Ages	Placebo (n)	RU-0211 (n)
Group 1	18 ≤ age < 50	161	153
Group 2	50 ≤ age < 65	81	92
Group 3	65 ≤ age	31	26

Reviewer's table, based on sponsors' data, page 88 of 108, 2.7.3, Summary of Clinical Efficacy

As noted below in Table 22, for subjects in all three age groups, the difference in baseline SBM frequency between placebo and RU-0211 48 mcg was not statistically significant. At all post-baseline time points, the median SBM frequencies were higher for subjects taking RU-0211 48 mcg than those taking placebo. Significant differences were detected only in Age Group 1 (18 ≤ age < 50) and Age Group 2 (50 ≤ age < 65). In these two groups, the differences were significant at Weeks 1, 2, 3, and 4 to $p \leq 0.0217$. The median SBM frequency rates in Age Group 3 were higher than those in the placebo group at all post-baseline time points; however, none were statistically significant.

Figure 6 below is a graphic depiction of the mean SBM frequency rates by Age group over time. The dashed line indicates criteria for enrollment; < 3 SBMs per week. The asterisk indicates statistical significance in subjects treated with RU-0211 48 mcg in Age group 1 and 2.

Figure 6: Mean SBM Frequency Rates by Age Group (ITT with LOCF: WCG)



Sponsor's figure, Figure 2.7.3.3-4, page 89 of 108, Summary of Clinical Efficacy

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Table 23: Summary of Weekly Responder Status by Age+ (ITT with LOCF) – WCG

Category	Study Arm	Statistic	Baseline	Week 1	Week 2	Week 3	Week 4	Change In BM Baseline To Week 1	Change In BM Baseline To Week 4
18 ≤Age< 50	Placebo N=161	Median	1.50	3.00	3.00	3.00	3.00	1.50	1.50
	RU-0211 48 mcg N=153	Median P-value~	1.50 0.5481	5.00 <0.0001	4.00 0.0004	5.00 <0.0001	4.07 <0.0001	3.50	2.57
50 ≤Age< 65	Placebo N=81	Median	1.50	4.00	3.00	3.00	3.00	2.51	1.50
	RU-0211 48 mcg N=92	Median P-value~	1.50 0.3123	5.00 0.0009	4.00 0.0026	5.00 0.0007	4.00 0.0217	3.50	2.50
65 ≤ Age	Placebo N=31	Median	1.50	3.00	2.00	3.00	3.00	1.50	1.50
	RU-0211 48 mcg N=26	Median P-value~	1.00 0.0522	5.00 0.0897	3.50 0.2902	3.50 0.2130	5.00 0.0690	4.00	4.00

Reviewer's table, modified from Table 1.3.3.1, pages 298 of 347, Integrated Summary of Efficacy
+ Frequency Rates are calculated as 7x [(Number of SBMs or BMs) / (Number of Days Observed for that Week)].
~ Tests for differences between groups are based on van Elteren tests stratified by pooled center for the individual studies and stratified by study for the Pooled Group analysis.

Medical Officer's Comments

Table 23 above demonstrates that the SBM frequency rates analyzed by age mirror those found in the primary efficacy analysis for SBM found in Table 4. The age analysis of RU-0211 illustrated a clinically relevant ≥ 3.5 increase in spontaneous bowel movements at Week 1 (the primary efficacy endpoint) in all three Age Groups. By Week 4, RU-0211 showed consistent clinically efficacy of a ≥ 2.5 increase in SBM in all three Age Groups. Age Group 3 (65 ≤ Age) did not reveal statistical significance in any post-baseline time point; however, the median SBM frequency rates were higher than placebo throughout Weeks 1 through 4 and the clinical relevance of RU-0211 on increasing SBM frequency was still evident. Because of the relatively smaller sample size in Group 3 (65 ≤ Age) and the noticeable disparity in the baseline constipation status between treatment groups in this age group (RU-0211, 1.00; Placebo, 1.50), the medical officer is cautious to derive any meaningful conclusions regarding lack of efficacy in this Age Group.

Table 24: Summary of Weekly Responder Status by Age (ITT with LOCF) – WCG

Category	Treatment Arm	Responder Status[1]	Week 1 (%)	Week 2 (%)	Week 3 (%)	Week 4 (%)	(Δ%) RU-0211 Versus Placebo Full responders
18 ≤Age≤ 50	Placebo N=161	Subjects assessed	161/161 (100.0)	161/161 (100.0)	161/161 (100.0)	144/220 (86.8)	
		Full Responder	**68/161 (42.2)**	**65/161 (40.4)**	**52/161 (32.3)**	**45/144 (31.3)**	
		Moderate Responder	27/161 (16.8)	21/161 (13.0)	22/161 (13.7)	25/144 (17.4)	
		Non Responder	66/161 (41.0)	75/161 (46.6)	87/161 (54.0)	74/144 (51.4)	
	RU-0211 48 mcg N=153	Subjects assessed	142/153 (92.8)	142/153 (92.8)	142/153 (92.8)	129/224 (83.0)	Δ% Weeks 1/4 **24.3/26.8**
		Full Responder	**93/142 (66.5)**	**82/142 (57.7)**	**83/142 (58.5)**	**75/129 (58.1)**	
		Moderate Responder	19/142 (13.4)	18/142 (12.7)	17/142 (12.0)	15/129 (11.6	
		Non Responder	30/142 (21.1)	42/142 (29.6)	42/142 (29.6)	39/129 (30.2)	
		P-value[2]	**<0.0001**	**0.0014**	**<0.0001**	**<0.0001**	
50 ≤Age< 65	Placebo N=81	Subjects assessed	80/81 (98.8)	80/81 (98.8)	80/81 (98.8)	66/81 (98.8)	
		Full Responder	**43/80 (53.8)**	**26/80 (32.5)**	**28/80 (35.0)**	**25/66 (37.9)**	
		Moderate Responder	8/80 (10.0)	15/80 (18.8)	10/80 (12.5)	7/66 (10.6)	
		Non Responder	29/80 (36.3)	39/80 (48.8)	42/80 (52.5)	34/66 (51.5)	
	RU-0211 48 mcg N=92	Subjects assessed	91/92 (98.9)	91/92 (98.9)	91/92 (98.9)	75/92 (98.9)	Δ% Weeks 1/4 **19.8/19.4**
		Full Responder	**67/91 (73.6)**	**55/91 (60.4)**	**55/91 (60.4)**	**43/75 (57.3)**	
		Moderate Responder	9/91 (9.9)	8/91 (8.8)	5/91 (5.5)	7/75 (9.3)	
		Non Responder	15/91 (16.5)	28/91 (30.8)	31/91 (34.1)	25/75 (33.3)	
		P-value[2]	**0.0049**	**0.0010**	**0.0029**	**0.0215**	

Reviewer's table, modified from sponsor's table 1.3.3.2, page 299 of 347, Integrated Summary of Efficacy

1. Full Responder: defined as a responder with ≥ 4 SBMs per week; Moderate Responder: defined as a responder with ≥ 3 but < 4 SBMs per week; Non-Responder: defined as a subject with < 3 SBMs for a given week, who dropped out during the given week due to lack of efficacy, or any subject who used rescue medication during or within 24 hours prior to the given week.

2. Tests for differences between groups are based on van Elteren tests stratified by study

Table 25: Summary of Weekly Responder Status by Age Continued

Category	Treatment Arm	Responder Status[1]	Week 1 (%)	Week 2 (%)	Week 3 (%)	Week 4 (%)	(Δ%) RU-0211 Versus Placebo Full responders
65 ≤ Age	Placebo N=31	Subjects assessed	31/31 (100.0)	31/31 (100.0)	31/31 (100.0)	29/31 (93.5)	
		Full Responder	**12/31 (38.7)**	**13/31 (41.9)**	**8/31 (25.8)**	**9/29 (31.0)**	
		Moderate Responder	5/31 (16.1)	1/31 (3.2)	5/31 (16.1)	5/29 (17.2)	
		Non Responder	14/31 (45.2)	17/31 (54.8)	18/31 (58.1)	15/29 (51.7)	
	RU-0211 48 mcg N=26	Subjects assessed	26/26 (100.0)	26/26 (100.0)	26/26 (100.0)	23/26 (88.5)	Δ% Weeks 1/4 22.8/34.2
		Full Responder	**16/26 (61.5)**	**13/26 (50.0)**	**13/26 (50.0)**	**15/23 (65.2)**	
		Moderate Responder	16/26 (11.5)	0/26 (3.8)	0/26 (0.0)	1/23 (4.3)	
		Non Responder	16/26 (26.9)	12/26 (46.2)	13/26 (50.0)	7/23 (30.4)	
		P-value[2]	0.0676	0.5045	0.2108	0.0322	

Reviewer's table, modified from sponsor's table 1.3.3.2, page 300 of 347, Integrated Summary of Efficacy

1. **Full Responder: defined as a responder with ≥ 4 SBMs per week; Moderate Responder: defined as a responder with ≥ 3 but < 4 SBMs per week; Non-Responder: defined as a subject with < 3 SBMs for a given week, who dropped out during the given week due to lack of efficacy, or any subject who used rescue medication during or within 24 hours prior to the given week.**
2. Tests for differences between groups are based on van Elteren tests stratified by study

Medical Officer Comments

The proportion of full responders (i.e., those subjects with ≥ 4 SBMs per week) in Age Groups 1 and 2 were significantly higher in the RU-0211 48 mcg group than in the placebo group at all time points (p ≤ 0.0215). Specifically, the proportion of RU-0211 48 mcg full responders in Age Group 1 was at least 57.5% at all time points and at least 17 percentage points (at times 26 points) higher than the proportion of full responders in the placebo group. The proportion of RU-0211 48 mcg full responders in Age Group 2 was at least 57.3% at all time points and at least 18 percentage points (at times 29 points) higher than the portion of full responders in the placebo group.

The difference between placebo and RU-0211 48 mcg was only statistically significant for Age Group 3 at Week 4. Although statistical significance was not demonstrated at Weeks 1, 2, and 3 in Age Group 3, the proportion of full responders in the RU-0211 48 mcg group was higher than the placebo group at all post-baseline time points. The proportion of RU-0211 48 mcg full responders in Age Group 3 was at least 50% at all time points and at least 8 percentage points (at times 34 percentage points) higher than the portion of full responders in the placebo group. The percentage of full responders in this Age Group was only 7% less than the younger age groups.

In all three Age Groups, the proportion of full responders was highest for Week 1 (42.2% for placebo in Age Group 1; 66.5% for RU-0211 48 mcg in Age Group 1; 53.8% for placebo in Age Group 2; 73.6% for RU-0211 48 mcg in Age Group 2; 38.7% for placebo in Age Group 3;

61.5% for RU-0211 48 mcg in Age Group 3). The percentage difference between Age Group 1 full responders in the RU-0211 48 mcg group versus placebo at Weeks 1 and 4 was 24.3 and 26.8%, respectively. The percentage difference between Age Group 2 full responders in the RU-0211 48 mcg group versus placebo at Weeks 1 and 4 was 19.8 and 19.4%. The percentage difference between Age Group 3 full responders in the RU-0211 48 mcg group versus placebo at Weeks 1 and 4 was 22.8 and 34.2%.

The aforementioned age analyses demonstrate that RU-0211 appeared to be similarly effective in all 3 age groups.

Analysis by IBS Subgroup

The diagnosis of IBS was not a part of the conduct of the clinical trials for lubiprostone. For the pivotal studies SC0131 and SC0232; however, IBS status was collected via subjects self-reporting their diagnosis of IBS at the time of study entry. Information on IBS status was not collected in Study SC9921; thus, that study was excluded from this analysis. For all analyses by IBS subgroup, the numbers of subjects (n) analyzed were as follows: 46 IBS subjects took placebo, 45 IBS subjects took RU-0211 48 mcg, 194 non-IBS subjects took placebo, and 194 non-IBS subjects took RU-0211 48 mcg.

The median baseline rate for both treatment arms in both pooled groups was 1.50. At each post-baseline assessment time point in both pooled groups, the median SBM frequencies were higher for subjects taking RU-0211 48 mcg than for subjects taking placebo, and at each time point, the difference was statistically significant ($p \leq 0.0207$ for IBS subjects; $p \leq 0.0005$ non-IBS subjects).

Table 26: Summary of SBM Frequency Rates[+] by IBS Subgroup (Well-Controlled Group) (Intent-to-Treat Population with Last-Observation-Carried-Forward Population)

Category	Study Arm	Statistic	Baseline	Week 1	Week 2	Week 3	Week 4	Change In BM Baseline To Week 1	Change In BM Baseline To Week 4
Pooled IBS	Placebo N=46	Median	1.50	3.00	3.00	2.00	2.00	1.50	0.50
	RU-0211 48 mcg N=45	Median **P-value[~]**	1.50 0.4884	5.00 **0.0050**	5.00 **0.0193**	5.00 **0.0004**	4.00 **0.0207**	**3.50**	**2.50**
Pooled Non-IBS	Placebo N=194	Median	1.50	3.00	3.00	3.00	3.00	1.50	1.50
	RU-0211 47 mcg N=194	Median **P-value[~]**	1.50 0.0574	5.00 **<0.0001**	4.00 **0.0005**	5.00 **<0.0001**	4.20 **<0.0001**	**3.50**	**2.70**

Reviewer's table, modified from Table 1.3.4.1, pages 304 of 347, Integrated Summary of Efficacy

+ Frequency Rates are calculated as 7x [(Number of SBMs or BMs) / (Number of Days Observed for that Week)].

~ Tests for differences between groups are based on van Elteren tests stratified by study.

Medical Officer's Comments

Table 26 above demonstrates that the SBM frequency rates analyzed by IBS subgroup are analogous to those found in the primary efficacy analysis for SBM found in Table 4. The IBS analysis of RU-0211 illustrated a clinically relevant ≥ 3.5 increase in spontaneous bowel movements at Week 1 in both subgroups. By Week 4, RU-0211 showed consistent clinical efficacy with a ≥ 2.5 increase in SBM in both the IBS and non-IBS subgroup.

Table 27: Summary of Weekly Responder Status by IBS Subgroup (ITT with LOCF) – WCG

Category	Treatment Arm	Responder Status[1]	Week 1	Week 2	Week 3	Week 4	(Δ%) RU-0211 Versus Placebo Full responders
IBS Subgroup	Placebo N=46	Subjects assessed	46/46 (100.0)	46/46 (100.0)	46/46 (100.0)	46/46 (100.0)	IBS Δ% Weeks 1/4 28.7/19.9
		Full Responder	**21/46 (45.7)**	**18/46 (39.1)**	**14/46 (30.4)**	**11/46 (31.3)**	
		Moderate Responder	6/46 (13.0)	4/46 (8.7)	4/46 (8.7)	4/46 (8.7)	
		Non Responder	19/46 (41.3)	24/46 (52.2)	28/46 (60.9)	31/46 (67.4)	
	RU-0211 48 mcg N=45	Subjects assessed	43/45 (95.6)	43/45 (95.6)	43/45 (95.6)	43/45 (95.6)	
		Full Responder	**32/43 (74.4)**	**25/43 (58.1)**	**25/43 (58.1)**	**22/43 (51.2)**	
		Moderate Responder	4/43 (9.3)	2/43 (4.7)	1/43 (2.3)	3/43 (7.0)	
		Non Responder	7/43 (16.3)	16/43 (37.2)	17/43 (39.5)	18/43 (41.9)	
		P-value[2]	0.0056	0.0773	0.0155	0.0076	
Non-IBS Subgroup	Placebo N=194	Subjects assessed	193/194 (99.5)	193/194 (99.5)	193/194 (99.5)	193/194 (99.5)	Non-IBS Δ% Weeks 1/4 20.7/25.1
		Full Responder	**89/193 (46.1)**	**76/193 (39.4)**	**63/193 (32.6)**	**68/193 (35.2)**	
		Moderate Responder	27/193 (14.0)	26/193 (13.5)	27/193 (14.0)	33/193 (17.7)	
		Non Responder	77/193 (39.9)	91/193 (47.2)	103/193 (53.4)	92/193 (47.7)	
	RU-0211 48 mcg N=194	Subjects assessed	184/194 (94.8)	184/194 (94.8)	184/194 (94.8)	184/194 (94.8)	
		Full Responder	**123/184 (66.8)**	**106/184 (57.6)**	**108/184 (58.7)**	**111/184 (60.3)**	
		Moderate Responder	26/184 (14.1)	21/184 (11.4)	18/184 (9.8)	20/184 (10.9)	
		Non Responder	35/184 (19.0)	57/184 (31.0)	58/184 (31.5)	53/184 (28.8)	
		P-value[2]	<0.0001	0.0004	<0.0001	<0.0001	

Reviewer's table, modified from sponsor's table 1.3.4.4, page 308 of 347, Integrated Summary of Efficacy

1. **Full Responder: defined as a responder with ≥ 4 SBMs per week; Moderate Responder: defined as a responder with ≥ 3 but < 4 SBMs per week; Non-Responder: defined as a subject with < 3 SBMs for a given week, who dropped out during the given week due to lack of efficacy, or any subject who used rescue medication during or within 24 hours prior to the given week.**
2. Tests for differences between groups are based on van Elteren tests stratified by study

Medical Officer Comments

The proportion of full responders (i.e., those subjects with ≥ 4 SBMs per week) in both IBS subpopulations was significantly higher in the RU-0211 48 mcg group than in the placebo group at all time points except Week 2 of the IBS subgroup. Although the difference between placebo and RU-0211 48 mcg was not statistically significant for Week 2 for IBS subjects, the magnitude of the effect of RU-0211 on increasing SBM frequency and improving responder rates was generally similar for both IBS and non-IBS subjects. Specifically, the proportion of full responders in the RU-0211 48 mcg IBS subgroup was at least 51.2% at all time points and at least 19 percentage points (at times 28 points) higher than the proportion of full responders in the placebo group. The proportion of full responders in the RU-0211 48 mcg non-IBS subgroup was at least 57.6% at all time points and at least 18 percentage points (at times 26 points) higher than the portion of full responders in the placebo group. In both subgroups, the proportion of full responders was highest for Week 1 (74.4% for placebo for IBS; 45.7% for RU-0211 48 mcg for IBS; 46.1% for placebo for non-IBS; 66.8% for RU-0211 48 mcg for non-IBS). The percentage difference between IBS full responders in the RU-0211 48 mcg group versus placebo at Weeks 1 and 4 was 28.7 and 19.9%, respectively. Similarly, the percentage difference between non-IBS full responders in the RU-0211 48 mcg group versus placebo at Weeks 1 and 4 was 20.7 and 25.1%.

The aforementioned IBS analyses demonstrate that there does not appear to be an obvious relationship between subjects having IBS and their response over time to treatment with RU-0211 48 mcg.

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Subject Disposition:

As noted below in Tables 28 and 29, of the subjects in the well-controlled pooled group, a total of 544 were treated. Of those subjects treated, 273 subjects took placebo and 271 subjects took RU-0211 48 mcg/day. Overall, 485 subjects (88.8%) completed their respective studies, i.e., they completed the end of study visit. In the placebo group, 253 subjects (92.0%) completed, and in the RU-0211 48 mcg/day group, 232 subjects (85.6%) completed.

Table 28: Subject Disposition: Well-Controlled Group (All Randomized Subjects)

	SC0131			SC0232		
Variable	Placebo N=124 (%)	RU-0211 48 mcg N=120 (%)	Total N= 244 (%)	Placebo N=118 (%)	RU-0211 48 mcg N=119 (%)	Total N=237 (%)
Subjects Assessed	124 (100)	120 (100)	**244 (100)**	118 (100)	119 (100)	**237 (100)**
Treated	122 (98.4)	120 (100)	**242 (99.2)**	118 (100)	119 (100)	**237 (100)**
Not Treated	2 (1.6)	0 (0.0)	**2 (0.8)**	0 (0.0)	0 (0.0)	**0 (0.0)**
Completed Subjects	118 (95.2)	106 (88.3)	**224 (91.8)**	107 (90.7)	99 (83.2)	**206 (86.9)**

Reviewer's table, modified from Table 2.7.3.3-1, page 32 of 108, Summary of Clinical Efficacy for RU-0211

Table 29: Subject Disposition: Well-Controlled Group (All Randomized Subjects)

	SC9921			Pooled Group		
Variable	Placebo N=124 (%)	RU-0211 48 mcg N=120 (%)	Total N= 244 (%)	Placebo N=118 (%)	RU-0211 48 mcg N=119 (%)	Total N=237 (%)
Subjects Assessed	33 (100.0)	32 (100.0)	**65 (100.0)**	275 (100.0)	271 (100.0)	**546 (100.0)**
Treated	33 (100.0)	32(100.0)	**65 (100.0)**	273 (99.3)	271 (100.0)	**544 (99.6)**
Not Treated	0 (0.0)	0 (0.0)	**0 (0.0)**	2 (0.7)	0 (0.0)	**2 (0.4)**
Completed Subjects	28 (84.8)	27 (84.4)	**55 (84.6)**	253 (92.0)	232 (85.6)	**485 (88.8)**

Reviewer's table, modified from Table 2.7.3.3-1, page 34 of 108, Summary of Clinical Efficacy for RU-0211

Table 30: Subject Disposition: Long-Term Safety Subjects (All Randomized Subjects)

	SC01S1	SC01S2	SC02S3	Pooled Group
Variable	RU-0211 48 mcg N=308 (%)	RU-0211 48 mcg N=250 (%)	RU-0211 48 mcg N=325 (%)	Pooled Group N=883 (%)
Subjects Assessed	308 (100.0)	250 (100.0)	325 (100.0)	**883 (100.0)**
Treated	306 (100.0)	248 (100.0)	324 (99.7)	**878 (99.4)**
Not Treated	2 (0.0)	2 (0.0)	1 (0.3)	**5 (0.6)**
Completed Subjects	165 (53.6)	127 (50.8)	153 (47.1)	**445 (50.4)**

Reviewer's table, modified from Table 2.7.3.3-1, page 36 of 108, Summary of Clinical Efficacy for RU-0211

A summary of subject disposition for the long-term safety subjects is presented above in table 30. Overall, for the pooled group, 878 subjects were treated, and 445 subjects (50.4%) completed their respective studies.

6.1.5 Clinical Microbiology

No microbiology information was included in this application.

6.1.6 Efficacy Conclusions

The clinical program with RU-0211 (lubiprostone) 48 mcg (24 mcg b.i.d), consisting of two adequate and well-controlled Phase III efficacy studies and three phase III, long-term safety and efficacy studies, demonstrates that administration of RU-0211 24 mcg b.i.d. — chronic idiopathic constipation — in the adult population. Statistical significance was attained for the primary efficacy endpoint; the frequency of spontaneous bowel movements (SBMs) at Week 1, for both pivotal studies. Statistical significance for RU-0211 24 mcg b.i.d. over placebo for the treatment of chronic idiopathic constipation was also observed in the following secondary efficacy variables: frequency of SBMs at Weeks 2, 3, and 4; weekly responder rates (at each week and all weeks); percentage of subjects with an SBM within 24 hours after first dose of study drug; time to first SBM; average stool consistency; average degree of straining; constipation severity; and treatment effectiveness.

The frequency rate of spontaneous bowel movements (SBMs) during Week 1 was the protocol defined primary efficacy endpoint for the two pivotal studies in this application. A spontaneous bowel movement was defined by the sponsor as any bowel movement that did not occur within 24 hours after rescue medication use. This endpoint was appropriate as it provided an objective measurement of the effect of RU-0211 on subject constipation. Week 1 was chosen as the time

point in the primary efficacy variable rather than a later time point as the effectiveness of a medication that provides rapid onset of chronic constipation relief would need to show efficacy within the first week of treatment. Perhaps a more clinically meaningful primary endpoint, however; notably more stringent, would have been a responder analysis based upon spontaneous bowel movement frequency rates of ≥ 3 spontaneous bowel movements per week for all 4 weeks. This endpoint would have captured not only the rapidity of effect for lubiprostone, but also its durability of response. The Agency's statistical reviewer for this NDA performed such an analysis on the intent-to-treat population without using the last-observation-carried-forward method to impute missing values. In this re-analysis, both pivotal studies, SC0131 and SC0232 showed RU-0211 were superior to placebo with treatment differences of 24% and 16%, respectively.

The secondary efficacy endpoints were many and included SBM frequency rates during Weeks 2, 3, and 4; SBMs within 24 hours of first RU-0211 dose; Time to first SBM; Responder analyses (at each week and all weeks); Weekly stool consistency; Weekly stool straining; Weekly severity of constipation; Weekly global treatment effectiveness; Weekly abdominal bloating; and Weekly abdominal discomfort.

Study SC0131 enrolled 242 subjects (120 – RU-0211, 122 – placebo) throughout 20 centers in the United States and randomly allocated them to either RU-0211 24 mcg b.i.d. or placebo. In Study SC0131's efficacy analysis, the median SBM frequency rate during Week 1 was significantly higher ($p = 0.0001$) in the 48 mcg RU-0211 group (5 SBM/week) than in the placebo group (3 SBM/week). Statistical significance in Study SC0131 was also seen for the SBM frequency rate during Weeks 2, 3, and 4 (median 4-5 SBM/week versus 2-3 SBM/week for RU-0211 and placebo groups, respectively). This statistically significant increase in SBM frequency rate translates into a clinically meaningful increase in spontaneous bowel movements from one SBM every 4-5 days to one SBM every 1-2 days. Study SC0131 also demonstrated the statistical significance of RU-0211 over placebo in most of the secondary endpoints including; the percentage of SBM within 24 hours of first study drug administration, time to first SBM, average stool consistency, average degree of straining, weekly severity of constipation, and weekly treatment effectiveness. Although Study SC0131 did not show consistent statistical significance for the weekly abdominal bloating and discomfort secondary endpoints, the results for these secondary efficacy variables were clinically meaningful and trended in favor of the efficacy of RU-0211 48 mcg/day.

Study SC0232 enrolled 237 subjects (119 – RU-0211, 118 – placebo) throughout 20 centers in the United States and randomly allocated them to either RU-0211 mcg b.i.d. or placebo. In the primary efficacy analysis, the median SBM frequency rate during Week 1 was significantly higher ($p < 0.0001$) in the 48 mcg RU-0211 group (5 SBM/week) than in the placebo group (3.5 SBM/week). Statistical significance in Study SC0232 was also seen for the SBM frequency rate during Weeks 2, 3, and 4 (median 4-5 SBM/week versus 3 SBM/week for RU-0211 and placebo groups, respectively). Similar to pivotal study SC0131, this statistically significant increase in SBM frequency rate translates into a clinically meaningful increase in SBM from 1 SBM every 4 to 5 days to 1 SBM every 1 to 2 days. Similar to Study SC0131, Study SC0232 also demonstrated the statistical significance of RU-0211 over placebo in most of the secondary endpoints including; the percentage of SBM within 24 hours of first study drug administration,

time to first SBM, average stool consistency, average degree of straining, weekly severity of constipation, and weekly treatment effectiveness. Although Study SC0232 did not show statistical significance for the weekly abdominal bloating and discomfort secondary endpoints, the results for these secondary efficacy variables were clinically meaningful and trended in favor of the efficacy of RU-0211 48 mcg/day.

The overall efficacy of RU-0211 (lubiprostone) 24 mcg b.i.d. revealed not only improvements in subject regularity with respect to spontaneous bowel movement frequency, but also contributed to several improvements in subjective quality of life assessments. These improvements were true in short-term studies (up to 4 weeks) and long-term studies (up to 48 weeks).

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The variables used to assess safety in this New Drug Application for RU-0211 (lubiprostone) 24 mcg b.i.d. fo[redacted]hronic idiopathic constipation [redacted] in the adult population were many. Similar methods for safety monitoring were used across all five Phase III trials including: adverse event (AE) and vital sign recording, comprehensive physical examinations including a bilateral hand X-rays, clinical laboratory tests including hematology, serum chemistry, urinalysis, and electrocardiography.

The overall summary of adverse events for the Well-controlled group is illustrated below in Table 31. Across the 3 well-controlled studies (SC0131, SC0232, and SC9921), 42.5% of placebo subjects and 63.8% of subjects taking RU-0211 48 mcg reported at least 1 adverse event (AE), a difference that was statistically significant ($p<0.0001$). With an increasing dose level, 62.1% of subjects taking <48 mcg RU-0211, 63.8% of subjects taking 48 mcg RU-0211, and 69.7% of subjects taking >48 mcg RU-0211, reported at least 1 AE. Nineteen percent of placebo subjects and 47.6% of RU-0211 48 mcg subjects reported at least 1 treatment-related AE; a difference that was statistically significant ($p<0.0001$). With an increasing dose level, 34.5% of subjects taking <48 mcg RU-0211, 47.6 % of subjects taking 48 mcg RU-0211, and 60.6% of subjects taking >48 mcg RU-0211 reported treatment-related AEs. Two placebo subjects (0.7%) and 1 RU-0211 48 mcg subject (0.4%) reported an SAE, none of which were considered treatment related. No subjects in any treatment group died. Overall, 1.5% of placebo subjects and 10.7% of RU-0211 48 mcg subjects discontinued because of an AE; a difference that was statistically significant ($p<0.0001$). Upon dose escalation, 3.4% of subjects taking <48 mcg RU-0211, 10.7% of subjects taking 48 mcg RU-0211, and 9.1% of subjects taking >48 mcg RU-0211 discontinued because of an AE.

Table 31: Overall Summary of Adverse Events in the Well-Controlled Group[1]

Category	Placebo	RU-0211 <48 mcg	RU-0211 48 mcg	RU-0211 >48 mcg	All Active Doses	Statistic
Subjects N (%)	N=273 (100%)	N=29 (100%)	N=271 (100%)	N=33 (100%)	N=333 (100%)	P-value[3]
At least one AE	116 (42.5)	18 (62.1)	173 (63.8)	23 (69.7)	214 (64.3)	<0.0001
At least one treatment-related AE[2]	52 (19.0)	10 (34.5)	129 (47.6)	20 (60.6)	159 (47.7)	<0.0001
At least one SAE	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	1.0000
At least one treatment-related SAE[2]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Discontinued due to an AE	4 (1.5)	1 (3.4)	29 (10.7)	3 (9.1)	33 (9.9)	<0.0001
Died due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Reviewer's table, modified from Table 2.7.4.2-3, page 33 of 131, Summary of Clinical Safety for RU-0211
1 This group is a subset of the General and Overall Safety Group.
2 Includes events with a relationship to study medication of missing or "possibly", "probably", or "definitely" related.
3 Tests for differences between the 48 mcg group and Placebo are based on Fisher's exact test.

7.1.1 Deaths

No subjects died during the treatment period or the follow-up period for any of the studies.

7.1.2 Other Serious Adverse Events

The occurrence of SAEs in the study population was relatively low. Overall, for the pooled group in the Well-controlled cohort, two subjects in the placebo group 2/273 (0.7%) and one subject 1/271 (0.4%) in the RU-0211 48 mcg group reported SAEs. No SAE was reported in the two main efficacy studies; SC0131 or SC0232. The only SAE in the 48 mcg group (subject SC9921-04-013) who experienced chest pain which was deemed unrelated to study drug by investigators, occurred in the dose finding study, SC9921. No SAE was reported in the 29 subjects exposed to < 48 mcg/day of lubiprostone or in the 33 subjects exposed to > 48 mcg/day of lubiprostone.

For the pooled group in the overall safety group, four placebo subjects (1.1%) and 32 RU-0211 subjects (2.9%) reported at least 1 SAE. No SAE in the placebo group was reported by more than one subject. The four placebo subjects experienced a total of six SAEs; 1 subject in study SC0131, 2 subjects in study SC01S2 SP1, and 1 subject in SC0232 reported at least 1 SAE. Two subjects each reported two SAEs:

- Subject SC01S2-SP1-02-R0203 experienced severe intervertebral disc protrusion and severe lumbar spinal stenosis
- Subject SC01S2-SP1-04-R0405 experienced severe pneumonia aspiration and sleep apnea syndrome of unidentified intensity

The other SAEs reported by placebo subjects were gastroesophageal reflux disease and skull fracture. All SAEs reported by placebo subjects were considered by the sponsor to be unrelated to treatment.

For the RU-0211 48 mcg group, 32 subjects reported a total of 45 SAEs that were considered treatment-emergent. Of those 45 SAEs, 1 subject was in study SC9921, 7 subjects were in study SC01S1, 11 subjects were in study SC01S2, and 13 subjects were in SC02S3. Subjects reporting multiple SAEs for the RU-0211 treatment group were as follows:

- **Subject SC01S1-21-R2158** experienced bronchitis and dehydration, both of *moderate* intensity, and neither of which was considered treatment-related.
- **Subject SC01S2-SP2-01-R0116** experienced abdominal adhesions and oophorectomy, both of *mild* intensity, and neither of which was considered treatment-related.
- **Subject SC01S2-SP2-11-R1103** experienced chest pain and compression fracture, both of which were *moderate* in intensity, and neither of which was considered treatment-related.
- **Subject SC01S2-SP2-16-R1603** experienced intervertebral disc disorder, neck pain, and pseudoarthrosis, all of which were *severe* in intensity, and none of which was considered treatment-related.
- **Subject SC01S2-SP2-20-R2016** experienced dehydration and pyelonephritis, both of which were *severe* in intensity, and neither of which was considered treatment-related.
- **Subject SC02S3-05-R0507** experienced diarrhea that was *severe* in intensity and considered possibly related to study drug; and diverticulitis that was *moderate* in intensity and considered not treatment-related.
- **Subject SC02S3-06-R0607** experienced bladder prolapse, rectal prolapse, and uterine prolapse, all of which were *severe* in intensity, and none of which was considered treatment-related.
- **Subject SC02S3-07-R0710** experienced bipolar disorder and depression, both of *severe* intensity and neither considered treatment-related.
- **Subject SC02S3-07-R0712** experienced clavicle fracture, loss of consciousness, and scapula fracture, all of *severe* intensity and not considered treatment-related.
- **Subject SC02S3-15-R1503** experienced a head injury and a subdural hematoma, both of *severe* intensity and neither considered treatment-related.

Medical Officer Comments:

The investigators for these trials considered most of the aforementioned SAEs not treatment-related. Given the known intended pharmacodynamic effect of the study drug and the fact that there are reported events of dehydration, syncope, and uterine prolapse, the medical officer cannot agree with certainty that these SAEs are unrelated to lubiprostone therapy.

Most of the SAE preferred terms in the aforementioned studies were each reported by 1 subject, and no single SAE preferred term was reported by more than 2 subjects. The SAE preferred terms reported by more than 1 subject were appendicitis, diverticulitis, syncope, chest pain, and dehydration. Additionally, no SOC had a reported SAE frequency > 1%, and only gastrointestinal disorders (0.6%) exhibited a frequency that was > 0.5% of all subjects taking RU-0211 48 mcg. Although not exemplified by those subjects reporting multiple SAEs, the majority of adverse events were either mild or moderate.

Only two SAEs were considered ***possibly treatment-related*** by the investigator. They are detailed below:

- **Subject SC01S2-SP2-18-R1804** was a 27-year-old Caucasian female with a history of constipation since January 1994. Concomitant medications for this subject were Benadryl, Paxil, Bisacodyl, cortisone, Vistaril, and Dulcolax. The subject became pregnant during the study, and discontinued the study on Day 241 because of the pregnancy. On Day 438, she gave birth to a child with bilateral club feet. The club feet event was reported as an SAE because it was a congenital anomaly to the offspring of a study participant. The subject's pregnancy was not considered an AE by the Sponsor. The investigator considered the SAE of congenital clubfoot to be possibly related to the study drug.
- **Subject SC02S3-05-R0507** was a 64-year-old Caucasian female with no prior reported history of constipation. Potentially relevant medical history included gastroesophageal reflux disease (GERD). Concomitant medications for this subject were Robaxin, Albuterol, zinc, Premarin, progesterone, BuSpar, Aldactone, Lasix, vitamin B, Vicodin, Celebrex, Aciphex, Aristocort, Benadryl, Bactrim DS, Atarax, Depo-Medrol, influenza vaccine, loperamide hydrochloride, promethazine, Lisinopril, Verapamil, and Peri-Colace. On Day 272, the subject experienced severe diarrhea and moderate diverticulitis, which resolved on Day 273. The investigator considered these events to be unrelated to the study drug and the subject completed the study.

Medical Officer's Comments:
As the incidence of talipes is 1 in every 1000 live births, making it a relatively common congenital anomaly, and the pre-clinical data found lubiprostone to be non-teratogenic according to the Agency's pharmacologists, it is difficult for the medical reviewer to assign the one incidence of clubfoot to the study drug with certainty.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.4 Overall profile of dropouts

As noted below in Table 32, the most common reason for discontinuation from the study in the placebo group was lack of efficacy 4.0%. In the RU-0211 48 mcg group, the most common reason for discontinuation from the study was due to an adverse event (10.7%).

Table 32: Subject Discontinuation for the Well-Controlled Group – All Randomized Subjects (Pooled)

Reason for Discontinuation	Placebo N=275 (100%) N (%)	RU-0211 48 mcg N=271 (100%) N (%)
Adverse Event	4 (1.5)	29 (10.7)
Protocol Violation	0 (0.0)	0 (0.0)
Subject Voluntary Withdrawal	2 (0.7)	3 (1.1)
Lack of Efficacy	11 (4.0)	2 (0.7)
Lost to Follow-up	3 (1.1)	5 (1.8)
Did Not Meet Criteria	0 (0.0)	0 (0.0)
Other	2 (0.7)	0 (0.0)

As noted below in Table 33, the most common reason for discontinuation from the study in the placebo group was lack of efficacy (3.0%). In the RU-0211 48 mcg group, the most common reasons for discontinuation from the study were adverse events (19.7%), lack of efficacy (14.8%), subject voluntary withdrawal (5.9%), and lost to follow-up (4.9%). The 19.7% adverse event rate in this overall safety cohort encompasses the adverse event reporting from the three year long open-label safety and efficacy studies.

Table 33: Subject Discontinuation in the Overall Safety Group (Pooled)

Reason for Discontinuation	Placebo N=369 (100%) N (%)	RU-0211 48 mcg N=1119 (100%) N (%)
Adverse Event	5 (1.4)	220 (19.7)
Protocol Violation	0 (0.0)	5 (0.4)
Subject Voluntary Withdrawal	2 (0.5)	66 (5.9)
Lack of Efficacy	11 (3.0)	166 (14.8)
Lost to Follow-up	3 (0.8)	55 (4.9)
Did Not Meet Criteria	0 (0.0)	1 (0.1)
Other	2 (0.5)	13 (1.2)

Reviewer's table, modified from Table 2.7.4.1-4, page 21 of 131, Summary of Clinical Safety

7.1.5 Adverse events associated with dropouts

Table 34 below is a summary of adverse events leading to study withdrawal for the Well-controlled group cohort. A discussion of this data will follow.

Table 34: Summary of Adverse Events[1] Leading to Withdrawal (Well-Controlled Group)

	Pooled Group					
System Organ Class (SOC)	**Placebo N=273 (100%)**	**RU-0211 <48 mcg N=29 (100%)**	**RU-0211 48 mcg N=271 (100%)**	**RU-0211 >48 mcg N=33 (100%)**	**All Active Doses N=333 (100%)**	**P-value[2]**
Number	N (%)	N (%)	N (%)	N (%)	N (%)	Number
At least one adverse event leading to withdrawal	**4 (1.5)**	1 (3.4)	**29 (10.7)**	3 (9.1)	33 (9.9)	**<0.0001**
Gastrointestinal D.O.	**3 (1.1)**	1 (3.4)	**21 (7.7)**	2 (6.1)	24 (7.2)	**0.0001**
Nausea	0 (0.0)	1 (3.4)	14 (5.2)	1 (3.0)	16 (4.8)	
Diarrhea	0 (0.0)	0 (0.0)	4 (1.5)	1 (3.0)	5 (1.5)	
Abdominal pain	1 (0.4)	0 (0.0)	4 (1.5)	0 (0.0)	4 (1.2)	
Flatulence	1 (0.4)	0 (0.0)	4 (1.5)	0 (0.0)	4 (1.2)	
Dry mouth	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.6)	
Stomach discomfort	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.6)	
Abdominal rigidity	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Dry throat	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Eructation	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Fecal incontinence	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Feces discolored	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Esophageal pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Abdominal distension	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Abdominal pain upper	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
System Organ Class (SOC)	**Placebo N=273 (100%)**	**RU-0211 <48 mcg N=29 (100%)**	**RU-0211 48 mcg N=271 (100%)**	**RU-0211 >48 mcg N=33 (100%)**	**All Active Doses N=333 (100%)**	**P-value[2]**
General D.O and Administration site conditions	**1 (0.4)**	0 (0.0)	**6 (2.2)**	0 (0.0)	6 (1.8)	0.0678
Edema	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.6)	
Chest discomfort	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Chest pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Discomfort	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Feeling abnormal	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Edema peripheral	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Rigors	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Fatigue	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Nervous System D.O.	**2 (0.7)**	0 (0.0)	**6 (2.2)**	0 (0.0)	6 (1.8)	0.1753
Headache	2 (0.7)	0 (0.0)	5 (1.8)	0 (0.0)	5 (1.5)	
Dizziness	0 (0.0)	0 (0.0)	4 (1.5)	0 (0.0)	4 (1.2)	
Paresthesia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	

Respiratory, thoracic and mediastinal D.O.	**0 (0.0)**	0 (0.0)	**6 (2.2)**	0 (0.0)	6 (1.8)	**0.0149**
Dyspnea	0 (0.0)	0 (0.0)	5 (1.8)	0 (0.0)	5 (1.5)	
Pharyngolaryngeal pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Throat tightness	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Psychiatric D.O.	**0 (0.0)**	0 (0.0)	**2 (0.7)**	0 (0.0)	2 (0.6)	**0.2477**
Anxiety	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Insomnia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Nervousness	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Stress symptoms	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Skin and Subcutaneous tissue D.O.	**0 (0.0)**	0 (0.0)	**2 (0.7)**	0 (0.0)	2 (0.6)	**0.2477**
Hyperhidrosis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Rash	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Cardiac Disorders	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Palpitations	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	1 (0.3)	
Bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	1 (0.3)	
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	1 (0.3)	
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	1 (0.3)	
Metabolism and nutrition D.O.	**0 (0.0)**	0 (0.0)	**1 (0.4)**	0 (0.0)	1 (0.3)	**0.4982**
Dehydration	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	

Reviewer's table, modified from Table 2.2.9.1, pages 1275-1283 of 2971, Integrated Summary of Safety

As noted above, in the pooled population, 1.5% of placebo and 10.7% of RU-0211 48 mcg subjects withdrew because of an adverse event. This difference was statistically significant ($p<0.0001$) and similar results were observed in study SC0131 (placebo 0.8%; RU-0211 7.5%) and study SC0232 (placebo 0.8%; RU-0211 12.6%) but not in study SC9921 (placebo 6.06%; RU-0211 all doses 9.57%). Overall, 1.1% of placebo subjects and 7.7% of RU-0211 48 mcg subjects withdrew because of an adverse event in the System Organ Class (SOC), Gastrointestinal Disorders. Gastrointestinal adverse events in the RU-0211 48 mcg group that led to withdrawal for at least 1% of subjects were nausea (5.2%), diarrhea (1.5%), abdominal pain (1.5%), and flatulence (1.5%). No gastrointestinal adverse events that led to withdrawal were reported by as much as 1% of placebo subjects. A significant difference was also found between the treatment groups in the Respiratory, thoracic and mediastinal disorders SOC; 2.2% of RU-0211 48 mcg subjects withdrew because of these adverse events, while no placebo subjects did ($p=0.0149$). Dyspnea (1.8%), pharyngolaryngeal pain (0.4%), and throat tightness (0.4%) were the adverse events that led to withdrawal in the RU-0211 48 mcg group. No other significant differences were observed in any other SOC.

As noted below in Table 35, the types and frequencies of the individual adverse events leading to study withdrawal in the Long Term Safety cohort (24 – 48 weeks) were generally similar to those observed in the Well-controlled safety group cohort. Gastrointestinal disorders were once again the most common SOC for adverse events leading to withdrawal. Adverse events in the pooled group that led to withdrawal **for at least 1% of subjects** were nausea (7.9%), headache (3.4%), diarrhea (1.9%), peripheral edema (1.5%), abdominal distension (1.4%), abdominal pain (1.4%), vomiting (1.4%), and dyspnea (1.0%).

Table 35: Summary of Adverse Events Leading to Withdrawal (Long-term Safety Population)

System Organ Class	Pooled Group RU-0211 48 mcg N=878 (100%)
At Least One Adverse Event Leading to Withdrawal N (%)	161 (18.3)
Gastrointestinal Disorders	**107 (12.2)**
Nausea	**69 (7.9)**
Diarrhea	**17 (1.9)**
Abdominal Distension	**12 (1.4)**
Abdominal Pain	**12 (1.4)**
Vomiting	**12 (1.4)**
Flatulence	7 (0.8)
Abdominal Discomfort	3 (0.3)
Dry mouth	3 (0.3)
Constipation	2 (0.2)
GERD	2 (0.2)
Abdominal pain lower	1 (0.1)
Abdominal rigidity	1 (0.1)
Anal discomfort	1 (0.1)
Defecation urgency	1 (0.1)
Dyspepsia	1 (0.1)
Fecal incontinence	1 (0.1)
Frequent bowel movements	1 (0.1)
Gastrointestinal discomfort	1 (0.1)
Gastrointestinal pain	1 (0.1)
Irritable bowel syndrome	1 (0.1)
Esophageal pain	1 (0.1)
Rectal hemorrhage	1 (0.1)
Stomach discomfort	1 (0.1)
Stools watery	1 (0.1)
Tongue discoloration	1 (0.1)
Nervous System Disorders	39 (4.4)
Headache	**30 (3.4)**
Dizziness	8 (0.9)
General D.O. and Administration Site Conditions	12 (3.7)
Peripheral edema	**5 (1.5)**
Respiratory, thoracic and mediastinal D.O.	15 (1.7)
Dyspnea	**9 (1.0)**

Reviewer's table, modified from Table 2.2.9.3, pages 1285-1290 of 2971, Integrated Summary of Safety

Table 36 below is a summary of adverse event incidence rates by the System/Organ/Class classification scheme.

Table 36: Summary of Adverse Event Incidence Rates by System/Organ/Class

SYSTEM/ORGAN/CLASS N (%)	Placebo N=367 (100)	RU-0211 All Active Doses N=1321 (100)
At least one adverse event	138 (37.6)	1016 (76.9)
Gastrointestinal Disorders	**59 (16.1)**	**748 (56.6)**
Infections and Infestations	29 (7.9)	271 (20.5)
Nervous System Disorders	34 (9.3)	260 (19.7)
General D.O. and Administration site conditions	10 (2.7)	159 (12.0)
Musculoskeletal and Connective tissue D.O.	7 (1.9)	137 (10.4)
Respiratory, thoracic, and mediastinal D.O.	15 (4.1)	107 (8.1)
Skin and subcutaneous D.O.	17 (4.6)	85 (6.4)
Investigations	6 (1.6)	65 (4.9)
Injury, poisoning and procedural complications	7 (1.9)	58 (4.4)
Psychiatric Disorders	7 (1.9)	48 (3.6)
Reproductive system and breast D.O.	3 (0.8)	29 (2.2)
Vascular Disorders	1 (0.3)	29 (2.2)

Reviewer's table, modified from Table 2.7.4.2-20, page 70 of 131, Summary of Clinical Safety for RU-0211

Medical Officer's Comments:

As noted above in Table 36, the majority (12.2%) of adverse events that led to subject withdrawal in the long-term safety cohort were found within the Gastrointestinal Disorder System Organ Class, which included nausea, diarrhea, abdominal distension, and abdominal pain. As noted in Table 41, the most common System Organ Class reported for adverse events as a whole were Gastrointestinal Disorders, with 56.5% of RU-0211 subjects reporting. For the Gastrointestinal Disorder SOC, the frequency of adverse events in the All Active Doses group of RU-0211 was at least twice the frequency in the placebo group. The sponsor notes that based on lubiprostone's mechanism of action, certain gastrointestinal side effects in subjects taking RU-0211 were key pharmacodynamic adverse events and were not unexpected. The medical officer is cautious to dismiss these adverse events as simply 'expected' pharmacodynamic events as their frequency in the All Active Doses group was at least twice the frequency in the placebo group that reflect clinically meaningful adverse trends that may effect patient compliance. The medical officer is reassured; however, that despite the aforementioned adverse events, only 12% withdrew from the study and the general health of the subjects in the overall safety cohort did not appear to be compromised during long-term treatment with RU-0211 48 mcg. Accordingly, as noted below in Table 42, the majority of adverse events reported for which maximum severity were mild to moderate. See below discussion.

Adverse Events by Maximum Severity

Table 37 below is a summary of adverse event incidence rates by maximum severity for the Well-controlled population. For the pooled group, 19.8% and 30.6% of placebo and RU-0211 subjects, respectively, reported at least one adverse event for which maximum severity was ***mild***; 17.2% and 25.5% of subjects reported at least one adverse event for which the maximum severity was ***moderate***; and 5.1% and 8.1% reported at least one ***severe*** adverse event. Most of the severe adverse events were reported by less than 1% of subjects in either treatment group at the pooled group level with the following exceptions: nausea (2.1%), diarrhea (1.8%) and headache (1.5%) in the RU-0211 group. Of note, headache was reported as severe by 1.5% of the placebo group subjects.

Although not graphically depicted, in the Long-term safety cohort's pooled group, 23.0% of subjects reported at least one AE for which the maximum severity was mild, 38.2% of subjects reported at least one AE for which the maximum severity was moderate, and 17.9% of subjects reported at least one severe AE. Most of the severe AEs reported were in the gastrointestinal disorders SOC. Overall, 11.2% of subjects reported severe AEs in this SOC, with nausea (3.2%), diarrhea (2.5%), abdominal distension (1.6%), abdominal pain (1.7%), and vomiting (1.0%) being the only severe AEs reported by at least 1% of subjects in the pooled group. Other severe AEs that were reported by at least 1% of pooled group subjects were headache (1.3%) and dizziness (1.0%). Results were generally similar across the individual studies in the LTS cohort, except that the frequency of severe AEs in SC02S3 (25.3%) appeared to be higher than in SC01S1 (15.7%) and SC01S2 (10.9%).

Table 37: Adverse Event Incidence Rates by Severity (Well-Controlled Population)

System Organ Class Preferred Term	Pooled Group					
	Placebo N=273 (100%)			All Active Doses N=333 (100%)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
At Least One Adverse Event	54 (19.8)	47 (17.2)	14 (5.1)	102 (30.6)	85 (25.5)	27 (8.1)
Gastrointestinal Disorders	25 (9.2)	15 (5.5)	8 (2.9)	80 (24.0)	52 (15.6)	18 (5.4)
Nausea	8 (2.9)	7 (2.6)	0 (0.0)	65 (19.5)	30 (9.0)	**7 (2.1)**
Diarrhea	0 (0.0)	3 (1.1)	0 (0.0)	5 (1.5)	12 (3.6)	**6 (1.8)**
Abdominal pain	0 (0.0)	6 (2.2)	1 (0.4)	11 (3.3)	7 (2.1)	2 (0.6)
Flatulence	3 (1.1)	2 (0.7)	0 (0.0)	3 (0.9)	9 (2.7)	0 (0.0)
Abdominal Distension	1 (0.4)	4 (1.5)	2 (0.7)	4 (1.2)	4 (1.2)	1 (0.3)
Abdominal Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.2)	2 (0.6)	1 (0.3)
Abdominal Pain upper	4 (1.5)	0 (0.0)	2 (0.7)	3 (0.9)	4 (1.2)	0 (0.0)
Loose Stools	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.2)	1 (0.3)	1 (0.3)
Vomiting	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.3)	5 (1.5)	0 (0.0)
Dyspepsia	3 (1.1)	1 (0.4)	0 (0.0)	4 (1.2)	1 (0.3)	0 (0.0)
Abdominal Pain lower	2 (0.7)	2 (0.7)	0 (0.0)	3 (0.9)	1 (0.3)	0 (0.0)
Dry mouth	0 (0.0)	1 (0.4)	0 (0.0)	3 (0.9)	1 (0.3)	0 (0.0)
Stomach discomfort	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.2)	0 (0.0)
Abdominal rigidity	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Abdominal tenderness	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)
Fecal incontinence	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)
Nervous System Disorders	10 (3.7)	12 (4.4)	5 (1.8)	25 (7.5)	19 (5.7)	7 (2.1)
Headache	7 (2.6)	9 (3.3)	**4 (1.5)**	16 (4.8)	15 (4.5)	**5 (1.5)**
Dizziness	1 (0.4)	3 (1.1)	0 (0.0)	13 (3.9)	3 (0.9)	1 (0.3)
Migraine	0 (0.0)	2 (0.7)	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.3)

Reviewer's table, modified from Table 2.2.3.1, page 807 of 2971, Integrated Summary of Safety

Medical Officer's Comments

The aforementioned adverse event rate analysis of the Well-controlled group at the pooled group level is consistent with the maximum severity analyses performed at the individual study level (SC0131, SC0232, and SC9921). There were no significant differences within the Well-controlled group at the study level, the pooled level, or between the treatment groups in the frequency of severe adverse events in any body system. The Long-term safety cohort results were slightly dissimilar to the Well-controlled group in that there were quantitatively less mild adverse events reported slightly more severe adverse events reported; 23.0% versus 30.6% of

subjects reported at least 1 AE for which the maximum severity was mild, 38.2% versus 25.5% of subjects reported at least 1 AE for which the maximum severity was moderate, and 17.9% versus 8.1% of subjects reported at least 1 severe AE, for the LTS and WCG cohorts, respectively. After cross comparison and exploration of the data, the medical officer is still uncertain why the frequency of severe AEs in study SC02S3 was higher than the other two Long-term studies, particularly SC01S2 (SP2) which was of similar design.

7.1.6 Common Adverse Events

An overall summary of commonly reported adverse events, i.e., those reported by more than 1 % of subjects taking any dose of RU-0211 (All Active Doses), is presented below in Tables 38 and 39 for the Well-Controlled Group cohort. Across all active doses of RU-0211, 64.3% of study drug subjects and 42.5% of placebo subjects reported at least one adverse event, a difference that was statistically significant ($p<0.001$). By dose level, 62.1% of subjects taking < 48 mcg RU-0211, 63.8% of subjects taking 48 mcg RU-0211, and 69.7% of subjects taking > 48 mcg RU-0211 reported at least 1 adverse event. The most commonly reported adverse events in both the placebo and RU-0211 group were in the System Organ Class (SOC); Gastrointestinal Disorders. The incidence rate was also significantly higher for general disorders and administration site conditions (9.6% vs. 3.7%; $p=0.0057$).

The subjects taking 48 mcg RU-0211 reported 46.1% Gastrointestinal disorder related adverse events whereas the placebo group reported only 17.6%; this difference was statistically significant ($p<0.001$). Within the Gastrointestinal disorder SOC, nausea (31.4%), diarrhea (5.5%), and abdominal pain (5.5%) were reported by at least 5% of subjects taking RU-0211 48 mcg and the frequency of all of these adverse events was at least twice the frequency reported in the placebo group. Other adverse events reported by at least 5% of subjects taking RU-0211 48 mcg included headache (11.1%) and dizziness (5.9%) for which placebo subjects reported 7.7% and 1.5%, respectively.

Medical Officer's Comments:
It is of interest to the medical officer that gastrointestinal adverse events were noticeably more prevalent among subjects taking the study drug than among placebo subjects. The sponsor argues that these adverse events are not unexpected based upon the pharmacodynamic mechanism of RU-0211; an argument that may have merit as a dose dependent increase in adverse events was noted with RU-0211. Loose stools, abdominal discomfort, chest discomfort, and dyspnea; however, were all reported exclusively among RU-0211 48 mcg subjects. The differences between placebo and RU-0211 48 mcg at the SOC level (Nervous system disorders, Infections and Infestations, Respiratory, thoracic, and mediastinal disorders, and Skin and subcutaneous disorders) were not statistically significant. It is also important to note that the frequency of these events did not increase with increasing RU-0211 dose.

Table 38: Commonly Reported Adverse Events[1] in the Well-Controlled Group[2]

System Organ Class	Placebo	RU-0211 <48 mcg	RU-0211 48 mcg	RU-0211 >48 mcg	All Active Doses	Statistic
N (%)	N=273 (100%)	N=29 (100%)	N=271 (100%)	N=33 (100%)	N=333 (100%)	P-value[3]
At least one adverse event	116 (42.5)	18 (62.1)	173 (63.8)	23 (69.7)	214 (64.3)	**< 0.001**
Gastrointestinal Disorders	**46 (17.6)**	10 (34.5)	**125 (46.1)**	15 (45.5)	150 (45.0)	**<0.001**
Nausea	15 (5.5)	5 (17.2)	85 (31.4)	12 (36.4)	102 (30.6)	
Diarrhea	3 (1.1)	3 (10.3)	15 (5.5)	5 (15.2)	23 (6.9)	
Abdominal pain	7 (2.6)	1 (3.4)	15 (5.5)	4 (12.1)	20 (6.0)	
Flatulence	5 (1.8)	1 (3.4)	11 (4.1)	0 (0.0)	12 (3.6)	
Abdominal distension	7 (2.6)	0 (0.0)	8 (3.0)	1 (3.0)	9 (2.7)	
Abdominal discomfort	0 (0.0)	1 (3.4)	6 (2.2)	0 (0.0)	7 (2.1)	
Abdominal pain upper	6 (2.2)	0 (0.0)	6 (2.2)	1 (3.0)	7 (2.1)	
Loose stools	0 (0.0)	0 (0.0)	6 (2.2)	0 (0.0)	6 (1.8)	
Vomiting	2 (0.7)	0 (0.0)	5 (1.8)	1 (3.0)	6 (1.8)	
Dyspepsia	4 (1.5)	0 (0.0)	5 (1.8)	0 (0.0)	5 (1.5)	
Abdominal pain lower	2 (0.7)	0 (0.0)	4 (1.5)	0 (0.0)	4 (1.2)	
Dry mouth	1 (0.4)	0 (0.0)	4 (1.8)	0 (0.0)	4 (1.2)	
Stomach discomfort	1 (0.4)	0 (0.0)	4 (1.8)	0 (0.0)	4 (1.2	
Nervous System Disorders	28 (10.3)	2 (6.9)	43 (15.9)	6 (18.2)	51 (15.3)	0.057
Headache	21 (7.7)	1 (3.4)	30 (11.1)	5 (15.2)	36 (10.8)	
Dizziness	4 (1.5)	1 (3.4)	16 (5.9)	0 (0.0)	17 (5.1)	
Infections and Infestations	26 (9.5)	5 (17.2)	22 (8.1)	4 (12.1)	31 (9.3)	0.651
Sinusitis	5 (1.8)	0 (0.0)	5 (1.8)	2 (6.1)	7 (2.1)	
Upper resp. tract infection	3 (1.1)	0 (0.0)	4 (1.5)	1 (3.0)	5 (1.5)	
General Disorders and Administration site disorders	10 (3.7)	3 (10.3)	26 (9.6)	1 (3.0)	30 (9.0)	**0.006**
Fatigue	6 (2.2)	2 (6.9)	6 (2.2)	1 (3.0)	9 (2.7)	
Edema peripheral	1 (0.4)	0 (0.0)	6 (2.2)	0 (0.0)	6 (1.8)	
Chest discomfort	0 (0.0)	1 (3.4)	4 (1.5)	0 (0.0)	5 (1.5)	

Table 39: Commonly Reported Adverse Events[1] in the Well-Controlled Group[2] Continued

System Organ Class	Placebo	RU-0211 <48 mcg	RU-0211 48 mcg	RU-0211 >48 mcg	All Active Doses	Statistic
Respiratory, thoracic, and mediastinal disorders	14 (5.1)	1 (3.4)	17 (6.3)	2 (6.1)	20 (6.0)	0.585
Dyspnea	0 (0.0)	1 (3.4)	7 (2.6)	1 (3.0)	9 (2.7)	
Skin and subcutaneous tissue disorders	12 (4.4)	2 (6.9)	11 (4.1)	1 (3.0)	14 (4.2)	1.000
Rash	5 (1.8)	1 (3.4)	4 (1.5)	1 (3.0)	6 (1.8)	

Reviewer's table, modified from Table 2.7.4.2-3, page 37 and 38 of 131, Summary of Clinical Safety for RU-0211
1 Adverse Events reported by greater than 1% of subjects in the "All Active Doses" group.
2 This group is a subset of the General and Overall Safety Group.
3 Tests for differences between the 48 μg group and Placebo are based on Fisher's exact test.

Table 40 below highlights the adverse events shown in Tables 38 and 39 above that were reported by at least 1% of RU-0211 mcg subjects and at a frequency that was at least double the frequency reported in the placebo group. Adverse events that were at least *twice* as frequent among subjects taking RU-0211 48 mcg than among placebo subjects were flatulence, abdominal discomfort, loose stools, vomiting, abdominal pain lower, dry mouth, stomach discomfort, peripheral edema, chest discomfort, and dyspnea.

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Table 40: Adverse Events Reported More Commonly in RU-0211 48 mcg Subjects than Placebo Subjects[1]

System Organ Class	Placebo	RU-0211 48 mcg
N (%)	273 (100)	271 (100)
Gastrointestinal Disorders		
Nausea	15 (5.5)	85 (31.4)
Diarrhea	3 (1.1)	15 (5.5)
Abdominal Pain	7 (2.6)	15 (5.5)
Flatulence	5 (1.8)	11 (4.1)
Abdominal discomfort	0 (0.0)	6 (2.2)
Loose stools	0 (0.0)	6 (2.2)
Vomiting	2 (0.7)	5 (1.8)
Abdominal pain lower	2 (0.7)	4 (1.5)
Dry mouth	1 (0.4)	4 (1.5)
Stomach discomfort	1 (0.4)	4 (1.5)
Nervous System disorders		
Dizziness	4 (1.5)	16 (5.9)
General Disorders and site administration conditions		
Edema peripheral	1 (0.4)	6 (2.2)
Chest discomfort	0 (0.0)	4 (1.5)
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	0 (0.0)	7 (2.6)
Skin and subcutaneous disorders		
Hyperhidrosis	0 (0.0)	3 (1.1)
Cardiac disorders		
Palpitations	0 (0.0)	3 (1.1)

Reviewer's table, modified from Table 2.7.4.2-5, page 44 of 131, Summary of Clinical Safety for RU-0211
1 To be included in this table, an individual AE must have been reported by at least 1% of subjects taking RU-0211 48 mcg, and its frequency in the RU-0211 48 µg group must have been at least twice the frequency reported in the placebo group.

7.1.6.1 Eliciting adverse events data in the development program

The primary method of collecting adverse event information was by means of standard questioning and physical examination at each clinic visit. Spontaneous reports of adverse events were also captured in the patients' diaries of their global and abdominal assessments. Such spontaneous reports and adverse events were reported in the Case Report Forms (CRFs). If necessary, the Investigator could adjust the subjects' treatment dosage if it was thought there was a treatment-related adverse event. Any changes in dose were noted in the CRF.

7.1.6.2 Appropriateness of adverse event categorization and preferred terms

Each adverse event in this New Drug Application was categorized using a Systems Organ Class (SOC) classification and coded using a MedDRA dictionary of preferred terms. Any verbatim adverse event that could not be coded was assigned "UNCODED" as the body system and the verbatim term was used as the preferred term, so that the adverse event could be included in the summary table.

Medical Officer's Comments

The medical officer felt this system of adverse event categorization and coding was fully comprehensive, however; calculating the incidence of specific adverse events was difficult; for example, abdominal pain, was reported under abdominal pain-upper, abdominal pain-lower, abdominal pain, stomach discomfort, and abdominal discomfort.

7.1.6.3 Incidence of common adverse events

Across the three well-controlled studies (SC0131, SC0232, and SC9921), 42.5% of placebo subjects and 63.8% of subjects taking RU-0211 48 mcg reported at least one AE, a difference that was statistically significant ($p<0.0001$). With increasing dose, 62.1% of subjects taking < 48 mcg RU-0211, 69.7% of subjects taking > 48 mcg RU-0211, and 64.3% of subjects taking RU-0211 at any dose reported at least one AE. Similarly, 19.0% of placebo subjects and 47.6% of RU-0211 48 mcg subjects reported at least one treatment-related AE ($p<0.0001$); 34.5% of subjects taking < 48 mcg RU-0211, 60.6% of subjects taking > 48 mcg RU-0211, and 47.7% of subjects taking any dose of RU-0211 reported treatment-related AEs. Two placebo subjects (0.7%) and one RU-0211 48 mcg subject (0.4%) reported an SAE, none of which was considered treatment related. No subjects in any treatment group died. Overall, 1.5% of placebo subjects and 10.7% of RU-0211 48 mcg subjects discontinued because of an AE ($p<0.0001$); 3.4% of subjects taking < 48 mcg RU-0211, 9.1% of subjects taking > 48 mcg RU-0211, and 9.9% of subjects taking RU-0211 at any dose discontinued because of an AE. Similar results were observed at the study level, except that the difference in the proportion of subjects who discontinued because of an AE between placebo (6.1%) and RU-0211 48 mcg (15.6%) was not significant in SC9921 ($p=0.2576$).

Table 41: Overall Summary of Adverse Events

Category / Dose Group	Well-Controlled Group	Long-Term Safety	Overall Safety
	n/N (%)	n/N (%)	n/N (%)
Subjects reporting at least one Adverse Event			
Placebo	116/273 (42.5)	NA	138/367 (37.6)
RU-0211 48 mcg	173/271 (63.8)*	694/878 (79.0)	880/1113 (79.1)
All Active Doses	214/333 (64.3)	NA	1016/1321 (76.9)
Subjects reporting at least on Treatment-Related Adverse Event			
Placebo	52/173 (19.0)	NA	62/367 (16.9)
RU-0211 48 mcg	129/271 (47.6)*	481/878 (54.8)	646/1113 (58.0)
All Active Doses	159/333 (47.7)	NA	760/1321 (57.5)
Subjects reporting at least one Serious Adverse Event			
Placebo	2/273 (0.7)	NA	4/367 (1.1)
RU-0211 48 mcg	1/271 (0.4)	31/878 (3.5)	32/1113 (2.9)
All Active Doses	1/333 (0.3)	NA	32/1321 (2.4)
Subjects reporting at least on Treatment-Related Serious Adverse Event			
Placebo	0/273 (0.0)	NA	0/367 (0.0)
RU-0211 48 mcg	0/271 (0.0)	2/878 (0.2)	2/1113 (0.2)
All Active Doses	0/333 (0.0)	NA	2/1321 (0.2)
Subjects who Discontinued due to an Adverse Event			
Placebo	4/273 (1.5)	NA	5/367 (1.4)
RU-0211 48 mcg	29/271 (10.7)*	161/878 (18.3)	220/1113 (19.8)
All Active Doses	33/333 (9.9)	NA	225/1321 (17.0)

Reviewer's table, modified from Table 2.7.4.2-21, page 73 of 131, Summary of Clinical Safety for RU-0211
* Indicates a significant difference between placebo and RU-0211 48 mcg based on Fisher's exact test.

Medical Officer's Comments:
As described in Table 41, in all cohorts that included placebo and RU-0211 48 mcg subjects, the frequencies of reporting AEs and treatment-related AEs, as well as the frequency of discontinuing because of an AE, were higher among RU-0211 48 mcg subjects. These higher frequencies of AEs are somewhat expected given the extended exposure of subjects to RU-0211 48 mcg compared with placebo, especially in the Long-term safety and Overall-Safety cohorts; however, they still are of notable concern. Of note, across all three cohorts, there were no marked differences between placebo and RU-0211 48 mcg in the reporting of SAEs and treatment-related SAEs. This is somewhat reassuring in that the overall subject health was not compromised during the long-term treatment with RU-0211 48 mcg.

Of unknown significance to the medical officer is the high number of placebo subjects reporting at least one adverse event in the Well-controlled group (42.5%).

7.1.7 Identifying common and drug-related adverse events

Table 42 below summarizes the adverse events by causal relationship to the study drug for the Well-controlled group subjects. For the pooled group, 19.0% of placebo subjects and 47.7% of RU-0211 subjects reported at least one treatment-related AE. Treatment-related AEs consisted

of those AEs with a missing causal relationship, or a relationship to the study drug that was "possible", "probable", or "definite" in the opinion of the investigator.

Table 42: Treatment-related Adverse Events

System/Organ/Class	Placebo N=273	All Active Doses RU-0211 (WCG) N=333	Long-term Safety N=878
At least one adverse event	52 (19.0)	159 (47.7)	481 (54.8)
Preferred Term	n (%)	n (%)	n (%)
Gastrointestinal Disorders			
Nausea	9 (3.3)	93 (27.9) *	224 (25.5)
Diarrhea	2 (0.7)	19 (5.7) *	108 (12.3)
Abdominal pain	5 (1.8)	16 (4.8) *	44 (5.0)
Flatulence	4 (1.5)	11 (3.3) *	47 (5.4)
Abdominal discomfort	0 (0.0)	5 (1.5) *	9 (1.0)
Loose stools	0 (0.0)	6 (1.8) *	32 (3.6)
Vomiting	0 (0.0)	4 (1.2) *	29 (3.2)
Dry mouth	1 (0.4)	4 (1.2) *	10 (1.1)
Stomach discomfort	1 (0.4)	4 (1.2) *	-
Nervous System Disorders			
Headache	15 (0.3)	33 (9.9)	85 (9.7)
Dizziness	2 (0.7)	15 (4.5) *	23 (2.6)
General Disorders and site administration conditions			
Chest discomfort	0 (0.0)	5 (1.5) *	9 (1.0)
Peripheral Edema	1 (0.3)	-	16 (1.8)
Respiratory, thoracic, and mediastinal disorders			
Dyspnea	0 (0.0)	7 (2.1) *	12 (1.4)

Reviewer's table, modified from Tables 2.7.4.2-7 and 2.7.4.2-24, page 49 and 77 of 131, Summary of Clinical Safety for RU-0211

* Indicates that the reported frequency of a particular adverse event in the RU-0211 48 mcg group was at least twice the reported frequency in the placebo group within the same cohort.

\- Indicates that a particular adverse event was not considered treatment-related for more than 1% of RU-0211 All Active Doses subjects in a given cohort.

Medical Officer's Comments:

For the pooled group within the Well-Controlled Group cohort, 19.0% of placebo subjects and 47.7% of RU-0211 subjects reported at least one treatment-related AE. For the pooled group within the Long-Term Safety cohort, 17.1% of placebo subjects and 57.5% of RU-0211 subjects reported at least one treatment-related AE. For the pooled group in the Overall Safety cohort, 16.9% of placebo subjects and 57.5% of RU-0211 subjects reported at least one treatment-related AE. The differences observed in treatment-related AE reporting between placebo and RU-0211 subjects are similar in magnitude across all three pooled safety cohorts.

Of the aforementioned treatment-related AEs, the most concerning and possibly treatment-limiting adverse events were that of nausea, diarrhea, peripheral edema, and dyspnea. Nausea was almost nine times more common in the All-active dose group than in the placebo group.

Throughout the sponsor's Summary of Clinical Safety, nausea was the most commonly reported adverse event in each RU-0211 dose group. Diarrhea was almost five times more common in the All-active dose group than in the placebo group. Although peripheral edema was not considered treatment-related for more than 1% of RU-0211 subjects in the Well-controlled group, the adverse event was indicated as possibly treatment-related in the Long-term safety group. Dyspnea was approximately two times more common in the All-active dose group than in the placebo group. Summarized below is a further analysis of nausea, peripheral edema, diarrhea and dyspnea and their relationship to the study drug.

7.1.7.1 Additional analyses and explorations

Nausea:

As shown below in Table 43, most reported nausea adverse events were considered treatment-related by the investigator; average pooled range 27.2% – 30.8%. Interestingly, relatively few subjects discontinued secondary to nausea (maximum 8.8% in SC01S1) and relatively fewer subjects reported this adverse event as severe (maximum 5.6% in SC01S1).

Table 43: Summary of Important Frequencies for the Adverse Event of Nausea (All Active Doses[1])

Study or Cohort	Frequency of Nausea (%)	Frequency of Severe Nausea (%)	Frequency of Treatment-related Nausea (%)	Frequency of Withdrawal Because of Nausea (%)
SC0131	35.0	3.3	31.7	5.0
SC0232	24.4	0.8	21.0	5.0
SC9921	33.0	2.1	31.9	4.3
WCG Pooled[2]	30.6	2.1	27.9	4.8
SC01S1	27.8	**5.6**	25.2	**8.8**
SC01S2	21.0	0.8	19.8	5.2
SC02S3	31.5	2.8	30.2	9.0
LTS Pooled[3]	27.2	3.2	25.5	7.9
OS Pooled[4]	30.8	3.0	29.0	7.5

Reviewer's table, modified from Table 2.7.4.2-25, page 80 of 131, Summary of Clinical Safety for RU-0211

1 Study SC9921 included dose groups of RU-0211 < 48 µg and RU-0211 > 48 µg; all other studies included only the RU-0211 48 µg dose group.

2 Includes data from studies SC0131, SC0232, and SC9921.

3 Includes data from studies SC01S1, SC01S2 (SP2 only), and SC02S3.

4 Includes data from all cohorts (Healthy Normal data not shown).

The sponsor performed a cumulative hazard rate analysis for the occurrence of nausea on All-Active Doses of the general safety population and found that the likelihood of experiencing a first episode of nausea was greatest during the first week of treatment with RU-0211. The cumulative hazard rate for the All Active Doses group was 0.2723 for the interval that covers the fifth day after treatment initiation; for the interval that covers 270-365 days, the rate was 0.2895, an increase of 6% over the course of a 12-month treatment period. Also, the hazard rate for the

interval covering the first day after treatment initiation was 0.1558, or approximately 54% of the total risk for experiencing nausea at any time.

For the Long-term Safety cohort, the cumulative hazard rate was essentially unchanged during the extended treatment period. The rate was 0.2272 for the interval covering 22-28 days, and it was 0.2293 for the interval spanning 270-365 days, an increase of only 1% for experiencing nausea. The largest observed individual hazard rate for the Long-term Safety cohort was 0.1110 at the midpoint of the interval for 1-1 days, a rate that represented 48.4% of the total risk; 94.8% of the total risk for experiencing nausea was observed by the midpoint of the 5-5 day interval. After 366 days of treatment with RU-0211 48 mcg, the probability of experiencing at least 1 AE of nausea was 29% for Long-term safety subjects.

The sponsor also performed a Cox regression analysis that adjusted for gender and age. The Cox regression analysis showed that the rate at which subjects taking any dose of RU-0211 (after adjusting for gender and age) were to experience nausea was significantly increased relative to placebo (hazard ratio = 6.4960; $p<0.0001$). Similarly, after adjusting for treatment group and age group, the rate at which female subjects was significantly increased relative to male subjects (hazard ratio = 4.6860; $p<0.0087$).

Table 44: Cox Proportional Hazard Regression of Incidence Rates for the Time Until the First Occurrence of Nausea (WCG)

Total	Number of Events	Number Censored	Percent Censored
600	117	483	80.50

Reviewer's table, modified from Table 2.2.6.2, page 1207 of 2971, Integrated Summary of Safety

Variable	Standard Error	Wald Chi-Square	Hazard Ratio
All Active Doses/Placebo	0.2770	45.6469	6.4960
65 ≥ Age/Age < 65	0.4601	2.8987	0.4569
Female/Male	0.5887	6.8831	4.6860

Reviewer's table, modified from Table 2.2.6.2, page 1207 of 2907, Integrated Summary of Safety

Medical Officer's Comments:

Although nausea is the most common adverse event associated with RU-0211 across all treatment cohorts, it does not appear to outweigh any clinical benefit that might be derived from treatment with RU-0211. The cumulative hazard rate analysis for the All Active Doses cohort and the Long-term Group cohort suggests that subjects taking RU-0211 were not necessarily at an increased risk of developing or experiencing nausea over the course of long term treatment, rather the greatest risk for occurrence was within the first few days of treatment. Interpreting the hazard ratio in this analysis is difficult given that data was censored if there were no adverse events within the set interval time periods and no probability distribution curves were provided concurrently. It is reassuring to the medical officer; however, that the pooled data from the Long-term Safety cohort and the Overall Safety cohort have similar frequencies of withdrawal secondary to nausea; 7.9% and 7.5% respectively. This suggests that when data is inclusive of both shorter and longer duration studies, the rate

of withdrawal secondary to nausea was comparable and never more than 10% of subjects in any cohort. It is still unclear why the hazard rate for nausea was increased in female subjects.

Diarrhea:

For a drug whose mechanism is to increase chloride-rich intra-luminal intestinal fluid secretions, one potential adverse pharmacodynamic effect may be that of diarrhea. In the Overall safety cohort, 13.2% of those subjects who received lubiprostone 24 mcg b.i.d. reported diarrhea. Relatively few of those subjects (3.4%) reported their diarrhea as severe, and even fewer (2.2%) withdrew from treatment secondary to diarrhea.

As noted below in Table 45, the occurrence of diarrhea at 29 days for subjects taking 48 mcg RU-0211 was somewhat lower for the WCG cohort compared to the LTS cohort. In the WCG cohort, the incidence rate for RU-0211 48 mcg was noticeably higher than the rate for placebo subjects, but the rate of occurrence did not appear to increase with increasing RU-0211 dose.

Table 45: Cumulative Incidence Rates: Occurrence of Diarrhea at 29 Days

Dose Level	Well-controlled Pooled group	Long-term Safety Pooled group
Placebo	0.0115	NA
RU-0211 < 48 mcg	0.1034	NA
RU-0211 48 mcg	0.0574	0.0948
RU-0211 > 48 mcg	0.1538	NA
All Active Doses	0.0711	NA

Reviewer's table, modified from Table 2.7.4.2-11, page 55 of 131, Summary of Clinical Safety

For the LTS cohort the cumulative hazard rate was 0.0730 for the interval covering 22-28 days, and it was 0.0757 for the interval spanning 270-365 days, an increase of 0.0027 (4%) over time for experiencing diarrhea. The largest observed individual hazard rate for the LTS cohort was 0.0313 at the midpoint of the interval for 1-1 days, a rate that represented 41.3% of the total risk; 90.6% of the total risk for experiencing diarrhea was observed by the midpoint of the 7-7 day interval. After 366 days of RU-0211 48 mcg treatment, the probability of experiencing at least 1 AE of diarrhea was 19% for LTS subjects.

Table 46: Cox Proportional Hazard Regression of Incidence Rates for the Time Until the First Occurrence of Diarrhea (WCG)

Total	Number of Events	Number Censored	Percent Censored	Hazard Ratio
600	26	574	95.67	6.5818

Reviewer's table, modified from Table 2.2.6.3, page 1208 of 2971, Integrated Summary of Safety

The Cox regression analysis for the time until the first occurrence of diarrhea in the WCG cohort showed that the rate at which subjects taking any dose of RU-0211 were likely to experience diarrhea was significantly increased relative to placebo (hazard ratio = 6.5818; p = 0.0021). Due

to the low number of reported peripheral edema events, the regression analysis was not adjusted for age or gender.

Medical Officer's comments:
Based on lubiprostone's mechanism of action, diarrhea is an adverse event of somewhat expected frequency. Although 13.2% of those subjects in the Overall Safety group cohort who received lubiprostone 24 mcg b.i.d. reported diarrhea, the medical officer is less concerned that this adverse event is treatment limiting in that only 2.2% of patients withdrew from treatment secondary to diarrhea and only 3.4% reported their diarrhea as severe.. Upon further analysis, no serious adverse events were reported for electrolyte imbalance and no clinically significant changes were seen in electrolyte levels, as would be expected with severe diarrhea, throughout the Phase III clinical trials. Additionally, diarrhea does not appear to be a dose dependent side effect.

Peripheral Edema:

As noted below in Table 47, the occurrence of peripheral edema at 29 days for subjects taking 48 mcg RU-0211 was relatively low and similar for the Well-controlled group (WCG) and Long-term safety (LTS) group cohorts. In both cohorts, the occurrence rate for peripheral edema was higher for the RU-0211 48 mcg group than the rate for placebo subjects, however; the occurrence with respect to RU-0211 dose cannot be evaluated, since no reports of the event were made by subjects taking < 48 mcg RU-0211 or > 48 mcg RU-0211.

Table 47: Cumulative Incidence Rates: Occurrence of Peripheral Edema at 29 Days

Dose Level	Well-controlled Pooled group	Long-term Safety Pooled group
Placebo	0.00369	NA
RU-0211 < 48 mcg	0	NA
RU-0211 48 mcg	0.0232	0.0222
RU-0211 > 48 mcg	0	NA
All Active Doses	0.0188	0.0260

Reviewer's table, modified from Table 2.7.4.2-16, page 61 of 131, Summary of Clinical Safety

For the LTS cohort, the cumulative hazard rate was 0.0101 for the interval covering 22-28 days, and it was 0.0112 for the interval spanning 270-365 days, an increase of 0.0011 (11%) for experiencing peripheral edema. After 366 days of RU-0211 48 mcg treatment, the probability of experiencing at least 1 AE of peripheral edema was 6% for LTS subjects. The rate of occurrence at 366 days represents an approximate doubling of the rate at 29 days.

Table 48: Cox Proportional Hazard Regression of Incidence Rates for the Time Until the First Occurrence of Peripheral edema (WCG)

Total	Number of Events	Number Censored	Percent Censored	Hazard Ratio
601	7	594	98.84	5.0695

Reviewer's table, modified from Table 2.2.6.8, page 1213 of 2971, Integrated Summary of Safety

The Cox regression analysis for the time until the first occurrence of peripheral edema in the WCG cohort showed that the rate at which subjects taking any dose of RU-0211 were likely to experience peripheral edema was increased relative to placebo (hazard ratio = 5.0695), however; this was not statistically significant (p=0.1328). Due to the low number of reported peripheral edema events, the regression analysis was not adjusted for age or gender.

Medical Officer's comments:
Unlike the reported adverse event 'nausea' which has the greatest risk for occurrence within the first few days of treatment, the risk of peripheral edema appears to increase over time. As there is no long-term placebo controlled data for cross comparison in the LTS group cohort, however; the risk occurrence data is difficult to solely ascribe to RU-0211 treatment. Somewhat reassuring is that less than 2% of the subjects (32 of 878) in the Long-term safety cohort reported peripheral edema that was considered treatment-related and that none of the peripheral edema adverse events were considered serious adverse events. In terms of severity, only one subject of the 32 adverse events of peripheral edema reported was claimed to be severe. Thus, even though the likelihood of experiencing peripheral edema nearly doubled from 4 weeks to 48 weeks, the clinical importance of this increase in relation to RU-0211 treatment appears to be nominal.

Dyspnea:

As noted below in Table 49, the occurrence of dyspnea at 29 days for subjects taking 48 mcg RU-0211 was relatively low and similar for the Well-controlled group (WCG) and Long-term safety (LTS) group cohorts. No reports of dyspnea were made by subjects taking placebo. It is interesting to note that the occurrence of dyspnea was not consistent with dose response. As shown below, the occurrence rate of dyspnea was higher in the < 48 mcg subjects and > 48 mcg subjects than in the 48 mcg subject cohort.

Table 49: Cumulative Incidence Rates: Occurrence of Dyspnea at 29 Days

Dose Level	Well-controlled Pooled group	Long-term Safety Pooled group
Placebo	0	NA
RU-0211 < 48 mcg	0.0364	NA
RU-0211 48 mcg	0.0261	0.0184
RU-0211 > 48 mcg	0.0303	NA
All Active Doses	0.0276	NA

Reviewer's table, modified from Table 2.7.4.2-18, page 63 of 131, Summary of Clinical Safety

For the LTS cohort, the cumulative hazard rate was 0.0155 for the interval covering 22-28 days, and it remained unchanged for the remainder of the intervals evaluated, indicating no increased risk over time for experiencing dyspnea. After 366 days of RU-0211 48 mcg treatment, the probability of experiencing at least 1 AE of dyspnea was 2% for LTS subjects. The frequency of dyspnea is essentially constant over time and does not increase with increased exposure to RU-0211.

Table 50: Cox Proportional Hazard Regression of Incidence Rates for the Time Until the First Occurrence of Dyspnea (WCG)

Total	Number of Events	Number Censored	Percent Censored	Hazard Ratio
601	9	592	98.50	24939660.9813

Reviewer's table, modified from Table 2.2.6.10, page 1215 of 2971, Integrated Summary of Safety

The Cox regression analysis for the time until the first occurrence of dyspnea in the WCG cohort could not be used to make a meaningful comparison between subjects taking RU-0211 and placebo, as there were no reports of dyspnea by subjects taking placebo. As shown above, which is somewhat reassuring, there was a relatively low number of reports of dyspnea in the WCG.

7.1.8 Laboratory Findings

As pre-determined in the study protocol, blood samples for hematology and biochemistry and urine samples for urinalysis were collected at baseline, throughout the study, and at the final assessment. Clinical significance was assessed based on pre-determined clinically significant low and high values for each parameter as defined in Appendix 2 of the sponsor's Statistical Analytic Plan. In addition to the below mentioned parameters, thyroid-stimulating hormone was measured at the start of each study to rule out hypothyroidism and serum pregnancy tests were performed on females of childbearing potential at Visits 1 and 5 to rule out pregnancy. Laboratory assays were performed by an accredited central laboratory facility, and the results were reviewed by the Investigator.

Hematology

Hematology parameters included: WBC count, lymphocytes, monocytes, eosinophils, basophils, lymphocytes x $10^3/\mu L$(Absolute), monocytes x $10^3/\mu L$(Absolute), basophils x $10^3/\mu L$(Absolute), hemoglobin, hematocrit, RBC count, Platelet count.

- For the **Well-Controlled group cohort**, the median values for each parameter at baseline and final assessment for the pooled group were within clinically acceptable normal ranges. There were no differences between placebo subjects and RU-0211 48 mcg subjects in the change from baseline estimates performed at the final assessment. For the pooled group overall, 2.7% of placebo subjects, 0% of RU-0211 < 48 mcg subjects, 1.2% of RU-0211 48 mcg subjects, and 6.3% of RU-0211 > 48 mcg subjects had at least 1 newly occurring clinically significant hematology value. Although all incidences were

low, there were more newly occurring clinically significant values for placebo subjects than for RU-0211 subjects. The highest incidence rates for clinically significant values in the placebo group were for a decline in percent eosinophils (1.3% for placebo vs. 0.5% for RU-0211 48 mcg) and a decline in percent monocytes (0.9% vs. 0.4%). The only clinically significant results in the RU-0211 > 48 mcg group were lowered WBC count and lymphocytes ABS, each reported by 1 subject.

- For the **Long-term safety group cohort**, the median values for each parameter at baseline and final assessment in the pooled group were not indicative of any adverse clinical trends. In the RU-0211 pooled group there was an increase in the mean change from baseline for monocytes (%) and basophils (%) during each of Weeks 12, 24, 36, and 48. At each time point, the increases in monocytes and basophils were < 10% of the baseline median making the changes unlikely to be of clinical importance. For the pooled group, 2.7% of placebo subjects, 0% of RU-0211 < 48 mcg subjects, 1.2% of RU-0211 48 mcg subjects, and 6.3% of RU-0211 > 48 mcg subjects had at least 1 newly occurring clinically significant hematology value. Although all incidences were low, the incidences of newly occurring clinically significant values were similar or higher for placebo subjects than for RU-0211 48 mcg subjects for all tests. The highest incidence rates in the placebo group were for percent eosinophils (1.3% for placebo vs. 0.5% for RU-0211 48 mcg) and percent monocytes (0.9% vs. 0.4%). The only clinically significant results in the RU-0211 > 48 mcg group were WBC count and lymphocytes ABS, each reported by 1 subject.

- For the **Overall Safety group cohort**, the median values for each parameter at baseline and final assessment for the pooled group were within clinically acceptable normal ranges. There were no dose-dependent trends in the median parameter values reported at baseline and final assessment nor in the changes from baseline for any parameter, with the possible exception of hemoglobin at final assessment. At final assessment, the mean changes in hemoglobin in the RU-0211 dose groups were -0.24% for < 48 mcg, -0.29% for 48 mcg, and -0.77% for > 48 mcg. Interestingly, the mean change in the placebo group at the same time point was -0.55%. Overall, 2.3% of placebo subjects, 0% of RU-0211 < 48 mcg subjects, 5.2% of RU-0211 48 mcg subjects, and 6.3% of RU-0211 > 48 mcg subjects had at least 1 newly occurring clinically significant hematology value. Monocyte (%) was reported by 0.7% of placebo subjects and 3.2% of RU-0211 48 mcg subjects, and eosinophil (%) was reported by 1.1% of placebo subjects and 0.9% of RU-0211 48 mcg subjects. The only clinically significant results in the RU-0211 > 48 mcg group were WBC count and lymphocytes ABS, each reported by 1 subject.

Medical Officer's Comments

The mean changes in hematology values from baseline, as discussed above, are clinically acceptable for a population of subjects with chronic idiopathic constipation who are otherwise considered generally healthy. Given that the frequencies of newly occurring clinically significant laboratory values were very low (<5% of subjects) for all parameters assessed in hematology, and there were no clinically meaningful sequelae (i.e. neutropenic fever

secondary to declining WBCs or severe anemia) the medical officer is more confident in the safety of the recommended therapeutic dose.

Biochemistry

Biochemistry parameters included: Total cholesterol, triglycerides, glucose, total protein, albumin, alkaline phosphatase, aspartate transaminase, alanine transaminase, gamma glutamyl transferase, lactate dehydrogenase, total bilirubin, direct bilirubin, blood urea nitrogen, uric acid, creatinine, sodium, potassium, chloride, calcium, phosphorus, and magnesium.

- For the **Well-controlled group cohort**, there were many trends in the biochemistry parameters. Median **glucose** value increased with increasing RU-0211 dose at final assessment (85.00 mg/dL for RU-0211 < 48 mcg vs. 87.00 mg/dL for RU-0211 48 mcg vs. 93.00 mg/dL for RU-0211 > 48 mcg. The median value in the placebo group at the same time point was 86.00 mg/dL. For **lactate dehydrogenase (LDH)**, mean and median decreases from baseline were observed in all treatment groups (including placebo). The mean decreases became larger with increasing RU-0211 doses (-0.63 U/L for RU-0211 < 48 mcg vs. -8.01 U/L for RU-0211 48 mcg vs. -8.66 U/L for RU-0211 > 48 mcg, and the mean decrease in the RU-0211 48 mcg group was larger than the mean decrease in the placebo group (-4.64 U/L). A large mean increase from baseline in **creatine phosphokinase** was observed in the RU-0211 > 48 mcg group (mean increase = 36.16 U/L. This result appears to be influenced by a maximum outlying value of 1842 U/L reported at the final assessment, considering that the median change from baseline in this dose group actually demonstrated a decrease (median change = -7.00 U/L). Median **uric acid** values at final assessment increased consistently with increasing RU-0211 dose (4.15 mg/dL for RU-0211 < 48 mcg vs. 4.20 mg/dL for RU-0211 48 mcg vs. 4.55 mg/dL for RU-0211 > 48 mcg. For **sodium**, mean decreases from baseline were observed in all treatment groups (including placebo), and the decreases became larger with increasing RU-0211 dose (-0.32 mEq/L for RU-0211 < 48 mcg vs. -0.57 mEq/L for RU-0211 48 mcg vs. -0.78 mEq/L for RU-0211 > 48 mcg. These changes are very small in magnitude (< 1%) compared with the observed baseline median values in each dose group. For **potassium**, mean decreases from baseline were observed in the placebo group (-0.03), the RU-0211 < 48 mcg group (-0.05), and the RU-0211 48 mcg group (-0.06); a mean decrease from baseline was observed in the RU-0211 > 48 mcg group (0.09). For **chloride**, mean decreases from baseline were observed in all treatment groups (including placebo), and the decreases became larger with increasing RU-0211 dose (-0.07 mEq/L for RU-0211 < 48 mcg vs. -0.33 mEq/L for RU-0211 48 mcg vs. -0.50 mEq/L for RU-0211 > 48 mcg. As noted for sodium above, these changes are also very small in magnitude (< 1%) compared with the observed baseline median values in each dose group.

The overall frequencies of shifts from normal at baseline to low; and shifts from normal at baseline to high at final assessment were generally low (most were < 5%) with the following exceptions:

- **Total cholesterol**, for which 11.8% of placebo and 12.1% of RU-0211 48 mcg subjects with normal baseline values shifted to high values; 18.6% of placebo subjects and 23.0% of RU-0211 48 mcg subjects with high baseline values shifted normal at final assessment.

- **Triglycerides**, for which 8.5% of placebo and 12.4% of RU-0211 48 mcg subjects with normal baseline values shifted to high values; 33.3% of placebo and 35.9% of RU-0211 48 mcg subjects with high baseline values shifted to normal at final assessment.

- **Glucose**, for which 5.2% of placebo and 7.1% of RU-0211 subjects with normal baseline values shifted to high values; 62.5% of placebo and 40.0% of RU-0211 with high baseline values shifted to normal at final assessment.

  For the Well-controlled pooled group overall, 10.5% of placebo subjects, 10.7% of RU-0211 < 48 mcg subjects, 12.8% of RU-0211 48 mcg subjects, and 18.8% of RU-0211 > 48 mcg subjects had at least 1 newly occurring clinically significant biochemistry value. In general, these results are in good agreement with the shift analyses. The highest incidences of newly occurring clinically significant values were seen for total cholesterol (3.6% for placebo; 3.6% for RU-0211 48 mcg), triglycerides (4.1%; 5.1%), and glucose (1.2%; 4.0%).

- For the **Long-term Safety cohort**, the median values for each parameter at baseline and final assessment in the pooled group were not indicative of any adverse clinical trends. There were small mean decreases at each time point for total cholesterol, total protein, albumin, gamma glutamyl transferase (GGT), uric acid, creatinine, sodium, potassium, calcium, phosphorus, and magnesium. Mean increases at each time point were observed for glucose and blood urea nitrogen (BUN), but the magnitude of the increases did not increase monotonically over time. For each of the parameters that exhibited mean increases or mean decreases at each time point, the changes were small in comparison with the respective baseline median values (< 5% in all cases), making the changes unlikely to be indicative of a negative safety result.

  For the Long-term Safety pooled group, 26.8% of subjects had at least 1 newly occurring clinically significant biochemistry value. Once again, the highest incidences of newly occurring clinically significant values were seen for triglycerides (13.7%), total cholesterol (11.9%), and glucose (3.9%). Shifts in creatine phosphokinase were reported by 3.2% of subjects, but no other test had an incidence rate that exceeded 2%. Note, however, that creatine phosphokinase was not analyzed for SC02S3, so the pooled group incidence rate for this test is based on a smaller number of subjects than the other tests.

- For the **Overall Safety cohort**, the median values for each parameter at baseline and final assessment for the pooled group were within clinically acceptable normal ranges. Dose-dependent trends in mean changes from baseline were observed for glucose (2.96 mg/dL for RU-0211 < 48 mcg vs. 3.16 mg/dL for RU-0211 48 mcg vs. 7.06 mg/dL for RU-0211 > 48 mcg; placebo change was 3.88 mg/dL), LDH (-0.63 U/L vs. -3.06 U/L vs. -8.66 U/L; placebo change was -4.62 U/L), and chloride (-0.07 mEq/L vs. -0.30 mEq/L vs. -0.50 mEq/L; placebo change was -0.02 mEq/L).

Overall, 11.0% of placebo subjects, 10.7% of RU-0211 < 48 mcg subjects, 24.2% of RU-0211 48 mcg subjects, and 18.8% of RU-0211> 48 mcg subjects had at least 1 newly occurring clinically significant biochemistry value. As in the other groups, the highest incidences of newly occurring clinically significant values were seen for total cholesterol (3.9% for placebo; 10.5% for RU-0211 48 mcg), triglycerides (4.2%; 11.9%), and glucose (1.7%; 4.1%), respectively. Creatine phosphokinase was reported as a newly occurring significant laboratory value by 1.3% of placebo subjects and 3.0% of RU-0211 48 mcg subjects. These incidences should be interpreted with caution, since the placebo subjects took the drug for a maximum of 4 weeks, while RU-0211 48 mcg subjects in the Long-term Safety cohort took the study drug for as much as 48 weeks.

Medical Officer's Comments
Most of the aforementioned biochemistry laboratory values are clinically acceptable for a population of subjects with chronic idiopathic constipation who are otherwise considered generally healthy. With the exception of total cholesterol, triglycerides, and glucose, which are difficult to interpret due to the lack of dietary restrictions and non-fasting conditions during blood draws, the frequencies of newly occurring clinically significant laboratory values were very low (< 5% of subjects) for all parameters. The medical officer is therefore, generally confident in the biochemistry laboratory safety data of the recommended therapeutic dose.

Urinalysis

Urinalysis parameters included: specific gravity and urine pH.

- For the **Well-controlled group cohort**, median values for both specific gravity and urine pH were similar between placebo subjects and RU-0211 48 mcg subjects. There were also no obvious differences across the RU-0211 dose groups. No differences were noted between placebo and RU-0211 48 mcg or across the RU-0211 dose groups in the analyses of the change from baseline. For the **Long-term safety group** cohort, there were no time-dependent trends for either parameter, with median pH being 6.50 at all time points, and median specific gravity being 1.02 at all time points. Mean changes at all time points were minimal for both parameters. The overall safety cohort did not differ noticeably from the WCG results.

  There were no reported newly occurring clinically significant urinalysis values in any of the cohorts.

Medical Officer's Comments
The urinalysis safety data is clinically acceptable for a population of subjects with chronic idiopathic constipation who are otherwise considered generally healthy.

7.1.9 Vital Signs

Vital sign parameters included: heart rate, systolic blood pressure, diastolic blood pressure, temperature, respiration rate, and weight.

- For the **Well-Controlled group cohort**, the mean and median values for placebo and RU-0211 48 mcg subjects were similar for all vital signs tested. Additionally, all median values were within accepted normal ranges. In both treatment groups, the median change from baseline at final assessment was 0.00.

  For the pooled group analysis, in the placebo and RU-0211 48 mcg groups, the proportion of subjects with a shift in any vital sign measurement from normal to low or normal to high was always less than 5% of pooled group subjects with normal baseline values, and there were no obvious differences between the 2 treatment groups.

- For the **Long-term safety group cohort**, median values for all vital signs remained essentially unchanged over time, and the observed median values were consistent with those that would be expected from an otherwise healthy subject population. The mean changes from baseline were very small, and were not consistently in the same direction nor did they increase over time.

  A summary of the shift analysis revealed that for **heart rate** in the pooled group, the proportion of subjects with normal baseline values that experience a shift from normal to low or normal to high never exceeded 1%. For **systolic blood pressure**, the proportion of subjects with shifts from normal to low was always less than 1% of pooled group subjects with normal baseline values; frequencies of shifts from normal to high were 3.6% at Week 12, 6.3% at Week 24, 7.6% at Week 36, 8.5% at Week 48, and 5.5% at final assessment. At these same time points, the proportions of pooled group subjects that shifted from high to normal were: 53.8%, 55.9%, 76.0%, 66.7%, and 63.6%. For **diastolic blood pressure**, the proportion of subjects with normal baseline values that experienced a shift from normal to low or normal to high never exceeded 4%. For both **temperature** and **respiration rate**, the proportion of subjects with normal baseline values that had shifts from normal to high or normal to low did not exceed 2.5%.

- For the **Overall Safety group cohort**, there was little difference observed between the placebo group and the RU-0211 48 mcg group for any vital sign measure, and there did not appear to be any obvious differences for any vital sign measure across the three RU-0211 dose groups.

  In this cohort, for the heart rate, temperature, and respiration rate, the proportion of subjects with shifts from normal to low or normal to high did not exceed 1% of subjects in the pooled group with normal baseline values for the placebo group and the RU-0211 48 mcg group. For the systolic blood pressure, the proportion of subjects with a shift from normal to low was 0.3% for placebo and 0.6% for RU-0211 48 mcg subjects; the proportion of subjects with a shift from normal to high was 4.4% for placebo and 5.1% for RU-0211 48 mcg subjects. For diastolic blood pressure, the proportion of subjects with a shift from normal to low was 2.0% for placebo and 3.0% for RU-0211 48 mcg subjects; the proportion of subjects with a shift from normal to high was 0.7% for placebo and 1.1% for RU-0211 48 mcg subjects.

Medical Officer's Comments

The vital signs safety data appears to be clinically acceptable for a population of subjects with chronic idiopathic constipation who are otherwise considered generally healthy. When comparing the safety data of the recommended therapeutic dose of RU-0211 (48 mcg) versus placebo, there does not appear to be an increased risk to subjects for developing vital sign or weight abnormalities when the study drug is administered for up to 48 weeks.

7.1.10 Physical Examinations

As pre-determined in the study protocol, physical examinations were performed on all subjects at baseline, throughout the study, and at final assessment. Physical examination parameters included assessment of the following body systems: abdominal/gastrointestinal, cardiovascular, chest/breast, general/other, HEENT/neck, lymphatic, musculoskeletal, neurological/psychiatric, respiratory, and skin/extremities. For the summaries of the Overall Safety cohort, back, chest/lungs, endocrine, genitourinary, and pulses were added to the list above.

- At the pooled group level for the **Well-Controlled group cohort**, across all body systems with a normal baseline evaluation, the frequencies of most shifts from normal to abnormal in the placebo and RU-0211 48 mcg groups were less than 2%, and for no body system did the shift from normal to abnormal in either treatment group exceed 4%. The body system with the highest frequency of shifts from normal to abnormal was abdominal/gastrointestinal, for which 2.9% of placebo subjects and 3.9% of RU-0211 48 mcg subjects experienced a shift from normal to abnormal. In both treatment groups, however, the proportion of subjects with shifts from abnormal to normal (46.2% for placebo; 37.9% for RU-0211 48 mcg) well exceeded the shifts from normal to abnormal. For HEENT/neck, there appeared to be a linear, dose-dependent increase in the proportion of subjects with a shift from normal to abnormal: 0% for RU-0211 < 48 mcg vs. 1.6% for RU-0211 48 mcg vs. 3.4% for RU-0211 > 48 mcg. Two subjects in each of SC0131 and SC0232 were responsible for the shifts in the 48 μg group, and 1 subject in SC9921 was responsible for the shift in the > 48 mcg group. The abnormalities (i.e., conjunctivitis, right ear erythema) were not suggestive of a systemic risk following RU-0211 treatment.

- At the pooled group level for the **Long-term group cohort**, across most body systems, the frequency of shifts from normal to abnormal remained essentially unchanged over 48 weeks and at the final assessment. In no body system did the frequency of shifts from normal to abnormal exceed 5% of the subjects with normal baseline evaluations. The highest proportion of shifts from normal to abnormal at each time point was in the abdominal/gastrointestinal body system. At the final assessment, the proportion of subjects with a shift from normal to abnormal in the abdominal/gastrointestinal body system was 4.2%.

- In the **Overall Safety group cohort**, the proportions of shifts from normal at baseline to abnormal at final assessment were generally higher in the RU-0211 48 mcg group compared with the placebo group. Although small, the difference was most notable in the following body systems: cardiovascular (1.2% vs 0.4%), HEENT/neck (1.9% vs.

0.4%), and musculoskeletal (1.6% vs. 0.4%). Interestingly, for each of these body systems, the proportion of subjects in the RU-0211 48 mcg group that shifted from abnormal to normal far exceeded the proportion that shifted from normal to abnormal. Similar to the WCG, although minimal and not suggestive of systemic risk, there again appeared to be a dose-dependent increase in the proportion of shifts from normal to abnormal in HEENT/neck.

Medical Officer's Comments

The physical examination data, when considered as a whole, is clinically acceptable for a population of subjects with chronic idiopathic constipation who are otherwise considered generally healthy. There does not appear to be an increased risk to subjects for developing any clinically significant abnormalities in any body system, either during extended treatment with RU-0211 or when comparing the safety of the recommended therapeutic dose of RU-0211 (48 mcg) to placebo.

7.1.11 Electrocardiograms (ECGs)

7.1.11.1 Overview of ECG testing in the development program, including brief review of preclinical results

Pre-Clinical Data

The effects of intraduodenally-administered RU-0211 at 10, 100 and 1000 μg/kg were evaluated on the cardiovascular and respiratory systems of anesthetized dogs. No effects were seen on heart rate, femoral artery blood flow, electrocardiogram, or respiration. In vitro cardiac ion channel testing has not been performed.

The sponsor completed a Phase I study and a Phase IIb study to evaluate the effects of RU-0211 on ECG parameters. The two studies are summarized briefly below.

I. A Definitive Phase I Study to Evaluate the Cardiac Safety of Oral RU-0211 in Healthy Volunteers.

The primary objective of this study was to define the electrocardiographic effects of RU-0211 with specific focus on the effect on cardiac repolarization using as the primary variable, individually corrected QTc duration (QTcI). Changes in all other electrocardiogram (ECG) parameters were also evaluated (heart rate, PR, and QRS intervals, and morphological changes).

This was a randomized, single-dose, parallel-group study evaluating the effects of 24 mcg RU-0211, 144 mcg RU-0211, Placebo, or 400 mg moxifloxacin (Avelox®) cardiac repolarization in 177 healthy adult volunteers. The moxifloxacin open-label active positive control was used to determine "assay sensitivity" in that the study can detect a small positive change (~5-10 ms) from baseline QTc duration. Cardiac assessments were collected through a 24-hour H-12 monitor. The cardiac effect of RU-0211 was evaluated via a comparison of the therapeutic and high doses of RU-0211 to the placebo and active control groups.

A standard 12-lead — Safety ECG was performed at screening, baseline (Day 0), 23.5-hours pre-dose, on Day 1, at 0.5 and 1 hour after dose administration, and prior to discharge (Day 2) approximately 23.5-hours following dose administration. Digital ECGs were obtained using a — . ECG continuous recorder, which captured ECGs on Day 0 (Baseline: -23.5, -12, -6, -4, -3.5, -3, -2.5, -2, -1.5, -1, -0.5 and 0 hours pre-dosing) and on Days 1-2 (Treatment/Discharge: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 12, and 23.5 hours post-dosing). The ECGs were stored on a flashcard about every 10 seconds and were not available for review until the card was received by the central ECG laboratory and analyzed. — served as the Chief Cardiac Consultant and provided the analysis for the ECG results.

ECG Analysis Plan

ECG interval and morphology changes were based on change from Baseline, where Baseline was the mean of the 36 recordings obtained on Day 0. Baseline ECGs were collected at -23.5, -12, -6, -4, -3.5, -3, -2.5, -2, -1.5, -1, -0.5 and 0 hours pre-dose. Treatment/Discharge ECGs were collected at the following times at and following dose administration 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 12, and 23.5 hours. A total of 36 ECGs were analyzed at Baseline (Day 0) and 33 ECGs on Days 1-2 for a total of 69 ECGs per subject. From the 177 subjects, a total of 11,040 ECGs were obtained for analysis. The ECG data were analyzed with the goal to describe central tendency and outlier effects for each of heart rate (HR), PR, QRS, QT, QTc intervals. New ECG morphological changes were defined as those "not present on any baseline ECG, but present on any post-treatment ECG". Baseline was defined as the mean of all of the values of ECG measurements taken on Day 0.

Heart Rate: There was a statistically significant increase in the heart rate change from baseline of 4 and 11 bpm, respectively, for the 24 mcg RU-0211 and 144 mcg RU-0211 compared to placebo. This change however, was not considered clinically significant. There were no tachycardic outliers for the 24 mcg RU-0211 dose group, but for the supra-therapeutic dose group of 144 mcg RU-0211, there was 15% more subjects meeting the 25% increase in heart rate from baseline to at least 100 bpm; (definition of tachycardia) compared to placebo.

PR and QRS: The mean change from baseline for the 24 mcg RU-0211 and 144 mcg RU-0211 groups compared to placebo for PR and QRS interval durations were -2 to -4 ms and 0 to -1 ms, respectively. There were no outliers for PR or QRS durations.

QT and QTc: The fact that RU-0211 showed minor heart rate increases in this study and in light of the known effect of heart rate on QT duration, individualized QTc with heart correction was calculated. QTcI (I for individually determined) is a formula for QT correction which is considered the most accurate method to correct QT for heart rate. QTcI was calculated by selecting the exponent of the standard QTc formula (i.e., QTcIx = QT/ (RR) **exponent) which, when plotting RR against QTcIx gave the slope closest to zero. The mean change from baseline in QTcI duration placebo corrected for the positive control moxifloxacin was 13 ms which is 3 ms above the usual 5-10 ms range. Moxifloxacin showed a clear QTcI increase compared to the other treatments and thus, adequately performed as a positive control providing assay sensitivity for this trial. For cardiac repolarization, the placebo control group showed a -9 ms change from baseline suggesting a good control of spontaneous variability. The placebo corrected mean

change from baseline for QTcI duration of the RU-0211 24 mcg dose was 0 ms and for the 144 mcg supra-therapeutic dose was +2 ms showing no signal of any effect of this agent on cardiac repolarization.

Morphology: There were slightly more subjects in the 24 mcg RU-0211 group with ST depression compared to the 144 mcg RU-0211 group, 3 subjects (7%) versus 2 subjects (4%), respectively. The moxifloxacin group had 3 subjects (7%) and the placebo group had 1 subject (3%). The 144 mcg RU-0211 group had 11 subjects (22%) with new T wave inversions compared to 5 subjects (11%) for the 24 mcg group, 3 subjects (8%) for the placebo group, and 4 subjects (10%) for the moxifloxacin group.

Outlier Analysis: The specific outlier analyses include new 500 ms absolute QTcI durations or a change from baseline of >60 ms. No subject met these criteria. The non-specific outlier criteria of 30-60 ms change from baseline occurred in 4 (10%) moxifloxacin subjects, 2 (4%) 144 mcg RU-0211 subjects, no 24 mcg RU-0211 subjects, and 1 (3%) placebo subjects. Therefore, only one additional subject on the supra-therapeutic dose of RU-0211 demonstrated a change of 30-60 ms compared to placebo and moxifloxacin revealed a 7% imbalance compared to placebo.

Medical Officer Comments/Conclusions:

Although this study was limited by its short duration (2 days), it had adequate subject enrollment encompassing 177 subjects with 69 ECGs per subject and over 11,000 ECGs. The study evaluated the effects of RU-0211 on ECGs parameters at two doses, half the proposed therapeutic dose (24 mcg) and 144 mcg, a supra-therapeutic dose. Although the proposed dose for this NDA (48 mcg/day; 24 mcg b.i.d.) was not studied, the ECG effects can be assumed to be captured in the studied therapeutic window. The study concluded that RU-0211 caused a minor increase in heart rate, although not clinically significant. There was no signal of any significance on cardiac conduction as measured by PR and QRS interval durations. The moxifloxacin positive control group showed assay sensitivity with a clear QTcI increase compared to the other treatment groups. The QTcI change from baseline for RU-0211 at the 144 mcg supra-therapeutic dose was only +2 ms whereas the 24 mcg group change was 0 ms. Considering the short half-life of RU-0211 in the body (1-2 hours), and the recommended two doses of 24 mcg RU-0211, which are to be separated by at least 5, preferably 8-10 hours, the aforementioned data appears to provide fairly strong evidence that RU-0211 does not effect cardiac repolarization and that subjects taking a single dose will be free from any effects from the previous administration in terms of cardiac safety.

II. Retrospective Review of ECGs from the Completed Phase IIb Constipation Study: Protocol RTU/0211SC9921. Double-Blind, Randomized, Placebo-Controlled, Multi-Center Phase IIb Study of the Safety and Efficacy of Oral RU-0211 in Patients with Chronic Constipation.

The objective of this retrospective study was to review electrocardiogram results and any changes from baseline until the end of treatment and to assess such data for any newly occurring clinically significant abnormalities.

The original study was a multi-center, Phase IIb trial with a parallel-group design, consisting of a 14-day drug-free washout period, followed by a 3-week, randomized, double-blind, placebo-controlled treatment period. One hundred twenty-nine (129) subjects with constipation were randomized to double-blind treatment allotting for approximately 30 ECGs per treatment group.

ECGs that were recorded at the study site for each subject were pulled from Sucampo Pharmaceuticals, Inc. (SPI) study files and sent to — a central ECG laboratory, for a retrospective high resolution measurement of the cardiac intervals and morphological assessment by the Senior Cardiac Safety Operations staff and QA Department blinded to the study treatment. One hundred and twenty-nine subjects were randomized and 250 ECGs were evaluated. Manual measurements of the RR, PR, QRS, and QT interval durations were performed as well as two derived variables, QTcB (Bazett correction) and QTcF (Fridericia correction).

Heart Rate: The placebo corrected change from baseline in heart rate on RU-0211 for the 24, 48 and 72 mcg dose groups was -1, +1, and 0 bpm respectively demonstrating that RU-0211 does not effect heart rate. There were no placebo corrected bradycardic outliers, but a single subject on 72 mcg had a sinus tachycardic episode, which is of no clinical relevance.

PR and QRS: The placebo corrected change from baseline on PR duration on RU-0211 for the 24, 48, and 72 mcg dose groups was +4, +1, and +2 msec and for QRS duration 0, -2, and +1 msec respectively. No outliers were observed.
QT and QTc: The placebo corrected change from baseline in QTcF duration on RU-0211 for the 24, 48, and 72 mcg dose groups were -4, -3 and –5 msec respectively, demonstrating no evidence of a central tendency effect of RU-0211 on repolarization. The outlier analyses reveal one subject in each RU-0211 treatment group that met the non-specific outlier criterion of a 30-60 msec change form baseline and no subject met the specific criteria of a new >500 msec, new abnormal U waves or a > 60 msec change from baseline.

Morphology: No new morphological findings on RU-0211 compared to placebo were observed.

Medical Officer Comments/Conclusions:

The evaluation of effects of RU-0211 on ECG parameters was limited in this study by single ECG analyses at the baseline and end of treatment time points. The sample size of 30 ECGs per treatment arm was also a limitation in this evaluation. Despite these limitations, RU-0211 at doses of 24, 48, and 72 mcg per day, for 3 weeks, as studied in this protocol, showed no evidence of any effect on heart rate, cardiac conduction (PR and QRS duration) or cardiac repolarization (QTcF analysis) as well as no evidence of new morphological changes.

7.1.12 Immunogenicity

The sponsor did not provide any clinical or adverse event data regarding immunogenicity in this New Drug Application.

7.1.13 Human Carcinogenicity

The sponsor did not provide any clinical or adverse event data regarding human carcinogenicity in this application; however, carcinogenicity studies with RU-0211 were conducted in rats and mice. It is of the Medical Officer's understanding that the sponsor performed a 104-week oral gavage study in SD rats, the rats received 0.02, 0.1, or 0.4 mg/kg/day of RU-0211. In the 104-week oral gavage study in B6 mice, the mice received 0.025, 0.075, 0.2 or 0.5 mg/kg/day of RU-0211. No drug-related histomorphologic changes were seen in the bone and marrow examined from the sternum and femur in either rats or mice. The NOAEL for histopathological changes in the non-glandular stomach of rats that received RU-0211 for at least 104 weeks was less than 0.02 mg/kg/day for expected hyperplasia, 0.02 mg/kg/day for benign squamous cell papilloma, and greater than 0.4 mg/kg/day for malignant carcinoma. This may be a species-specific response as the non-glandular stomach is unique to rats. In a 104-week oral gavage study in B6 mice, mucosal hyperplasia occurred in both the forestomach (non-glandular) and the glandular stomach of the B6 mice. The NOAEL for tumorigenic effects in mice that received RU-0211 for at least 104 weeks is > 0.5 mg/kg/day. An in-depth review of the Carcinogenicity studies can be found within the Agency's formal Pharmacology review.

7.1.14 Special Safety Studies

As RU-0211 did not demonstrate a tendency to result in life-threatening side effects in the preclinical and clinical studies and had a very limited potential for the development of serious or severe AEs, no specific monitoring or testing was required during the study that would be considered outside standard of care for a clinical trial of otherwise healthy subjects, with the exception of the bilateral hand X-rays. Bilateral hand X-ray studies were performed in the long-term safety studies (SC01S1 (24 weeks) and SC01S2-SP2 portion (48 weeks) at the request of the Agency because of the concern that RU-0211 might have deleterious effect on bone density following long-term exposure.

Table 51 below summarizes the shifts from baseline to final assessment in bilateral hand X-ray results as they were performed in Studies SC01S1 and SC01S2 (SP2 portion). In the pooled group, for the left hand, 5.5% of subjects with normal baseline evaluations had abnormal final assessment evaluations; for the right hand, 4.7% shifted from normal at baseline to abnormal at final assessment; and for both hands, 6.9% of subjects considered normal at baseline were abnormal at final assessment. Interestingly, for each of the three X-ray groupings in the pooled group, the frequency of shifts from abnormal to normal was at least double the frequency of shifts from normal to abnormal (left hand: 17.4% vs. 5.5%; right hand: 14.8% vs. 4.7%; both hands: 16.0% vs. 6.9%).

Table 51: Shift Table of X-ray Results; Safety Evaluable Patients [Long Term Safety[1]]

Parameter	Baseline	Final Assessment[2]	SC01S1 RU-211 48 mcg N=306 (%)	SC01S2[3] RU-0211 48 mcg N=248 (%)	Pooled Group RU-0211 48 mcg N=554 (%)
LEFT HAND	Normal	Normal	143/151 (94.7)	117/124 (94.4)	260/275 (94.5)
		Abnormal	8/151 **(5.3)**	7/124 **(5.6)**	15/275 **(5.5)**
		Missing	0/151 (0.0)	0/124 (0.0)	0/275 (0.0)
	Abnormal	Normal	9/64 **(14.1)**	11/51 **(21.6)**	20/115 **(17.4)**
		Abnormal	55/64 (85.9)	40/51 (78.4)	95/115 (82.6)
		Missing	0/64 (0.0)	0/51 (0.0)	0/115 (0.0)
	Missing	Normal	6/6 (100.0)	1/2 (50.0)	7/8 (87.5)
		Abnormal	0/6 (0.0)	1/2 (50.0)	1/8 (12.5)
		Missing	0/6 (0.0)	0/2 (0.0)	0/8 (0.0)
RIGHT HAND	Normal	Normal	143/150 (95.3)	118/124 (95.2)	261/274 (95.3)
		Abnormal	7/150 **(4.7)**	6/124 **(4.8)**	13/274 **(4.7)**
		Missing	0/150 (0.0)	0/124 (0.0)	0/274 (0.0)
	Abnormal	Normal	5/62 **(8.1)**	12/53 **(22.6)**	17/115 **(14.8)**
		Abnormal	57/62 (91.9)	41/53 (77.4)	98/115 (85.2)
		Missing	0/62 (0.0)	0/53 (0.0)	0/115 (0.0)
	Missing	Normal	8/8 (100.0)	1/1 (100.0)	9/9 (100.0)
		Abnormal	0/8 (0.0)	0/1 (0.0)	0/9 (0.0)
		Missing	0/8 (0.0)	0/1 (0.0)	0/9 (0.0)
BOTH HANDS	Normal	Normal	134/145 (92.4)	109/117 (93.2)	243/262 (92.7)
		Abnormal	10/145 **(6.9)**	8/117 **(6.8)**	18/262 **(6.9)**
		Missing	1/145 (0.7)	0/117 (0.0)	1/262(0.4)
	Abnormal	Normal	7/71 **(9.9)**	14/60 **(23.3)**	21/131 **(16.0)**
		Abnormal	64/71(90.1)	46/60 (76.7)	110/131 (16.0)
		Missing	0/71 (0.0)	0/60 (0.0)	0/131 (0.0)
	Missing	Normal	6/6 (100.0)	1/1 (100.0)	7/7 (100.0)
		Abnormal	0/6 (0.0)	0/1 (0.0)	0/7 (0.0)
		Missing	0.6 (0.0)	0/1 (0.0)	0/7 (0.0)

Reviewer's Table modified from Table 2.2.23.1, Section 2.7.4, Integrated Summary of Safety, Module 2, page 2630

1 This group is a subset of the General and Overall Safety Group

2 The last treatment period assessment

3 X-rays were not regularly obtained during the SP1 portion of SC01S2

Medical Officer's Comments

The shifts from normal to abnormal in all three X-ray groupings were all < 10%; and the shifts from abnormal to normal were all at least twice the percentage of shifts from normal to abnormal. Although a formal lumbar spine and hip bone densitometry analysis would provide a more accurate reflection of RU-0211's effect on bone metabolism, given the above analyses, there does not appear to be a negative impact on bone density, as measured via hand X-rays.

7.1.15 Withdrawal Phenomena and/or Abuse Potential

Subject safety under conditions of RU-0211 withdrawal was studied during the Randomized Withdrawal (RW) period of SC01S2 SP1. Subjects enrolled in this study took RU-0211 48 mcg as an open-label treatment for 4 weeks during the Active Treatment (AT) period, which was followed by a 3-week double-blinded, randomized, placebo-controlled RW period. Thus, subjects randomized to receive placebo during the RW period provided safety data corresponding to the withdrawal of RU-0211 treatment. When comparing the frequency of adverse events in the RW period to the AT period, the frequency of placebo subjects who reported adverse events during the RW period was reduced; placebo subjects who reported at least one AE (20.9% vs. 67.2%), reported at least one treatment-related AE (4.7% vs. 50.8%), and who discontinued because of an AE (2.3% vs. 20.3%), in the RW and AT periods, respectively. The corresponding proportions of RU-0211 subjects reporting at least one AE (27.3%) and at least one treatment-related AE (9.1%) during the RW period were slightly higher than the proportions for placebo subjects (20.9% and 4.7%, respectively), but none of these differences were statistically significant. Abdominal distension (4.7%) was the only adverse event reported by more than a single placebo subject during the RW period, and its frequency was the same as that reported during the AT period.

The rebound phenomena following withdrawal of RU-0211 treatment were also examined by evaluating the frequency of AEs reported during the seven days immediately following a subject's last dose of study drug. Based on RU-0211's short residence in the body (specifically, the elimination half-life is approximately 1-2 hours, with metabolites in 7-8 hours), a 7-day window after the last dose of study drug represents approximately 84-168 half-lives. The sponsor compiled a summary of adverse events that were reported within 7 days after the last dose of the study drug. These AEs were consistent with the overall AE profile of RU-0211 and do not constitute new safety concerns that arise following withdrawal from treatment with RU-0211.

In addition to the aforementioned RW study, the sponsor notes that the pharmacological profile of RU-0211 is not consistent with a drug that would have the potential for abuse or drug dependence.

Medical Officer's Comments

The sponsor performed a thorough Randomized-withdrawal analysis. Considering the lack of significant differences between placebo-RW subjects and RU-0211 48 mcg-RW subjects and the lack of newly occurring adverse events in the placebo RW subjects, there appears to be no obvious safety risks in subjects following immediate cessation or seven day withdrawal from RU-0211 48 mcg treatment.

7.1.16 Human Reproduction and Pregnancy Data

Six studies evaluating RU-0211 for potential fertility and reproductive performance effects (Segment I), teratological effects (Segment II), and perinatal-postnatal effects (Segment III) were conducted in rats and rabbits. RU-0211 at oral doses of up to 1000 mcg/kg/day (>1,000 times the human exposure at the therapeutic dose of 24 mcg b.i.d.) in male and female rats was

found to have no effect on parental reproductive function. No abnormal signals were seen in bone formation among fetuses or offspring within the aforementioned studies. Additionally, offspring born to females treated with RU-0211 and kept on active drug while offspring were nursing did not reveal any clinically relevant findings with respect to RU-0211 treatment. Following weaning, these offspring were mated and demonstrated no observable effects on fertility, reproductive performance, or problems with the second-generation offspring.

No adequate and well-controlled studies of RU-0211 in pregnant or lactating women were conducted. Pregnant women were excluded from all clinical trials of RU-0211, and any woman who became pregnant during a study was immediately discontinued from study participation. Four pregnancies were reported during the clinical development of RU-0211 under IND #59,623.

- Subject SC02S3-01-R0108 had negative pregnancy tests on — (Visit 1) and on — (Visit 5). The subject tested positive for pregnancy on — and stopped drug on that day, although the follow-up report from the site noted that the most recent dose was taken on — The subject could therefore have potentially been pregnant about 1 month while on study drug. The subject had a healthy baby.

- Subject SC01S2-SP2-04-R0411 had a negative pregnancy test on — (Visit 1). The subject stopped the drug on — and reported being 11 weeks pregnant on — The site reported that the subject was exposed to drug for approximately 1 week while pregnant. The subject was lost to follow-up.

- Subject SC01S2-SP2-18-R1804 had a negative pregnancy test on — (Visit 6). She had a positive pregnancy test on — (Visit 7), and she stopped the drug on — The subject potentially could have been pregnant for 1 month while on drug. The subject had a baby boy on — The baby was healthy, but with bilateral club feet. This congenital anomaly SAE was considered possibly related to the study drug by the investigator.

- Subject SC0232-04-R0405 had a negative pregnancy test on February (Visit 1). The subject started drug on — however no pregnancy test was given at that time. The subject stopped the medication on — after a positive pregnancy test. She potentially could have been pregnant for 2 months on drug. The subject had a healthy baby girl on —

One ectopic pregnancy was reported during the conduct of Study SPI/0211SIB-0211 under IND — The subject had a positive pregnancy test after reporting that she missed 3 doses of Loestrin®, and the took all 3 doses on the same day. An ectopic pregnancy was found, which was reported as "resolved" approximately two days later.

Abortifacient Potential Studies

Studies designed to evaluate the adverse effects; specifically abortion and/or fetal resorption, were conducted in guinea pigs and rhesus monkeys with orally administered RU-0211via capsule.

SPI/SR05-016 was a dosage range toxicity study in pregnant guinea pigs in which the effects of oral RU-0211 at doses of 0, 5, 20, 40 and 80 mcg/kg/day were evaluated on days 40 through 53 of presumed gestation. Four guinea pigs in the 40 mcg/kg/day group and six in the 80 mcg/kg/day group were aborted and sacrificed, respectively. The 5, 20, 40 and 80 mcg/kg/day dosages of RU-0211 caused dosage-dependent reductions in body weight gains and/or body weight losses for all tabulated intervals within this period and gestation periods. Mortality occurred in three and four guinea pigs in the 40 and 80 mcg/kg/day dosage groups, respectively. Of these, two and three guinea pigs were found dead (40 and 80 mcg/kg/day dosage groups, respectively) and one guinea pig in each of the 40 and 80 mcg/kg/day dosage groups were sacrificed because of moribund condition. In the 5 mcg/kg/day group, one guinea pig was sacrificed due to moribund condition and two were sacrificed due to abortion. Neither mortality nor abortions were observed in the 20 mcg/kg/day dose group.

SPI/SR05-001 was a dosage range toxicity study in pregnant rhesus monkeys in which the effects of oral RU-0211 at doses of 0, 10, and 30 mcg/kg/day were evaluated during days 110 through 130 of gestation. The sponsor's rationale for choosing the aforementioned doses were as follows: Rhesus monkeys are supposedly 20 times more sensitive to abortifacient activities of compounds than are rats; the rat NOEL was thought to be 200 mcg/kg/day, making the corresponding dose in monkey 10 mcg/kg/day. No monkeys died, and no abnormalities were observed in clinical signs, food consumptions, body weight or serum progesterone in any group. Early delivery on Day 149 of gestation was observed in one monkey in the 30 mcg/kg group and in one monkey in the 10 mcg/kg group. The neonates were delivered naturally and alive. No abnormalities were observed in body weight, external features, or general health condition in these neonates. Accordingly, these deliveries were judged normal. An abortion on Day 141 of gestation was observed in one monkey in the 10 mcg/kg group.

Medical Officer's Comments

The sponsor noted that as some adverse effects were observed in the SPI/SR05-016 study at the 5 mcg/kg/day dose but not at the 20 mcg/kg/day dose, these effects were likely related to animal sensitivity and to significant changes in environmental conditions (i.e., housing, feed, water source, stress-induced maternal toxicity, etc.). Despite this fact, the medical officer cannot dismiss the fact that increases in mortality, fetal loss, and adverse clinical signs were still observed at doses of 40 mcg/kg/day and higher. The data is confounded by historical data that indicates that a true abortifacient effect in the guinea pig species occurs at approximately 30 minutes post drug ingestion, whereas in this study, the fetal loss occurred at days 4 through 8. The guinea pig data was also confounded by the fact that there was maternal death as well as fetal loss. This would suggest that there is indeed drug toxicity, however; the role of the drug in causing fetal loss is much less clear.

The sponsor indicated that the one abortion that was observed in study SPI/SR05-001 in the 10 mcg/kg rhesus monkey group was unrelated to the study drug. The sponsor judged the abortion as unrelated to the study drug due to the low overall incidence and the fact that no abortions occurred in the higher dose group (30 mcg/kg). Per the Agency's Pharmacologists, the dosage range chosen for the rhesus monkey abortifacient study was underestimated; making it inadequate and inconclusive.

Beyond the aforementioned studies, the medical officer has some additional concerns not addressed by the sponsor regarding RU-0211's reproductive toxicological potential. The prescription anti-ulcer drug Cytotec® (misoprostol), a prostaglandin E_1 analogue has been used off-label intravaginally with Mifeprex® (mifepristone) as an abortifacient via uterine stimulation and cervical ripening. Given that RU-0211 is also a unique prostaglandin E_1 metabolite analogue; there are still outlying concerns that it too could be used intravaginally off label. As RU-0211 has never been tested in pregnant women and the animal studies are inconclusive, the medical officer cannot estimate with certainty the risk of RU-0211, when used off-label, on a population of child-bearing, female subjects with chronic idiopathic constipation who are otherwise considered generally healthy.

A dual review of the reproductive toxicology of RU-0211 will be summarized in both the Agency's Division of Reproductive/Urology Pharmacology review and the Agency's Division of Gastroenterology Pharmacology review.

7.1.17 Assessment of Effect on Growth

The study population in this New Drug Application included adults age 18 years and older. The application therefore, has no applicable information regarding the effect of RU-0211 on growth.

7.1.18 Overdose Experience

Oral RU-0211 has been tested in humans at doses up to 144 mcg/day which is 3 times greater than the proposed indicated dose of 24 mcg b.i.d. There have been 2 confirmed reports of overdose with RU-0211 and 1 report of a possible overdose.

- The **first case** involved a male toddler who ingested 7-8 capsules of 24 mcg RU-0211 that had been given to subject SC02S3-07-R0707. The toddler experienced 4 episodes each of vomiting and diarrhea along with a stomach ache. He was admitted to the hospital for observation and was discharged without incident.
- The **second case** involved subject SC0131-03-R0304 who self-administered a total of 96 mcg RU-0211 per day for 14 days. The subject experienced no adverse events during this time.
- Another possible overdose involved study subject SC01S2-SP2-03-R0315 who was unable to account for 13 capsules of RU-0211. It was thought that a toddler or infant had ingested the missing medication. The toddler and infant were admitted to the hospital for observation, and both were discharged without incident. No adverse events were reported in the adult, toddler, or infant.

Of note, in a Phase I cardiac study, 51 subjects were dosed with a single oral administration of 144 mcg RU-0211. Thirty-nine of the 51 subjects experienced an adverse reaction with the most common being nausea, vomiting, diarrhea, dizziness, headache, watery stools, retching, and abdominal pain. Based on the safety and tolerability profile of RU-0211, it is expected that an overdose could potentially be associated with the following symptoms: nausea, vomiting, headache, diarrhea, abdominal pain, flatulence, and possible dehydration. Treatment for overdose should be directed toward the support of all vital functions and prompt institution of symptomatic therapy.

7.1.19 Post-marketing Experience

This is the initial marketing application for RU-0211 in the United States or any country therefore post-marketing experience is not applicable.

7.2 Adequacy of Patient Exposure and Safety Assessments

Among the Well-controlled group, the Long-term safety group, and the Overall-safety group cohorts, there was adequate patient exposure in terms of appropriate drug dosages, duration of treatment, and total number of patients. The demographic subsets of patients were slightly limited as for lack of racial diversity and lack of geriatric patients; however, consistency therein was well maintained across the study groups. Beyond the limitations in the sponsor's reproductive pharmacology/toxicology studies, the overall clinical efficacy and safety tests were applicable and potentially important findings were adequately explored.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A graphic description of the primary clinical data sources for this New Drug Application is shown below in Table 52. Efficacy was the primary objective for the two Phase III, well-controlled studies (SC0131, SC0232) and the one Phase II study (SC9921). Safety was the primary objective for the three Phase III long-term safety studies (SC01S1, SC01S2-SP2, and SC02S3). The effects of RU-0211 withdrawal were examined during the 7-week randomized-withdrawal SP1 period of study SC01SS2. The clinical pharmacology of RU-0211 was evaluated in two Phase I studies (RTU/RU0211-99101 and RTU/RU0211-99102). Other supportive studies that were included in this application included a Phase I radiolabeled metabolic disposition study, a Phase Ib pharmacokinetic, metabolic disposition, food effect study, and a Phase I thorough QTc study.

Table 52: Clinical Trials; Primary Clinical Data

Study	Design	Study Objective	Duration	Group, Dose, # of Subjects Treated/Completed
99101	Randomized rising dose tolerance, leap frog	Safety, tolerance, pharmacokinetics, pharmacodynamics	3 single doses per subject, separated by a 7-day washout	Period 1, 6 mcg, 6/6 Period 2, 24 mcg, 6/6 Period 3, 72 mcg , 6/6 Period 1, 12 mcg, 6/6 Period 2, 48 mcg, 6/6 Period 3, 96 mcg, 6/6 Group 1, Placebo, 2/2 Group 2, Placebo, 2/2
99102	Double-blind, multiple, rising oral, tolerance	Safety, tolerance, pharmacokinetics, pharmacodynamics	7 days (t.i.d. dosing for 6 days with a single dose on Day 7)	Group 1, 24 mcg T.I.D. 6/6 Group 2, 30 mcg T.I.D. 6/6 Group 3, 36 mcg T.I.D. 6/6 **Oral Placebo** Group 1 2/2 Group 2 2/2

Reviewer's Table modified from Table 2.7.32-1, Summary of Clinical Efficacy for RU-0211, page 13 of 108

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Table 53: Clinical Trials; Primary Clinical Data and Populations Exposed Continued

Study	Design	Study Objective	Duration	Group, Dose, # of Subjects Treated/Completed
SC9921	Double-blind, randomized multicenter, placebo	Safety and Efficacy	3 weeks	24 mcg, 29/26 48 mcg, 32/27 72 mcg, 33/28 Placebo, 33/28
SC0131	Double-blind, randomized multicenter, placebo	Efficacy and Safety	4 weeks	48 mcg, 120/106 Placebo, 122/118
SC01S1	Open-label, multicenter	Safety	24 weeks	48 mcg, 306/165
SC01S2-SP1	4-week active treatment; 3-week double-blind, randomized withdrawal; multicenter	Evaluation of post-treatment response	7 weeks	4-week AT 48 mcg, 128/87 3-week RW 48 mcg, 45/41 Placebo, 42/41
SC01S2-SP2	Open-label, multicenter	Safety	48 weeks	48 mcg, 248/127
SC0232	Double-blind, randomized, multicenter	Efficacy and Safety	4 weeks	48 mcg, 119/99 Placebo, 118/107
SC02S3	Open-label, multicenter	Safety	48 weeks	48 mcg, 324/153

Reviewer's Table modified from Table 2.7.32-1, Summary of Clinical Efficacy for RU-0211, pages 14-15 of 108

For ease of safety evaluation, the study populations were categorized into unique patient cohorts. The three patient cohorts which will be emphasized throughout this review include: the Well-controlled group cohort, the Long-term safety cohort, and the Overall safety cohort.

The **Well-controlled safety cohort** included studies SC0131, SC0232, and SC9921. In studies SC0131 and SC0232, RU-0211 48 µg and placebo were compared in double-blind trials. Study SC9921 consisted of four treatment arms, all with t.i.d. dosing: placebo, RU-0211 24 mcg (24 mcg in the morning plus placebo doses at midday and in the evening), RU-0211 48 mcg (24 mcg in the morning and evening plus a placebo dose mid-day), and RU-0211 72 mcg (24 mcg t.i.d.). The RU-0211 24 mcg dose was summarized as RU-0211 < 48 mcg, and the RU-0211 72 mcg dose was summarized as RU-0211 > 48 mcg. Results from each study and the pooled group are presented for this cohort.

The **Long-term safety cohort** included studies SC01S1 (24 weeks), SC01S2-SP2 (48 weeks), and SC02S3 (48 weeks). The only dose group represented in this cohort was 48 mcg, although safety data in which the dose was decreased during a LTS study were reported in the RU-0211 48 mcg group. A pooled analysis combining all three studies was also included in this cohort.

The **Overall safety cohort** includes 11 studies in the clinical program which were pooled together and analyzed according to the dose groups. The overall safety cohort consists of studies: 99101, 99102, SA-0011, SA-0312, SA-0411, SC9921, SC0131, SC01S1, SC01S2 [SP2], SC0232, and SC02S3.

Table 54 below is a summary of subject disposition and extent of exposure for placebo and RU-0211 48 mcg subjects in the Overall Safety group.

Table 54: Summary of Subject Disposition / Extent of Exposure – All Randomized Subjects [Overall Safety Group and Well-Controlled Group]

Variable	Overall Safety Group		Well Controlled Group	
	Placebo N=369 n (%)	RU-0211 48 mcg N=1119 n (%)	Placebo N=275 n (%)	RU-0211 48 mcg N=271 n (%)
Subjects Assessed	369 (100.0)	1119 (100.0)	275 (100.0)	271 (100.0)
Treated[1]	367 (99.5)	1113 (99.5)	273 (99.3)	271 (100.0)
Not Treated[1]	2 (0.5)	6 (0.5)	2 (0.7)	0 (0.0)
Completed Subjects	346 (93.8)	593 (53.0)	253 (92.0)	232 (85.6)
Reasons for Discontinuation				
Adverse Event	5 (1.4)	220 (19.7)	4 (1.5)	29 (10.7)
Protocol Violation	0 (0.0)	5 (0.4)	0 (0.0)	0 (0.0)
Subject Violation Withdrawal	2 (0.5)	66 (5.9)	2 (0.7	3 (1.1)
Lack of Efficacy	11 (3.0)	166 (14.8)	11 (4.0)	2 (0.7)
Lost to Follow-up	3 (0.8)	55 (4.9)	3 (1.1)	5 (1.8)
Did Not Meet Entry Criteria	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Other	2 (0.5)	13 (1.2)	2 (0.7)	0 (0.0)
Duration of Exposure[2]				
≥ 1 Day	367/369 (99.5)	1113/1119 (99.5)	273/275 (99.3)	271/271 (100.0)
≥ 1 Week	311/318 (84.3)	1060/1119 (94.7)	268/275 (97.5)	251/271 (92.6)
≥ 2 Weeks	303/318 (82.1)	1000/1119 (89.4)	260/275 (94.5)	233/271 (86.0)
≥ 3 Weeks	271/318 (73.4)	967/1119 (86.4)	242/275 (88.0)	225/271 (83.0)
≥ 4 Weeks	201/242 (83.1)	903/1087 (83.1)	201/275 (83.1)	171/271 (71.5)
≥ 12 Weeks	-	612/932 (65.7)	-	-
≥ 24 Weeks	-	494/932 (53.0)	-	-
≥ 36 Weeks	-	301/624 (48.2)	-	-
≥ 48 Weeks	-	221/624 (35.4)	-	-
Number of Days on Study Drug[3]				
n	367 (99.5)	1113 (99.5)	271 (98.5)	267 (98.5)
Mean	22.8	153.1	27.0	25.0
SD	9.83	131.82	5.46	8.23
Median	28.0	120.0	29.0	28.0
Range	1.0 – 35.0	1.0 – 421.0	5.0 – 35.0	1.0 – 39.0

Reviewer's Table modified from Tables 2.7.4.1-3 and 2.7.4.1-4, Summary of Clinical Safety, pages 19/21 of 131

1 Percentages are the total which fall into the particular category divided by the number of subjects assessed.

2 Percentages are calculated as the number of subjects on study drug divided by the number of randomized subjects who were expected to remain on study drug based on the respective study design.

3 Number of Days on Study Drug = (Date of Last Dose - Date of First Dose + 1). Values were considered missing for this analysis if the date of last dose was unknown.

As graphically illustrated above, in the **Overall safety cohort**, 369 placebo subjects were assessed, 367 subjects were treated, and 346 subjects (93.8%) completed their respective studies; 1119 RU-0211 48 mcg subjects were assessed, 1113 subjects were treated, and only 593 subjects (53.0%) completed their respective studies. In the placebo group, the most common reason for discontinuation was lack of efficacy (3.0%) whereas in the RU-0211 48 µg group, the most common reasons were adverse events (19.7%), lack of efficacy (14.8%), subject voluntary withdrawal (5.9%), and lost to follow-up (4.9%). The RU-0211 frequency of discontinuation because of lack of efficacy is likely artificially reduced in this overall safety cohort as this cohort includes subjects from the well-controlled group cohort who were only on the study drug for 4 weeks and discontinued because of lack of efficacy at a much lower rate (0.7%). The median number of days on study drug was 28.0 for placebo subjects and 120.0 for RU-0211 48 µg subjects. In the placebo group, 99.5% of assessed subjects were on study drug for at least 1 day, 73.4% of subjects were on study drug for at least 3 weeks, and 83.1% of those expected to be on study at 4 weeks were on study drug for at least 4 weeks; in the RU-0211 48 mcg group, 86.4% of subjects were on study drug for at least 3 weeks, 83.1% were on study drug for at least 4 weeks, 53.0% were on study drug for at least 24 weeks, and 35.4% were on study drug for at least 48 weeks. Note that at each time point, the percentage was based on the number of subjects expected to be on study drug at that time, e.g., subjects in SC9921, which had a 3-week treatment period, were not included in the percentage of subjects still on study drug for at least 4 weeks.

As noted above in Table 54 for the **Well-Controlled group**, 275 placebo subjects were assessed, 273 placebo subjects were treated, and 253 subjects (92.0%) completed their respective studies; 271 RU-0211 48 mcg subjects were assessed and treated, and 232 subjects (85.6%) completed their respective studies. In the placebo group, the most common reason for discontinuation was lack of efficacy (4.0%); in the RU-0211 48 mcg group, the most common reason was AE (10.7%). The median number of days on study drug was 29.0 for placebo subjects and 28.0 for RU-0211 48 mcg subjects. In the placebo group, 88.0% of subjects were on study drug for at least 3 weeks, and 83.1% were on study drug for at least 4 weeks; in the RU-0211 48 mcg group, 83.0% of subjects were on study drug for at least 3 weeks, and 71.5% were on study drug for at least 4 weeks.

The median average daily medication exposure for subjects in the < 48 mcg RU-0211 dose group was 24.00 mcg; for subjects in the < 48 mcg RU-0211 dose group, the median average daily exposure was 43.35 mcg, and for subjects in the > 48 mcg dose group, the median average daily exposure was 72.00 mcg. The mean percent compliance for the overall safety cohort subjects was 90.7 % and 87.3% of subjects were at least 70% compliant; the mean percent compliance for placebo subjects was 96.01%, and the value varied between 87.75% and 97.15% across the RU-0211 dose groups.

7.2.2 Demographics

The overall summary of demographics for the Well-Controlled Population is presented below in Table 55. As graphically depicted, the median subject age was 47 years (range: 20-81 years); 57.9% of subjects were < 50 years old, 31.4% of subjects were aged ≥ 50 and < 65 years, and 10.7% of subjects were ≥ 65 years old. Of the 606 subjects assessed overall, 541 (89.3%) were female and 496 (81.8%) were Caucasian. Of the 479 subjects assessed for IBS status, 91 subjects

(19.0%) reported that they had IBS, and 388 (81.0%) reported that they did not have IBS. Median age, age group distribution, gender distribution, race group distribution, and IBS status were similar between the placebo group and RU-0211 48 µg group, as well as across individual studies.

Table 55: Summary of Demographics for the Well-Controlled Population (SC0131, SC0232, and SC9921).

Variable	Statistic	Placebo	RU-0211 48 mcg	Total[2]
Age (years)	n (%)	273(100.0)	271 (100.0)	606 (100.0)
	Mean	47.2	47.4	47.4
	SD	13.08	12.20	12.64
	Median	48.0	46.0	47.0
	Range	21.0-81.0	20.0-80.0	20.0-81.0
Age Group n (%)	Subjects assessed	273 (100.0)	271 (100.0)	606 (100.0)
	<50[3]	1161 (59.0)	153 (56.5)	351 (57.0)
	≥50 and <65[3]	81 (29.7)	92 (33.9)	190 (31.4)
	≥65[3]	31 (11.4)	26 (9.6)	65 (10.7)
Gender n (%)	Subjects assessed	273 (100.0)	271 (100.0)	606 (100.0)
	Male[3]	27 (9.9)	32 (11.8)	65 (10.7)
	Female[3]	246 (90.1)	239(88.2)	541 (89.3)
Race n (%)	Subjects Assessed	273 (100.0)	271(100.0)	606 (100.0)
	Caucasian[3]	220 (80.6)	224(82.7)	496 (81.8)
	Black[3]	27 (9.9)	24 (8.9)	61 (10.1)
	Asian[3]	3 (1.1)	4 (1.5)	7 (1.2)
	Hispanic[3]	20 (7.3)	16 (5.9)	36 (5.9)
	Other[3]	3 (1.1)	3 (1.1)	6 (1.0)
IBS Status n (%)	Subjects assessed	240 (87.9)	239 (88.2)	479 (79.0)
	Yes[3]	46 (19.2)	45 (18.8)	91 (19.0)
	No[3]	194 (80.8)	194 (81.2)	388 (81.0)

Reviewer's table, modified from sponsor's Table 2.7.4.1-5, Integrated Summary of Safety, pages 23 of 131

1 This group is a subset of the General and Overall Safety Group.

2 This column includes RU-0211 < 48 µg subjects and RU-0211 > 48 µg subjects, in addition to placebo and RU-0211 48 µg subjects

3 Percentages are the total which fall into the particular category divided by the number of subjects assessed.

Table 56: Demographics for Subjects in the Long-Term Safety Group-ITT Population

Variable	Statistics/ Category	SC01S1 RU-0211 48 mcg	SC01S2 RU-0211 48 mcg	SC02S3 RU-0211 48 mcg	Pooled Group RU-0211 48 mcg
Subject #	N (%)	304 (100.0)	246 (100.0)	321 (100.0)	871 (100.0)
Age (years)	Mean	48.7	51.2	53.1	51.0
	SD	12.83	13.85	13.87	13.62
	Median	49.0	51.0	52.0	50.0
	Range	19 - 80	20 - 85	20 - 86	19 - 86
Height (cm)	Mean	165.7	167.0	165.6	166.0
	SD	8.26	8.78	8.41	8.48
	Median	165.1	165.1	165.1	165.1
	Range	132.1-193.0	134.1-195.6	138.4-193.0	132.1-195.6
Weight (kg)	Mean	71.3	75.0	73.0	73.0
	SD	14.27	15.12	16.74	15.50
	Median	68.9	72.6	68.4	70.3
	Range	42.2-124.7	45.4-134.7	43.5-165.5	42.2-165.5
Subjects assessed	< 50	161 (53.0)	113 (45.9)	141 (43.9)	415 (47.6)
	≥ 50 & < 65	102 (33.6)	84 (34.1)	110 (34.3)	296 (34.0)
	≥ 65	41 (13.5)	49 (19.9)	70 (21.8)	160 (18.4)
Gender	Male	32 (10.5)	40 (16.3)	49 (15.3)	121 (13.9)
	Female	272 (89.5)	206 (83.7)	272 (84.7)	750 (86.1)
Race	Caucasian	271 (89.1)	216 (87.8)	270 (84.1)	757 (86.9)
	Black	20 (6.6)	20 (8.1)	24 (7.5)	64 (7.3)
	Asian	2 (0.7)	2 (0.8)	2 (0.6)	6 (0.7)
	Hispanic	8 (2,6)	7 (2.8)	24 (7.5)	39 (4.5)
	Other	3 (1.0)	1 (0.4)	1 (0.3)	5 (0.6)
IBS Status	Yes	76 (25.0)	43 (17.5)	64 (19.9)	183 (21.0)
	No	228 (75.0)	203 (82.5)	357 (80.1)	688 (79.0)

Reviewer's table, modified from Table 2.7.3.3-3, pages 44 of 108, Summary of Clinical Efficacy

As noted above in Table 56, the overall mean age was 51.0 years of age, while in the individual studies, the mean age ranged from 48.7 years (SC01S1) to 53.1 years (SC02S3). Of the 871 subjects treated in the long-term safety group, 415 (47.6%) were < 50 years old, 296 (34.0%) were ≥ 50 and < 65 years old, and 160 (18.4%) were ≥ 65 years of age. The proportion of

subjects ≥ 65 years old was 13.5% in SC01S1, 19.9% in SC01S2 (SP2), and 21.8% in SC02S3. As observed in the well-controlled group subjects, the majority of long-term safety subjects were female (86.1%) and most were Caucasian (86.9%). Gender and race were generally similar across all three long-term studies. Of the 871 treated subjects, 183 (21.0%) reported having IBS, and 688 (79.9%) did not. Study SC01S1 subjects reported slightly more IBS (25.0%) than did the other two long-term safety studies; 17.5% and 19.9% for Studies SC01S2 and SC02S3 respectively. Other demographic statistics, such as the mean height and weight, were generally similar across the three long-term safety studies.

The overall summary of demographics for the overall safety (OS) population is presented below in Table 57. As graphically depicted, the median subject age was 47 years (range: 18-86 years); 57.0% of subjects were < 50 years old, 29.3% of subjects were aged ≥ 50 but < 65 years, and 13.7% of subjects were ≥ 65 years old. Of the 1688 subjects assessed overall, 1389 (82.3%) were female and 1444 (85.5%) were Caucasian. Of the 1364 subjects assessed for IBS status, 274 subjects (20.1%) reported that they had IBS, and 1090 (79.9%) reported that they did not have IBS.

Table 57: Summary of Demographics for the Overall Safety Cohort

Variable	Statistic	Placebo	RU-0211 <48 mcg	RU-0211 48 mcg	RU-0211 >48 mcg	All Active Doses	Total
Age (years)	n (%)	367 (100.0)	73 (100.0)	1113 (100.0)	135 (100.0)	1321 (100.0)	1688 (100.0)
	Mean	44.5	32.5	50.3	31.5	47.4	46.8
	SD	14.74	14.63	13.46	13.77	15.12	15.08
	Median	46.0	25.0	50.0	27.0	48.0	47.0
	Range	18.0-81.0	18.0-78.0	19.0-86.0	18.0-74.0	18.0-86.0	18.0-86.0
Height (cm)	n (%)	366 (99.7)	73.0 (100.0)	1111 (98.8)	135 (100.0)	1319 (99.6)	1685 (99.8)
	Mean	166.1	168.0	165.8	171.8	166.6	166.5
	SD	9.19	9.67	8.59	9.88	8.98	9.02
	Median	165.1	167.6	165.1	171.5	165.1	165.1
	Range	132.1-188.0	147.3-208.3	132.1-195.6	147.3-195.6	132.1-208.3	132.1-208.3
Weight (kg)	n (%)	367 (100.0)	73 (100.0)	1108 (99.6)	135 (100.0)	1316 (99.6)	1683 (99.7)
	Mean	71.7	71.3	72.7	73.7	72.7	72.5
	SD	14.29	10.54	15.50	15.31	15.24	15.04
	Median	69.4	70.8	69.9	72.1	70.3	70.0
	Range	44.9-129.3	49.0-95.3	41.5-165.5	44.0-138.6	41.5-165.5	41.5-165.5
Age Group n (%)	Subjects assessed	367 (100.0)	73 (100.0)	1113 (100.0)	135 (100.0)	1321 (100.0)	1688 (100.0)
	<50[1]	232 (63.2)	62 (84.9)	547 (49.1)	121 (89.6)	730 (55.3)	962 (57.0)
	≥50 and <65[1]	98 (26.7)	9 (12.3)	380 (34.1)	8 (5.9)	397 (30.1)	495 (29.3)
	≥65[1]	37 (10.1)	2 (2.7)	186 (16.7)	6 (4.4)	194 (14.7)	231 (13.7)
Gender n (%)	Subjects assessed	367 (100.0)	73 (100.0)	1113 (100.0)	135 (100.0)	1321 (100.0)	1688 (100.0)
	Male[1]	64 (17.4)	23 (31.5)	146 (13.1)	66 (48.9)	235 (17.8)	299 (17.7)
	Female[1]	303 (82.6)	50 (68.5)	967 (86.9)	69 (51.1)	1086 (82.2)	1389 (82.3)
Race n (%)	Subjects Assessed	367 (100.0)	73 (100.0)	1113 (100.0)	135 (100.0)	1321 (100.0)	1688 (100.0)
	Caucasian[1]	302 (82.3)	63 (86/3)	958 (86.1)	121 (89.6)	1142 (86.4)	1444 (85.5)
	Black[1]	34 (9.3)	5 (6.8)	85 (7.6)	9 (6.7)	99 (7.5)	133 (7.9)
	Asian[1]	3 (0.8)	3 (4.1)	11 (1.0	1 (0.7)	15 (1.1)	18 (1.1)
	Hispanic[1]	25 (6.8)	2 (2.7)	52 (4.7)	3 (2.2)	57 (4.3)	82 (4.9)
	Other[1]	3 (0.8)	0 (0.0)	7 (0.6)	1 (0.7)	8 (0.6)	11 (0.7)
IBS Status n (%)	Subjects assessed	283 (77.1)	0 (0.0)	1081 (97.1)	0 (0.0)	1081 (81.1)	1364 (80.8)
	Yes[1]	55 (19.4)	0 (0.0)	219 (20.3)	0 (0.0)	219 (20.3)	274 (20.1)
	No[1]	228 (80.6)	0 (0.0)	862 (79.7)	0 (0.0)	862 (79.7)	1090 (79.9)

Reviewer's table, modified from sponsor's Table 2.1.3.5, Integrated Summary of Safety, pages 206 and 207 of 2971
1 Percentages are the total which fall into the particular category divided by the number of subjects assessed.

Medical Officer Comments:
Comparisons of demographic characteristics across the different dose groups are difficult to make in the overall safety population as it contains subjects from the Healthy Normal cohort, which enrolled different types of patients than did the Phase II and Phase III studies. The demographics; however, between the well-controlled group and the overall safety population are very similar. In both safety cohorts, females were the majority; 89.3% and 82.3%, the predominant race was Caucasian; 81.8% and 85.5%, and IBS status was positive in 19% and 20.1% of subjects in the well-controlled population and the overall safety populations, respectively. Median subject age was also similar among the well-controlled and the overall safety populations with 57.9% and 57.0% of patients < 50 years of age, 31.4% and 29.3% of patients' ≥ 50, and 10.7% and 13.7% of patients >65 years of age, respectively.

7.2.3 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There were no secondary clinical data sources used to evaluate safety for the New Drug Application.

7.2.4 Post-marketing Experience

This is the initial marketing application for RU-0211 in the United States or any country therefore post-marketing experience is not applicable.

7.2.5 Literature

The sponsor provided 30 pieces of literature as references to support this New Drug Application. Of the 30 listed references, twelve were cited from peer-reviewed journals dating from 1966 to 2004. Two of the references were ICH guidances, nine were actual sponsor trials, three were meeting minutes between the Agency and the sponsor, and the rest discussed various topics including prostaglandins, irritable bowel syndrome, and chronic constipation. Several of the cited references were merely abstracts and did not include the full text article. The sponsor's literature review was not ideal in that it contained many older references (some almost 40 years old) on prostaglandins and did not contain any literature describing the potential of prostaglandins to be used off-label or their side-effects as a class. The medical reviewer performed an additional literature search utilizing the Agency's databases and on-line resources to support this New Drug Application review.

7.2.6 Adequacy of Overall Clinical Experience

According to the ICH Guidance (E1) on extent and duration of exposure needed to assess clinical exposure for a drug, this New Drug Application had an adequate number of subjects exposed to RU-0211 (lubiprostone).

To characterize a pattern of adverse drug events over time, the ICH Guidance (E1) also recommends that the select number of patients should be treated for 6 months at the dosage levels intended for clinical use. This New Drug Application for RU-0211 (lubiprostone) had an adequate exposure duration ranging from 4 to 48 weeks.

The Well-controlled safety cohort trials were adequately and appropriately designed in that they were randomized, double-blinded, placebo-controlled, parallel-grouped, and multi-centered.

There are several limitations in this New Drug Application. It is the medical officer's opinion that RU-0211's safety in pregnant women or women who could become pregnant has not been fully explored and adequately defined. Additionally, the medical officer doesn't feel these limitations hinder the approvability of the NDA rather subject the application to further post-marketing commitments. The patient database is not reflective of the truly intended market population of RU-0211 as it has a limited number of geriatric patients studied.

7.2.7 Adequacy of Special Animal and/or In Vitro Testing

The Agency's Pharmacology Division concluded that there were adequate preclinical animal studies performed to examine the safety of RU-0211. The only inadequacy noted in the preclinical studies was the underestimated dose chosen for the rhesus monkey abortifacient potential study (Study SPI/SR05-001).

7.2.8 Adequacy of Routine Clinical Testing

It is the reviewer's opinion that the routine clinical testing of subjects in this New Drug Application was adequate. The sponsor performed adequate monitoring of safety parameters including laboratory values, vital signs, physical assessments, and electrocardiograms. The safety parameters were performed with appropriate frequency and scrutiny.

7.2.9 Adequacy of Metabolic, Clearance, and Interaction Workup

From the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics, the sponsor adequately characterized the general elimination pathways of lubiprostone, however; they did not adequately characterize the unique metabolic enzymes responsible for the drugs elimination.

The sponsor also adequately illustrated the potential for drug-drug interactions with RU-0211 (lubiprostone) in so far as its role as a cytochrome P450 enzyme inducer/inhibitor. The sponsor, however; did not adequately evaluate RU-0211 (lubiprostone) within drug-drug interaction studies as the potential substrate.

A thorough summary of the pharmacodynamics and pharmacokinetics of RU-0211 (lubiprostone) can be found within the Agency's Clinical Pharmacology and Biopharmaceutics Review.

7.2.10 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

It is the reviewer's opinion that the adequacy of the risk/benefit profile of RU-0211 (lubiprostone) has been adequately studied save the following outstanding issues discussed within this review: Preclinical and clinical reproductive toxicology, RU-0211 use in subjects with renal impairment, and RU-0211 use in subjects with hepatic impairment. Although not completely optimal, the submitted data were adequate for this reviewer to perform a safety review and make recommendations.

7.2.11 Assessment of Quality and Completeness of Data

The overall safety and efficacy data supplied within this New Drug Application was thorough and well organized. The sponsor provided an adequate database within this NDA from which to review the proposed indication. There were, however; some important data, as mentioned above, that was not adequately explored.

7.2.12 Additional Submissions, Including Safety Update

Prior to this New Drug Application, Investigation New Drug Application # 59,623 was one such IND that directly supported this NDA as it included an indication for the treatment of chronic idiopathic constipation.

The sponsor submitted a 4-month safety update report on 27 July 2005 in which, per the sponsor, no new safety information was found that would reasonably affect the draft labeling.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

It is this reviewer's opinion that the adequacy of dose finding in this New Drug Application was appropriate. The sponsor's non-clinical studies revealed that a 0.6 mcg/kg dose of RU-0211 increased intestinal fluid secretion by, on average, 50% in dosed animals. The first Phase I study SC99101 evaluated placebo and single RU-0211 doses ranging from 6 mcg to 96 mcg. An overall clinical assessment of the frequency, characteristics, and symptoms associated with the dose levels evaluated in this study indicated that 96 mcg was the maximum tolerated single dose of RU-0211. The second Phase I study, SC99102, sought to determine the maximum tolerated dose of RU-0211 when administered t.i.d. Based upon the results of study SC99101, the doses chosen for this study were 72 mcg (24 mcg t.i.d.), 90 mcg (30 mcg t.i.d.), and 108 mcg (36 mcg t.i.d.). The results of this study revealed that there is a saturation of the pharmacodynamics of RU-0211 at the 24 mcg t.i.d. dose level. The final Phase IIb dose finding study SC9921

evaluated dose levels of 24 mcg/day, 48 mcg/day (24 mcg b.i.d.), and 72 mcg/day (24 mcg t.i.d.) over a 3-week treatment period. The results of this study showed that all 3 doses of RU-0211 were more effective than placebo in relieving constipation, however; the RU-0211 24 mcg group did not yield as many statistically significant results as the higher dose groups. In general, the likelihood for experiencing most AEs in this study did not appear to increase with increasing RU-0211 dose. The AE for which the frequency increased most dramatically with RU-0211 dose was nausea (0% of placebo patients, 17.2% of RU-0211 24 mcg patients, 43.8% of RU-0211 48 mcg patients, and 36.4% of RU-0211 72 mcg patients). As indicated, there were nearly twice the events of nausea in the 48 mcg dose group than in the 24 mcg dose group. Of the total 127 adverse events, only two events of nausea were considered severe; one subject in the 48 mcg dose group and one subject in the 72 mcg dose group.

Given the aforementioned data, the sponsor chose the 48 mcg/day dose because it was the minimum effective dose with the most desirable safety profile that produced a statistically significant effect in the primary efficacy analysis and most secondary efficacy analyses. An argument can be made that the sponsor should have chosen the 24 mcg/day dose, as it had less AEs of nausea and yet was still more efficacious than placebo. This reviewer believes that the appropriate dose was selected for this New Drug Application from this dose finding study because the number of severe AEs was similar in both treatment arms and because the 48 mcg group (24 mcg b.i.d.) can ultimately be individually tapered to avoid such assumed pharmacodynamic effects as nausea.

RU-0211 (lubiprostone) has not been adequately tested in subjects with renal nor hepatic impairment; therefore recommendations on dose modifications in such special populations cannot be made.

The effects of food were evaluated in a single clinical trial. In this trial, volunteers were administered a 72 µg dose of ^{3}H-RU-0211, either after an overnight fast or 30 minutes after ingesting a standard meal. Blood samples were collected before dosing and through 120 hours after dosing, and 24-hour urine and fecal collections were obtained before and through 5 days after dosing. Dosing under fed conditions resulted in a decrease in the maximum concentration (C_{max}) for both plasma and whole blood samples. Despite the reductions in C_{max}, dosing with or without food did not appear to have an effect on total radioactivity absorption, based on similar mean values for AUC_{0-t} and AUC_{∞}. Under both fasted and fed conditions, there appeared to be little or no uptake of radioactivity by red blood cells. Overall, other than a reduced C_{max} and an associated increase in the time to C_{max} (T_{max}), the effects of food intake on dosing with RU-0211 appeared to be minimal.

8.2 Drug-Drug Interactions

RU-0211 was evaluated for its potential to inhibit 8 specific isoforms of cytochrome P450 in pooled human liver microsomes. The concentration of RU-0211 necessary for 50% inhibition of each isoform (IC_{50}) was measured using a substrate appropriate for each isoform. The isoforms tested (with substrates shown parenthetically) were CYP1A2 (phenacetin), CYP2A6 (coumarin), CYP2B6 (bupropion), CYP2C9 (tolbutamide), CYP2C19 [(*S*)-mephenytoin], CYP2D6 (dextromethorphan), CYP2E1 (chlorzoxazone), and CYP3A4 (midazolam and testosterone).

Incubation of RU-0211 in suspensions of human hepatic microsomes resulted in no significant concentration-dependent inhibition of any of the isoforms tested.

A second drug-drug interaction study was conducted was conducted to assess the potential of RU-0211 to induce cytochrome P450 isoforms CYP1A2 (marker substrate = phenacetin; metabolite = acetaminophen), CYP2B6 (bupropion; hydroxybupropion), CYP2C9 (tolbutamide; hydroxytolbutamide), and CYP3A4 (testosterone; 6β-hydroxytestosterone) in primary cultures of human hepatocytes. The results of the study showed that RU-0211 did not cause any significant (greater than 40%, or at least 0.4-fold) increases in CYP activity and/or immunoreactive protein at the concentrations evaluated.

A third study was undertaken to determine if any of the cytochrome P450 isoforms most commonly associated with drug metabolism are involved in the biotransformation of RU-0211 to 15-hydroxy-RU-0211. The isoforms (inhibitors) tested were CYP1A2 (furafylline), CYP2A6 (pilocarpine), CYP2B6 (thio-TEPA), CYP2C8 (quercetin), CYP2C9 (sulfaphenazole), CYP2C19 [(*S*)-mephenytoin], CYP2D6 (quinidine), CYP2E1 (4-methylpyrazole), CYP3A4 (ketoconazole), and CYP4A11 (lauric acid and 17-octadecynoic acid [ODYA]). Results from the human liver microsomes incubations showed no significant inhibition of 15-hydroxy-RU-0211 formation by any CYP-specific inhibitor, with the possible exception of lauric acid. Biotransformation to 15-hydroxy-RU-0211 was found to take place in human microsomes independent of P450 isozymes.

The three RU-0211 interaction studies with cytochrome P450 isoforms demonstrated that RU-0211 is not expected to interfere with the metabolism of concomitant drugs. Conversely, the metabolism of RU-0211 should not be influenced by the presence of concomitant drugs, and the biotransformation of RU-0211 to its primary metabolite (15-hydroxy-RU-0211) is independent of cytochrome P450 enzymes.

Medical Officer's Comments

It is the medical officer's opinion, based on the aforementioned studies and conclusions; no drug-drug restrictions or concomitant medication usage limitations should be expected or required for constipated subjects taking RU-0211 in the general population.

8.3 Special Populations

- Safety and effectiveness of RU-0211 (lubiprostone) in pediatric patients has not been established. The sponsor requested, and was granted a deferral of pediatric studies in this New Drug Application.
- The clinical studies for RU-0211 (lubiprostone) included a somewhat limited proportion of subjects aged 65 and older (9.7% - Well-controlled study cohort; 18.4% - Long-term safety cohort). The results for the primary efficacy endpoint between RU-0211 and placebo in this age cohort were not statistically significant. Despite the lack of statistical significance, the actual observed values of effectiveness provide evidence that RU-0211 48 mcg achieved clinical meaningfulness and performed equally well in the 65 and older subgroup. The results of the primary endpoint were clinically meaningful as they showed an increase of 4 SBM/week by week 1 and similarly by week 4. The sponsor's responder analysis (responder defined as a subject with ≥ 4 SBM per week) also showed that the

mean SBM frequency rates were higher for weeks 1 – 4 in subjects older than 65 taking RU-0211 48 mcg than those age matched subjects taking placebo. The sponsor's all-weeks change-from-baseline responder analysis also indicated that subjects ≥ 65 years of age had an increase in SBM by week 4 of 56.5% - RU-0211 vs. 34.5% - placebo.

- RU-0211 has not yet been adequately studied in subjects who have **renal impairment.**
- RU-0211 has not yet been adequately studied in subjects who have **hepatic impairment.**
- There have been no adequate and well-controlled studies of RU-0211 (lubiprostone) in pregnant women.
- The excretion of RU-0211 or its metabolites in the milk of **nursing mothers** has not yet been evaluated.

8.4 Pediatrics

The safety and effectiveness of RU-0211 (lubiprostone) in pediatric patients has not been established. The sponsor requested, and was granted a deferral of pediatric studies in this New Drug Application.

8.5 Advisory Committee Meeting

There was no Advisory Committee Meeting required for this New Drug Application.

8.6 Literature Review

The sponsor provided 30 pieces of literature as references to support this New Drug Application. Of the 30 listed references, twelve were cited from peer-reviewed journals dating from 1966 to 2004. Two of the references were ICH guidances, nine were actual sponsor trials, three were meeting minutes between the Agency and the sponsor, and the rest discussed various topics including prostaglandins, irritable bowel syndrome, and chronic constipation. Several of the cited references were merely abstracts and did not include the full text article. The sponsor's literature review was not ideal in that it contained many older references (some almost 40 years old) on prostaglandins and did not contain any literature describing the potential of prostaglandins to be used off-label or their side-effects as a class. The medical reviewer performed an additional literature search utilizing the Agency's databases and on-line resources to support this New Drug Application review.

8.7 Post-marketing Risk Management Plan

The sponsor has not submitted a Post-marketing risk management plan for this New Drug Application.

Medical Officer's Comments
After a thorough safety review and analysis, the medical officer does not believe a post-marketing risk management plan is needed for RU-01211 (lubiprostone).

8.8 Other Relevant Materials

The proposed tradename — of RU-0211 (lubiprostone) underwent review by the Office of Drug Safety; Division of Medication Errors and Technical Support. The Division of Medication Errors and Technical Support did not recommend the use of the proprietary tradename — Sucampo Pharmaceuticals, Inc., proposed two additional tradenames for lubiprostone which include AMITIZA and — . They are currently being reviewed by the Office of Drug Safety; Division of Medication Errors and Technical Support for use as potential proprietary tradenames.

9 OVERALL ASSESSMENT

9.1 Conclusions

The clinical program with RU-0211 (lubiprostone) 48 mcg (24 mcg b.i.d.), consisting of two adequate and well-controlled Phase III efficacy studies and three phase III, long-term safety and efficacy studies, demonstrates that administration of RU-0211 24 mcg b.i.d. — chronic idiopathic constipation — in the adult population. Statistical significance was attained in both pivotal studies up to 4 weeks for the primary efficacy endpoint: the frequency of spontaneous bowel movements (SBMs) at Week 1. The baseline spontaneous bowel movement frequency rate was 1.50 for both placebo subjects and RU-0211 subjects in studies SC0131 and SC0232. In both individual studies (SC0131 and SC0232), the median SBM frequency rates in the RU-0211 group for Weeks 1, 2, 3, and 4 were higher (range: 4.00-5.00) than that in the placebo group (range: 2.00-3.50). This difference was statistically significant at Weeks 1 – 4 in SC0131 and SC0232. In the pooled group overall for Weeks 1 through 4, the difference in SBM frequency between the two groups was statistically significant ($p<0.0001$ at each time point). Statistical significance for RU-0211 24 mcg b.i.d. over placebo for the treatment of chronic idiopathic constipation was also observed in the following secondary efficacy variables: frequency of SBMs at Weeks 2, 3, and 4; weekly responder rates (at each week and all weeks); percentage of subjects with an SBM within 24 hours after first dose of study drug; time to first SBM; average stool consistency; average degree of straining; constipation severity; and treatment effectiveness.

Study SC0131 enrolled 242 subjects (120 – RU-0211, 122 – placebo) throughout 20 centers in the United States and randomly allocated them to either RU-0211 24 mcg b.i.d. or placebo. In Study SC0131's efficacy analysis, the median SBM frequency rate during Week 1 was significantly higher ($p = 0.0001$) in the 48 mcg RU-0211 group (5 SBM/week) than in the placebo group (3 SBM/week). Statistical significance in Study SC0131 was also seen for the SBM frequency rate during Weeks 2, 3, and 4 (median 4-5 SBM/week versus 2-3 SBM/week for RU-0211 and placebo groups, respectively). This statistically significant increase in SBM frequency rate translates into a clinically meaningful increase in spontaneous bowel movements from one SBM every 4-5 days to one SBM every 1-2 days. Study SC0131 also demonstrated the statistical significance of RU-0211 over placebo in most of the secondary endpoints including; the percentage of SBM within 24 hours of first study drug administration (56.7% RU-0211 vs.

36.9% placebo), time to first SBM (p=0.006), average stool consistency (median 1.78-2.00 RU-0211 vs. 2.50-2.67 placebo), average degree of straining (median 1.42-1.67 RU-0211 vs. 2.00 placebo), weekly severity of constipation (2.00 RU-0211 vs. 2.00-3.00 placebo), and weekly treatment effectiveness (median 2.00 RU-0211 vs. 0.00 placebo). Although Study SC0131 did not show consistent statistical significance for the weekly abdominal bloating and discomfort secondary endpoints, the results for these secondary efficacy variables were clinically meaningful and trended in favor of the efficacy of RU-0211 48 mcg/day.

Study SC0232 enrolled 237 subjects (119 – RU-0211, 118 – placebo) throughout 20 centers in the United States and randomly allocated them to either RU-0211 mcg b.i.d. or placebo. In the primary efficacy analysis, the median SBM frequency rate during Week 1 was significantly higher ($p < 0.0001$) in the 48 mcg RU-0211 group (5 SBM/week) than in the placebo group (3.5 SBM/week). Statistical significance in Study SC0232 was also seen for the SBM frequency rate during Weeks 2, 3, and 4 (median 4-5 SBM/week versus 3 SBM/week for RU-0211 and placebo groups, respectively). Similar to pivotal study SC0131, this statistically significant increase in SBM frequency rate translates into a clinically meaningful increase in SBM from 1 SBM every 4 to 5 days to 1 SBM every 1 to 2 days. Similar to Study SC0131, Study SC0232 also demonstrated the statistical significance of RU-0211 over placebo in most of the secondary endpoints including; the percentage of SBM within 24 hours of first study drug administration (62.9% RU-0211 vs. 31.9% placebo), time to first SBM ($p<0.001$), average stool consistency (median 1.78 – 2.00 RU-0211 vs. 2.33 – 2.50 placebo), average degree of straining (median 1.40-1.56 RU-0211 vs. 1.82-2.00 placebo), weekly severity of constipation (median 2.00 RU-0211 vs. 2.00 placebo), and weekly treatment effectiveness (median 2.00 RU-0211 vs. 1.00 placebo). Although Study SC0232 did not show statistical significance for the weekly abdominal bloating and discomfort secondary endpoints, the results for these secondary efficacy variables were clinically meaningful and trended in favor of the efficacy of RU-0211 48 mcg/day.

The long-term efficacy of RU-0211 48 mcg was evaluated during the conduct of the following studies: SC01S1 (24-week open-label period), SC01S2 (SP2 only; 48-week open-label period), and 48-week open-label period). Due to the open-label design of these studies, the efficacy evaluations did not provide for direct comparison with placebo; rather they provided only comparative results with the same assessments performed in the double-blind, randomized studies.

Study SC01S1 was an open-label, long-term safety and efficacy study which enrolled 306 subjects with constipation who were treated with 48 mcg/day (24 mcg/day b.i.d.) of RU-0211, administered as needed, over a 24-week period. Overall, the improvements from baseline to each visit up to Week 24 and at the end of study assessment were statistically significant with respect to constipation severity ($p<0.0001$), abdominal bloating ($p<0.0001$), and abdominal discomfort ($p<0.0001$). There were also noticeable improvements in the mean treatment effectiveness scores (Week 1 – 1.86; Week 24 – 2.35; moderately effective), however; no inferential statistics were performed on these results because treatment effectiveness was not evaluated (and not applicable) at baseline. The results of Study SC01S1 support the results of the pivotal efficacy studies.

Study SC01S2-SP2 was an open-label, long-term safety and efficacy study which enrolled 298 subjects over a 48-week period. Subjects were administered 24 mcg of RU-0211 b.i.d. as needed, based on the subject's perceived severity of constipation and need for relief. Overall, the improvements from baseline to each week assessed up to Week 48 and at the end of study assessment were statistically significant with respect to constipation severity ($p<0.0001$), abdominal bloating ($p<0.0001$), and abdominal discomfort ($p<0.0001$). Similar to Study SC01S1, there were overall improvements in mean treatment effectiveness during the treatment period (Week 6 – 2.13; Week 48 -2.48), however; no inferential statistics were performed on these results because treatment effectiveness was not evaluated at baseline. The results of Study SC01S2-SP2 support the findings of the pivotal efficacy studies.

Study SC02S3 was an open-label, long term safety and efficacy study which enrolled 324 subjects with constipation who were treated with 24 mcg of RU-0211 b.i.d., administered as needed, over a 48-week treatment period. Overall, the improvements from baseline to each week assessed up to Week 48 and at the end of study assessment were statistically significant with respect to constipation severity ($p<0.001$), abdominal bloating ($p<0.001$), and abdominal discomfort ($p<0.001$). Analogous to studies SC01S1 and SC01S2-SP2, there were overall improvements in mean treatment effectiveness during the treatment period (Week 1 – 1.92; Week 48 – 2.64). Based upon the results of the subject-completed SF36 questionnaire, subject quality of life also showed sustained improvement (Physical function, and bodily pain and vitality) in this long-term study. The SF36 questionnaire indicated larger improvements at later time points (Weeks 24 and 48) than at earlier time points. The results of Study SC02S3 support the efficacy findings of the pre-specified pivotal studies.

The overall efficacy of RU-0211 (lubiprostone) 24 mcg b.i.d. revealed not only improvements in subject regularity with respect to spontaneous bowel movement frequency, but also contributed to several improvements in subjective quality of life assessments. These improvements were true in short-term studies (up to 4 weeks) and long-term studies (up to 48 weeks).

There were a total of 1688 subjects treated in the overall safety population of which 1321 received active drug and 367 received placebo. Of the 1321 subjects who received active drug, 1119 received RU-0211 48 mcg daily. Six hundred twenty two subjects allocated to RU-0211 48 mcg received the drug for 48 weeks (12 months) duration and three hundred and six subjects received the drug for 24 weeks (6 months) duration.

No subjects died during the treatment period or follow-up period for any of the studies included in this New Drug Application.

The occurrence of serious adverse events in the studied population was relatively low. Four placebo subjects (1.3%) reported 6 serious adverse events (SAEs), with no SAE preferred term being reported by more than one subject. Thirty-two subjects taking RU-0211 48 mcg (2.9%) reported treatment-emergent SAEs. The reported SAE preferred terms were generally rare, with most being reported by only a single subject. Appendicitis, diverticulitis, syncope, chest pain, and dehydration, all of which were considered unrelated to the study drug, were the only SAE preferred terms reported by more than 1 subject. Two SAEs were considered possibly treatment-

related: 1 SAE of diarrhea and 1 SAE subject who became pregnant while taking RU-0211 and gave birth to a child with talipes.

Across all active doses of lubiprostone (N=1175) in the well-controlled group and the long-term safety group studies, the most commonly reported adverse event preferred terms were nausea (30.9%), diarrhea (13.2%), headache (13.0%), abdominal distension (6.8%), abdominal pain (6.8%), and flatulence (5.9%). Comparatively for placebo (N=316), the corresponding reports of adverse events in the above preferred terms were; nausea (5.1%), diarrhea (0.9%), abdominal distension (2.8%), abdominal pain (2.2%), flatulence (1.9%), and headache (6.6%). Besides headache, the most commonly reported adverse events in the active drug group were gastrointestinal in nature, which appear to be representative of the pharmacodynamic effects of lubiprostone.

An analysis of cumulative adverse event incidence rates, time to first adverse events, and a Cox proportional hazard analysis for the occurrence of any adverse event (nausea, diarrhea, abdominal pain, vomiting, headache, dizziness, peripheral edema, fatigue, and dyspnea) indicated that, although subjects taking RU-0211 are more likely than placebo subjects to experience most adverse events, the risk for experiencing any of them is greatest within the first few days of treatment and does not increase over time to any appreciable degree. One exception to the above adverse event incidence rate hazard risk is that of peripheral edema. There was an increase of approximately 10% in the hazard rate for peripheral edema from days 22-28 until days 270-365, however; the clinical importance of this increase in relation to RU-0211 treatment seems to be minimal.

Somewhat expectantly for a drug targeting the gastrointestinal tract, 29.0% of the 30.9% subjects in the overall safety cohort who reported the adverse event nausea were deemed treatment-related. Among the 30.9% of subjects who reported nausea as and adverse event, only 3.0% reported their nausea as severe and no more than 7.5% of subjects withdrew from the study secondary to nausea.

The frequency of withdrawal for RU-0211 48 mcg (24 mcg b.i.d.) subjects in the well-controlled group was significantly higher than for placebo subjects. Overall, 1.1% of placebo subjects and 7.7% of RU-0211 48 mcg subjects withdrew because of Gastrointestinal adverse events. The breakdown of Gastrointestinal adverse events in the pooled population that led to withdrawal for at least 1% of subjects was nausea (5.2%), diarrhea (1.5%), abdominal pain (1.5%), and flatulence (1.5%). The types and frequencies of the individual AEs that led to withdrawal were generally similar across the long-term studies, and these results were similar to those observed in the well-controlled group. Gastrointestinal disorders were once again the most common System-Order-Class for AEs leading to withdrawal. Adverse events in the pooled group that led to withdrawal for at least 1% of subjects were nausea (7.9%), diarrhea (1.9%), abdominal pain (1.4%), abdominal distension (1.4%), vomiting (1.4%), headache (3.4%), and dyspnea (1.0%).

In spite of the fact that several adverse event preferred terms are elevated compared with placebo, the overall impact on subject quality of life from adverse events during treatment with RU-0211 can be viewed as minimal given the rate of withdrawal and degree of severity for such events.

The clinical and laboratory data presented in this application including biochemistry, hematology, urinalysis, vital signs and physical examination data appeared clinically acceptable for a population of subjects with chronic idiopathic constipation who are otherwise considered generally healthy.

The effects of lubiprostone (RU-0211) on ECG parameters were evaluated in two studies (Phase I and Phase IIb). RU-0211 at doses of 24, 48, and 72 mcg per day, for 3 weeks, showed no evidence of effect on heart rate, cardiac conduction, cardiac repolarization, or morphological changes.

RU-0211 (lubiprostone) was evaluated in special safety study (bilateral hand X-rays at baseline and at final assessment) to determine whether it had a deleterious effect on bone density following long-term exposure. Although formal lumbar and hip bone densitometry analysis would have provided a more accurate reflection of lubiprostone's effect on bone metabolism, lubiprostone did not appear to cause a negative impact on bone density.

The pharmacological profile of RU-0211 is not consistent with a drug that would have the potential for abuse of drug dependence. The overall safety profile in the sponsor's randomized-withdrawal study indicated that there appears to be no obvious safety risks following immediate cessation or withdrawal from RU-0211.

To date, no adequate and well-controlled studies of RU-0211 in pregnant or lactating women have been conducted. Despite the fact that pregnant women were excluded from all clinical trials of RU-0211, and any woman who became pregnant during a study was immediately discontinued from study participation, four pregnancies were reported during the development of RU-0211. Of the four pregnancies, two women had healthy babies, one was lost to follow-up, and one had a baby with bilateral club feet. There was also one ectopic pregnancy reported under IND — hat was noted to have "resolved" during short term follow-up. One limitation of this New Drug Application is the sponsor's non-clinical reproductive and developmental toxicity studies in guinea pigs and rhesus monkeys to determine the abortifacient potential of RU-0211. A detailed explanation of these studies will be provided in the Agency's formal pharmacology reviews. Briefly, both maternal death and fetal loss were seen in the sponsor's guinea pig study. The rhesus monkey study revealed one abortion, however; this study was deemed inadequate by the Agency's pharmacologists as the dose range chosen was based on rats and was underestimated. Given the lack of controlled human pregnancy data from the clinical trials and the non-clinical animal data, the labeling of RU-0211 should contain a contraindication for pregnant women or women who could become pregnant.

The addition of RU-0211 (lubiprostone) 24 mcg b.i.d. to the current armamentarium of treatments for constipation would provide treating physicians a viable alternative to the products currently on the market. The results of the clinical studies of RU-0211 24 mcg b.i.d. provide considerable efficacy along with safety and tolerability data up to 48 weeks duration in a population of patients with chronic idiopathic constipation when compared to no treatment at all. RU-0211 (lubiprostone), like most prescription medications, is accompanied by some mild and

often short-lived side effects, however; these effects are balanced by the rapid and sustained relief of chronic idiopathic constipation and the associated symptoms therein.

9.2 Recommendation on Regulatory Action

The medical officer recommends an approval action be taken for oral RU-0211 48 mcg/day (24 mcg capsules b.i.d.) for the treatment of chronic idiopathic constipation in the adult population. Approval of RU-0211 48 mcg/day (24 mcg capsules b.i.d.) for the treatment of chronic idiopathic constipation is contingent upon the sponsor incorporating the Food and Drug Administration's recommended changes to the RU-0211 drug label and adhering to the required Phase IV commitment studies.

9.3 Recommendation on Post-marketing Actions

The medical officer recommends that the sponsor perform a Phase IV commitment study to determine the safety and efficacy of lubiprostone in the pediatric population. This study should be in accordance with the Pediatric Research Equity Act of 2003.

As RU-0211 (lubiprostone) has not been adequately studied in subjects with renal impairment, the medical officer recommends that the sponsor perform a Phase IV study to assess the need for potential dose adjustment in such subjects.

9.4 Risk Management Activity

Based upon the pharmacology/toxicology data established in guinea pigs and rhesus monkeys concerning lubiprostone's potential to cause fetal loss in animals, labeling noting the drug's potential adverse effect in pregnant women or women who could become pregnant should be appropriated.

9.5 Other Phase 4 Requests

There are no other Phase IV requests in this New Drug Application.

9.6 Comments to Applicant

The medical officer has no additional comments for the applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

STUDY RTU/0211SC0131

Title: Multi-Center, Double-Blind, Randomized, Placebo-Controlled Phase III Study of the Efficacy and Safety of Oral RU-0211 for the Treatment of Occasional Constipation.

10.1.1 Objectives

The objectives of this study were to assess the efficacy and safety of oral 48 mcg RU-0211 compared to placebo for the treatment of constipation. Constipation was defined in this study as, on average, less than 3 spontaneous bowel movements (SBMs) per week. An SBM was defined as any bowel movement (BM) that did not occur within 24 hours after rescue medication use.

Study Design

This was a multi-center, parallel-group, double-blind, placebo-controlled study of approximately 57 days duration including follow-up. Two-hundred-forty-two subjects (120 subjects in the RU-0211 treatment arm and 122 in the placebo group) were enrolled at up to 20 centers in the United States. Following initial assessments, including a 15-day washout period, subjects received 4 weeks of double-blind medication. The study consisted of the Baseline/Washout Visit (Visit 1), a randomization visit (Visit 2), 2 interim visits (Visit 3, after 1 week of double-blind treatment and Visit 4, a telephone interview conducted after 2 weeks of double-blind treatment), and an end of treatment visit (Visit 5). A final telephone interview (Visit 6) was conducted approximately 14 days after Visit 5. Subjects completed abdominal assessments at Visits 1 through 6 and global assessments at Visits 2 through 6.

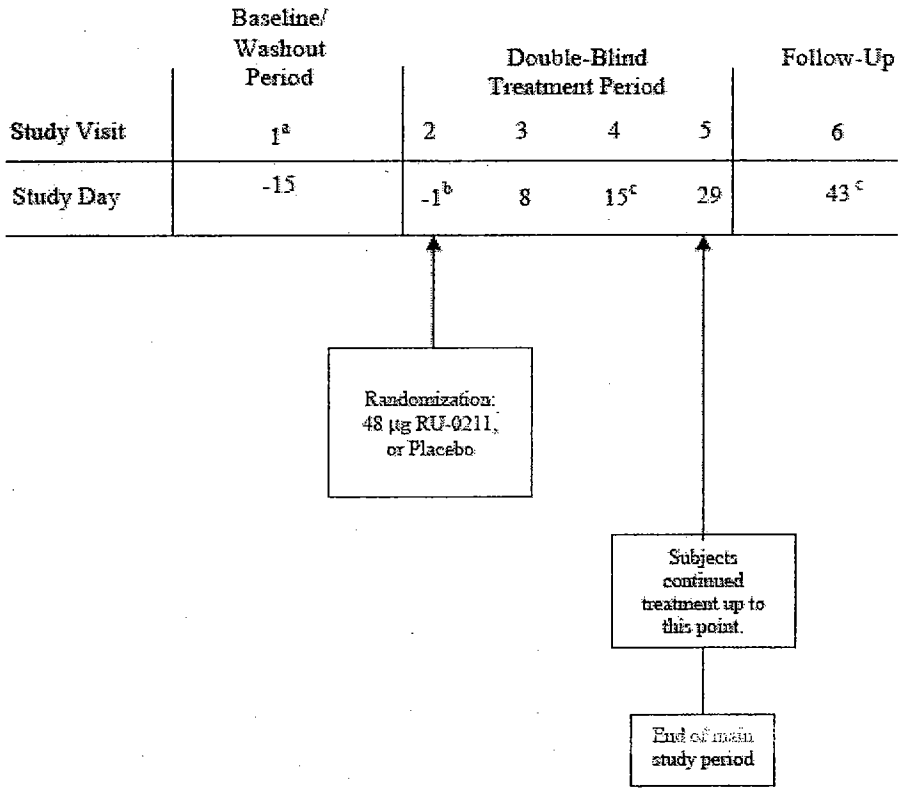
In order to qualify for randomization into the double-blind treatment phase, evidence of constipation (defined as less than 3 SBMs per week, on average) must have been demonstrated and recorded in the daily diary during the washout period. Study drug was self-administered orally for a total treatment period of 4 weeks; it was taken at breakfast and dinner with food and at least 8 ounces of water. Subjects documented bowel activity and symptoms in a daily diary. The frequency of SBMs during Week 1, Week 2, Week 3, and Week 4, responder rates at each week, the percentage of subjects with an SBM during the 24 hours since the first intake of study drug, the time to the first SBM, average degree of straining, average stool consistency, assessments of abdominal symptoms (bloating and discomfort upon waking in the morning), global assessments (treatment effectiveness and severity of constipation) and the safety and tolerability of administered doses relative to placebo were evaluated to determine the efficacy and safety of RU-0211. The study ran between September 2001 and August 2002. Treatment medication was given in one of the following combinations:

1. Two placebo capsules (one 0 mcg capsule taken b.i.d.) with food (breakfast and

dinner) and with at least 8 ounces of water

2. Two RU-0211 capsules (one 24 mcg capsule taken b.i.d.) with food (breakfast and dinner) and with at least 8 ounces of water

Figure 7: A graphic depiction of Study SC0131



[a] If a flexible sigmoidoscopy, with or without barium enema, or colonoscopy was performed at Visit 1, subjects waited 1 week before starting to fill out the daily diary. There were 3 weeks between Visits 1 and 2 for those subjects.
[b] The subject began treatment on the day following Visit 2 (Day –1), which for purposes of this study was considered Day 1.
[c] Telephone interview

Sponsor's figure, Clinical Study Report-SC0131ver4.1, page 15

Statistical Methods of Analysis:

The **primary efficacy variable** was the **frequency rate of SBMs during Week 1**. A spontaneous bowel movement was defined as any bowel movement that does not occur within 24 hours after rescue medication use. Since rescue medication use was disallowed during Week 1, the SBM rate should equal the BM rate. In the case of protocol violators, the analysis was based on SBMs. In order to adjust for early withdrawals, weekly SBM frequency rates were calculated as follows:

$$7 \times \text{Number of SBMs} / \text{Number of days}$$

where the number of days in the denominator was the number of days during the week that the subject was in the study. Weeks were calculated as 168-hour intervals starting with the exact time of the first intake of study drug. The number of days in the week was generally 7 unless a subject dropped out during a treatment week. If the number of days was less than 4, then the data was considered insufficient and the rate was missing. Results were analyzed by a van Elteren test stratified by center. Small centers (i.e., those that enrolled ≤ 8 subjects) were pooled.

Frequency rate of SBMs at Weeks 2, 3, and 4 were analyzed as discussed above for Week 1. If the number of days in the week was less than 4, then the most recent data from days during the previous week were combined with data from the current week in order to bring the number of days up to 4. If the number of days for a given week was 0, then the LOCF method was used to impute the frequency rate from the rate for the most recent week.

A longitudinal analysis of the frequency rates of SBMs and of all BMs was performed in order to assess the treatment effect over time. Missing values were not imputed for this analysis. The model included terms for treatment, time, center, and baseline. The time variable was defined by treatment Weeks 1, 2, 3, and 4. Treatment-by-time, treatment-by-center, and treatment-by-baseline interactions were included in the model and tested one at a time at the alpha=0.10 level.

The analysis of the primary and secondary efficacy variables was based on 4 subsets: ITT subjects with LOCF, ITT subjects without LOCF, ITT completers, and PP subjects.
No interim analysis was performed. To assess improvement from baseline, the Wilcoxon signed-rank test was performed for each treatment group for each study week. All tests for treatment effects were two-tailed, at a significance level of 5%. For all inferential analyses of efficacy, pooled center was used as a stratification variable.

Demographic data (age, gender, weight, height, and race) was summarized for each treatment group. The descriptive statistics will include mean for continuous variables and numbers and percentages for categorical variables. Baseline disease status was assessed by constipation history, BM frequency, and stool quality data from the diary for the screening period. The comparability between the treatment groups will be evaluated by t-tests for age, weight and height, van Elteren tests for ordinal scale baseline disease status variables, and chi-square tests for categorical variables. The comparability of centers with respect to the demographic and baseline variables will be evaluated by ANOVA for continuous variables, Kruskal-Wallis tests for ordinal scale variables, and chi-square tests for categorical variables. These analyses were

for intent-to-treat subjects. Physical examination, medical history, and surgical history will be summarized by treatment group and overall, but no inferential statistical comparisons were done.

The "last observation carried forward" (LOCF) technique will be used to impute missing values. For a given subject, the most recent non-missing treatment-period data point was carried forward to subsequent weeks where data are missing.

Adjustments for multiple efficacy variables was not used since the primary variable was clearly identified.

Table 58: Study SC0131; Study Schedule

	Baseline/Washout	Treatment Period				Follow-up
Visit #	1	2	3	4	5	6
Study Day	-15	-1[a]	8	15	29	43
Location	Office	Office	Office	Phone	Office	Phone
Informed Consent	X					
Medical History[b]	X					
Inclusion/Exclusion	X	X				
Randomization		X				
Barium enema and/or flex. Sigmoidoscopy or colonsoscopy	X[c]					
Physical exam	X				X	
Vital signs and wt.	X	X	X		X	
Lab tests	X				X	
Serum pregnancy	X[d]				X[c]	
Subject eligibility		X				
Concomitant meds recorded	X	X	X		X	
Abdominal assessments	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Global assessments		X	X	X	X	X
Adverse events			X	X	X	X
Diary dispensed	X	X	X			
Diary collected and checked		X	X		X	
Study drug dispensed		X[e]				
Study drug compliance			X	X	X	
Study drug returned					X	

a Subjects were to begin treatment on the day following Visit 2 (Day -1), which, for purposes of this study was considered Day 1, or, if the subject had recently used rescue medication, 48 hours after the most recent dose of rescue medication.
b Subjects with IBS and/or GERD were asked to rate the severity of their disease(s) at the time of the medical history (Visit 1) and (Visit 5)
c If a flexible sigmoidoscopy, with or without barium enema, or colonoscopy was performed at Visit 1, subjects waited 1 week before starting to fill out the daily diary. There were 3 weeks between Visits 1 and 2 for those subjects.
d Performed for females of childbearing potential
e Assessment was based on perceptions of bloating and discomfort upon walking in the morning
Reviewer's table, modified from Clinical Study Report-SC0131ver4.1, page 14

As noted above in Table 58, subjects were screened at Visit 1 to determine their eligibility to enroll in the trial. This visit took place approximately 15 days prior to the subject being placed on double-blind study drug. Subjects who had been routinely taking a daily fiber supplement, such as Metamucil® or PerDiem®, etc., for at least the 3 months preceding Visit 1 were allowed to remain on the supplement throughout the study and were instructed not to change dosage or schedule. The Sponsor did not provide rescue medications. However, after 3 consecutive days of not having an SBM, if a subject needed relief, the Investigator could prescribe a 10-mg bisacodyl (Dulcolax®) suppository. If this was not effective, a Fleet® enema was prescribed. If both rescue medications failed, additional rescue medications were prescribed after further discussion with the Investigator. All global and abdominal assessments were completed before taking rescue medications.

Subjects were instructed to return 14 days after the first day of the baseline/washout period for the Visit 2 evaluation. Subjects were instructed to return the completed daily diary. Visit 2 took place approximately 14 days after the Baseline/Washout Visit. Before any assessments were performed, subjects were asked to complete the abdominal and global assessments.

Subjects were instructed to return after approximately 1 week of double-blind treatment for the Visit 3 evaluations (Study Day 8). Subjects were instructed to complete the daily diary and return it to the clinic at Visit 3, along with the study drug container. Visit 3 took place after the subject had completed 1 week of double-blind treatment. Subjects were asked to fill out the abdominal and global assessments before any other assessments were performed.

Subjects were reminded that the next visit was a telephone interview that would take place approximately at the end of the second week of double-blind treatment (Visit 4; Study Day 15), and were instructed to continue dosing study drug, and return after the completion of the double-blind treatment for the End-of-Treatment evaluation (Visit 5; Study Day 29). Subjects were instructed to complete the daily diaries and return them to the clinic at Visit 5, along with the study drug containers. Visit 4 took place approximately 7 days after Visit 3, after approximately 2 weeks of double-blind treatment had been completed, and it was conducted as a telephone interview.

Visit 5 took place approximately 7 days after Visit 3, after approximately 2 weeks of double-blind treatment had been completed, and it was conducted as a telephone interview.

Visit 6 was a follow-up telephone interview that took place approximately 14 days after the completion of Visit 5 (Day 43).

Inclusion/Exclusion Criteria

For **inclusion criteria** in this study, the patient must:

- be a male or a non-pregnant (as per negative serum pregnancy test), non-breast-feeding female subject 18 years of age or over.
- have a history of constipation, defined as, on average, <3 SBMs per week as confirmed during the baseline/washout period.

- have 1 or more of the following symptoms relating to bowel movements for at least 6 months before the Baseline/Washout Visit:
  - ♦ very hard (little balls) and/or hard stools for at least a quarter of the bowel movements;
  - ♦ sensation of incomplete evacuation following at least a quarter of the bowel movements;
  - ♦ straining at defecation at least a quarter of the time.
- be willing and able to fill out his/her own diary and questionnaires.
- have read and understood the IRB-approved Informed Consent Form.

Exclusion criteria for this study encompassed patients who:

- had a documented mechanical obstruction (e.g., bowel obstruction due to tumor, hernia, etc.), with a megacolon/megarectum, or with a diagnosis of pseudo-obstruction.
- had known or suspected organic disorders of the large or small bowel; i.e., ulcerative colitis, Crohn's Disease, etc. Subjects under 50 years of age were to have the results of a flexible sigmoidoscopy or colonoscopy within the last 5 years. If the subject was age 50 or over, results of a barium enema with flexible sigmoidoscopy or a colonoscopy were required. Additionally, if there was evidence of weight loss, anemia, or rectal bleeding since any subject's last evaluative procedure, a flexible sigmoidoscopy with barium enema or colonoscopy was required.
- had suffered from secondary causes of constipation, was hospitalized for any gastrointestinal or abdominal surgical procedure during the 3 months before the start of the study, or ever had any bowel resection.
- had, per Investigator's discretion, clinically significant cardiovascular, liver, or lung disease, neurologic or psychiatric disorders (including active alcohol or drug abuse), other systemic disease, impaired renal function (i.e., serum creatinine concentration greater than 1.8 mg/dL) or was known to be human immunodeficiency virus positive or had acquired immune deficiency syndrome.
- had clinically significant abnormalities: hematology, urinalysis, or blood chemistry, per Investigator discretion.
- had clinically significant cancer within the last 5 years.
- was unwilling to stop administration of disallowed medications during the baseline/washout and treatment periods.
- had received antibiotic therapy during 4 weeks prior to randomization visit (Visit 2).
- was a female of childbearing potential without adequate contraceptive protection during the trial. Oral contraceptives, Depo Provera® or Norplant® must have been used for at least 3 months prior to randomization; intra uterine device, sterilization or a double barrier method or other acceptable methods of birth control were to be used during the trial.
- had history of any medical/surgical condition that might significantly interfere with the absorption, distribution, metabolism, or excretion of the study drug.
- had received an investigational drug during the 30 days preceding the washout/baseline phase of the study.
- had demonstrated a potential for non-compliance with study protocol (i.e., dosing schedule, visit schedule, or study procedures).
- Prescription and OTC laxatives (e.g., MiraLax®, ExLax®, etc.) other than those prescribed as a rescue medication by the Investigator.

- Rescue medications were not allowed during Week 1 of the treatment period or within 48 hours of the first dose, but they were allowed during the baseline/washout period and Weeks 2, 3, and 4 of the treatment period per Investigator discretion.

Demography and Disease History

A total of 242 patients were enrolled in this study to receive either 24 mcg of RU-0211 b.i.d. or placebo b.i.d. at 20 centers in the United States. Overall, the study population was predominantly female (217 of 242 subjects, 89.7%) and Caucasian (208 of 242, 86%). The mean age of subjects was 48.56 years (range: 22-80 years) and all subjects had a confirmed history of constipation. Variables like age, height, gender, race, constipation history, history of medical procedures like flexible sigmoidoscopy, barium enema, and colonoscopy did not differ significantly ($p > 0.05$) between the two treatment groups. The RU-0211 treatment group had slightly more subjects with Irritable Bowel Syndrome and Gastroesophageal Reflux Disease than did the placebo group however this was not significantly different ($p > 0.05$). Table 59 below graphically depicts subject demographics and disease history.

Table 59: Summary of Demographics and disease history (Intent-to-Treat Subjects)

Variable	Placebo (N = 122)	RU-0211 48 mcg (N = 120)	Total (N = 242)	P-value
Mean Age (years)	49.10	48.02	48.56	0.5053
Mean Height (inches)	65.15	64.99	65.07	0.6998
Gender (%) Male/Female	12/110 (9.8/90.2)	13/107 (10.8/89.2)	25/217 (10.3/89.7)	0.7988
Race (%)				
Caucasian	103 (84.4)	105 (87.5)	208 (86.0)	0.4884
Black	12 (9.8)	9 (7.5)	21 (8.7)	-
Asian	2 (1.6)	0 (0.0)	2 (0.8)	-
Hispanic	5 (4.1)	5 (4.2)	10 (4.1)	-
Other	0	1 (0.8)	1 (0.4)	-
Constipation Hx Yes/No (%)	122/0 (100)	120/0 (100)	242/0 (100)	-
Flex. Sigmoidoscopy Yes/No (%)	37/85 (30.3/69.7)	38/82 (31.7/68.3)	75/167 (31.0/69.0)	0.8218
Barium Enema Yes/No (%)	11/111 (9.0/91.0)	9/111 (7.5/92.5)	20/222 (8.3/91.7)	0.6684
Colonoscopy Yes/No	87/35 (71.3/28.7)	82/38 (68.3/31.7)	169/73 (69.8/30.2)	0.6138
Irritable Bowel Syndrome Yes/No	26/96 (21.3/78.7)	32/88 (26.7/73.3)	58/184 (24/76)	0.3292
Absent	2 (1.6)	3 (2.5)	5 (2.1)	-
Mild	12 (9.8)	10 (8.3)	22 (9.1)	-
Moderate	9 (7.4)	9 (7.5)	18 (7.4)	-
Severe	2 (1.6)	8 (6.7)	10 (4.1)	-
Very Severe	1 (0.8)	2 (1.7)	3 (1.2)	-
Gastroesophageal Reflux Disease Yes/No	34/88 (27.1/72.1)	36/70 (30/70)	70/172 (28.9/71.1)	0.7147
Absent	7 (5.7)	6 (5.0)	13 (5.4)	-
Mild	18 (14.8)	17 (14.2)	35 (14.5)	-
Moderate	7 (5.7)	10 (8.3)	17 (7.0)	-
Severe	2 (1.6)	3 (2.5)	5 (2.1)	-
Very Severe	0 (0.0)	0 (0.0)	0 (0.0)	-

Reviewer's table, modified from Clinical Study Report SC0131ver4.1, Table 11-1, pages 40-41

10.1.2 Adverse Events

An adverse event (AE) was any undesirable event occurring to a subject during the clinical study, whether or not it was considered related to the study product(s). Events that were absent at baseline and developed after the initiation of double-blind treatment and events that were present at baseline and worsened after initiation of double-blind treatment were to be recorded as AEs. Events with onset within 7 days after the last day of treatment were included in the AE tabulations and analysis. Events with onset more than 7 days and within 14 days after the last day of treatment were considered as falling outside of the treatment period and were excluded from the tabulations but were included in the listings.

The Principal Investigator was required to assess the severity of the event and the relationship to study drug for all AEs, according to the criteria below.

Severity:

- **Mild:** Transient symptoms, no interference with the subject's daily activities; acceptable.
- **Moderate:** Marked symptoms, moderate interference with the subject's daily activities, but still acceptable.
- **Severe:** Considerable interference with the subject's daily activities; unacceptable.

Relationship to Study Drug:

- **Unrelated:** Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, **OR** based upon available information regarding subject history, disease process, relationship of the AE to dosing and drug pharmacology, a relationship between the study drug and the AE is unlikely.
- **Possible:** The AE follows a reasonable sequence from the time of study drug administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- **Probable:** The AE follows a reasonable sequence from the time of study drug administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the study drug, and the suspect drug is the most likely of all causes.
- **Definite:** The AE follows a reasonable sequence from the time of study drug administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the drug, and no other reasonable cause exists.

A serious adverse event (SAE) was any experience that suggested a medical hazard, including any event that:

- was fatal;
- was life-threatening (an event in which the subject was at risk of death at the time of the event; it did not refer to an event that might have caused death had it been more severe);
- required hospitalization or prolonged the existing hospitalization;
- resulted in persistent or significant disability/incapacity;
- was a congenital anomaly; or
- was an important medical event (an event that may not fit the other criteria for an SAE listed above, but based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes listed above).

All SAEs that occurred on or after the day of the first dose of study drug until 14 days after the final dosing with double-blind study drug were to be reported immediately to PRA International.

The original terms used in the case report form by investigators to identify AEs were coded to MedDRA preferred terms. Any verbatim AE that could not be coded was assigned "UNCODED" as the body system and the verbatim AE was used as the preferred term, so that these AEs could be included in the summary tables. The incidence of an AE was defined as the number of subjects who experienced at least 1 episode during the study. AEs with onset dates before randomization or more than 7 days after the last day of treatment were considered as falling outside of the treatment period, and were excluded from the summaries. Events with completely or partially missing onset dates were included in the tabulations, unless the partial date information available clearly indicated that the event happened out of the treatment period.

Study SC0131

Of the 242 subjects in **Study SC0131**, 146 (60.3%) experienced at least one adverse event during the course of the study. At least one AE was reported by 70.0% of the subjects in the RU-0211 group and by 50.8% of the subjects in the placebo group. The difference between the RU-0211 group and placebo group was statistically significant ($p = 0.0026$). Among the total safety evaluable subjects, 62 (51.7%) of the RU-0211 group suffered a gastrointestinal disorder side effect whereas 26 (21.3%) of the placebo group suffered a gastrointestinal disorder side effect ($p<0.0001$).

A total of 87 subjects (36%) had AEs that were considered treatment related, 61 (50.8%) in the RU-0211 group and 26 (21.3%) in the placebo group ($p < 0.0001$).

Adverse events resulted in study discontinuation in a total of 10 subjects (4.1%), nine (7.5%) patients in the RU-0211 group and 1 (0.8%) in the placebo group ($p = 0.0097$).

A total of 15 subjects (6.2 %) had AEs that were considered severe, 6 (4.9%) in the placebo group and 9 (7.5%) in the RU-0211 group. The Fisher's exact test did not show any significant difference ($p = 0.4369$) between the groups.

The most frequent severe AEs, at the Systems Order Class (SOC) level, were gastrointestinal disorders in 10 subjects (4.1%), and nervous system disorders in 7 subjects (2.9%). A total of 10 subjects discontinued the study because of AEs; 9 in the RU-0211 group and 1 in the placebo group. In the RU-0211 group, 9 subjects who discontinued the study experienced a total of 24 AEs that required study drug withdrawal: 14 continuous, 8 intermittent, and 2 once-only events. The AEs that were continuous were: 4 events of nausea, 3 events of headache, and 1 event each of anxiety not elsewhere classified (NEC), dyspnea not otherwise specified (NOS), edema lower limb, edema upper limb, palpitation, abdominal pain NOS, and rash NOS. The intermittent events were as follows: 2 events each of nausea and flatulence and, 1 event each of diarrhea NOS, dry throat, esophageal pain, and dizziness. The 2 'once-only' events were diarrhea NOS and dry mouth. Intermittent severe headache, assessed as being probably related to study drug, was the AE in the 1 subject who discontinued the study from the placebo group.

In terms of severity of AEs, of the total 24 AEs in subjects who discontinued the study from the RU-0211 group, there were 5 severe events (2 events of headache and 1 each of nausea, anxiety, and diarrhea NOS), 18 moderate events (5 events of nausea, 2 events of flatulence, and 1 each of diarrhea NOS, edema lower limb, edema upper limb, dry throat, dizziness excluding vertigo, palpitations, dyspnea NOS, esophageal pain, abdominal pain NOS, rash NOS, headache NOS), and 1 mild (dry mouth). Of the total 24 AEs, 12 events were considered as possibly related to the drug treatment, 12 events each were considered as probably related to the drug treatment. The AEs possibly related to RU-0211 were: flatulence (2 events), headache NOS (2 events), edema lower limb, edema upper limb, dry mouth, dry throat, nausea, dizziness (excluding vertigo), esophageal pain, and rash NOS (each 1 event). The AEs probably related to RU-0211 were: nausea (5 events), diarrhea NOS (2 events), and palpitations, anxiety NEC, dyspnea NOS, abdominal pain NOS, and headache NOS (each 1 event).

Of the 122 subjects in the placebo group, severe gastrointestinal disorders and nervous system disorders were reported in 4 subjects (3.3%) each. Of the 120 subjects in the RU-0211 group, severe gastrointestinal disorders were reported in 6 (5.0%) and severe nervous system disorders in 3 subjects (2.5%).

At the event level, nausea and headache were the only 2 AEs reported by $\geq$ 5% of the 242 subjects. Nausea was reported by 49 subjects (20.2%) and headache by 24 subjects (9.9%). Of the 122 subjects in the placebo group, 10 (8.2%) reported headache and 7 (5.7%) reported nausea. Of the 120 subjects in the RU-0211 group, 42 (35.0%) reported nausea and 14 (11.7%) reported headache. Fisher's test indicated significant difference ($p<0.0001$) for nausea, but not for headache ($p = 0.3969$).

Overall, most of the AEs reported in this study were rated as mild or moderate. In the placebo group, 45 subjects (36.9%) reported AEs with a maximum intensity of mild compared to 59 subjects (49.2 %) in the RU-0211 group. Twenty-five subjects (20.5%) in the placebo group reported AEs with a maximum intensity of moderate compared to 44 subjects (36.7%) in the RU-0211 group, and 6 subjects (4.9%) in the placebo group reported AEs with a maximum intensity of severe compared to 9 subjects (7.5%) in the RU-0211 group. In the placebo group, nausea was either mild in 5 subjects (4.1%), or moderate in 2 subjects (1.6%), while in the RU-0211

group, nausea was rated as mild in 27 subjects (22.5%), moderate in 11 subjects (9.2%), and severe in 4 subjects (3.3%).

10.1.3 Withdrawals, Compliance, and Protocol Violations

Subject Disposition/Withdrawals

A total of 244 patients were randomized into the study: 124 subjects into the placebo group and 120 subjects into the 48 mcg RU-0211 group. Two subjects (0512 and 0609) in the placebo group were randomized but not treated, making a total of 122 subjects who were treated with the placebo and 120 subjects treated with RU-0211. A total of 224 subjects completed the study. The percentage of subjects completing the study was 95.2% in the placebo group and 88.3% in the 48 mcg RU-0211 group. The mean number of days the subjects were on the study drug was 27.8 in the placebo group and 26.5 in the RU-0211 group. A total of 20 subjects (8.2%; 14 RU-0211; 6 placebo) discontinued the study. The reasons for discontinuation were AEs (10 subjects, 4.1%), voluntary withdrawal (4 subjects, 1.6%), lack of efficacy, and lost to follow-up (3 subjects, 1.2%, each). The majority of the RU-0211 patients that discontinued the study discontinued due to an adverse event 9 (7.5%) while in the placebo group only 1 (0.8%) patient discontinued due to an adverse event. The most common reason for withdrawal in the placebo group was because of lack of efficacy or lost to follow-up (each 2 subjects). The number of patients discontinuing in the first week of the trial was similar for both the RU-0211 and placebo group with 4 (3.2%) patients and 5 (4.2%) patients, respectively. By weeks 2 and 3, more subjects were discontinuing from the RU-0211 group than the placebo group 5 (4.2%) vs. 1 (0.8%) and 4 (3.3%) vs. 0 (0.0%), respectively.

Table 60: Summary of Subject Disposition: All Randomized Subjects

Variable	Placebo N = 124 n (%)	RU-0211 48 mcg N = 120 n (%)	Total N = 244 n (%)
Subjects Randomized	124 (100.0)	120 (100.0)	244 (100.0)
Subjects Randomized but not Treated	2 (1.6)	0 (0.0)	2 (0.8)
Subjects Treated	122 (98.4)	120 (100.0)	242 (99.2)
Subjects Completed	118 (95.2)	106 (88.3)	224 (91.8)
Subjects Discontinued	6 (4.8)	14 (11.7)	20 (8.2)
Reason for Discontinuation			
Adverse Event	1 (0.8)	9 (7.5)	10 (4.1)
Protocol Violation	0 (0.0)	0 (0.0)	0 (0.0)
Subject Voluntary Withdrawal	1 (0.8)	3 (2.5)	4 (1.6)
Lack of Efficacy	2 (1.6)	1 (0.8)	3 (1.2)
Lost to Follow-up	2 (1.6)	0 (0.8)	3 (1.2)
Did Not Meet Entry Criteria	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Timing of Discontinuation			
Week 1	4 (3.2)	5 (4.2)	9 (3.7)
Week 2	1 (0.8)	5 (4.2)	6 (2.5)
Week 3	0 (0.0)	4 (3.3)	4 (1.6)
Week 4	0 (0.0)	0 (0.0)	0 (0.0)
After Week 4	1 (0.8)	0 (0.0)	1 (0.4)
Number of Days on Study Drug (mean)	27.8 (5.32)	26.5 (7.50)	27.1 (6.50)

Reviewer's table, modified from Clinical Study Report SC0131ver4.1, Table 14.1.2, pages 90-91

Compliance

Treatment compliance was estimated by using the study drug administration record in the subject's daily diary and CRF. The percent compliance was calculated by dividing the actual cumulative exposure to study drug by the exposure the subject should have received (based on the number of days the subject was on study drug). In general, the percent compliance was similar for the 2 treatment groups. In the placebo group, the compliance was 95.2%, and in the

RU-0211 group it was 95.1%. A total of 4 subjects, 3 in the placebo group and 1 in the RU-0211 group, had treatment compliance of < 70%.

Protocol Deviations

The following protocol violations were determined and entered into the database after "soft lock" and before "hard lock" and unblinding. Data of the protocol violators were removed from the per protocol subset for the applicable week. Protocol violators were identified using the following criteria:

- Any subject who took at least 1 of the prohibited concomitant medications listed in the protocol (laxatives, e.g., MiraLax®, ExLax®, etc.), that was not prescribed as a rescue medication by the Investigator, was a protocol violator during the week(s) in which the medication was taken.
- A subject who took rescue medications (e.g., Dulcolax® suppository, a Fleet® enema) during Week 1 of the treatment period was considered a protocol violator for Week 1.
- A subject who took fewer than 80% of the required double-blind doses for a given week was considered a protocol violator for that week.
- Any subject who took rescue medication prior to 72 hours since the last SBM was considered a protocol violator for the week during which the medication was taken and for the following week if the medication was taken within 24 hours of the start of the following week.

Across all 4 weeks, the percentages for protocol violations were similar in the 2 treatment groups and the most frequent violations were:

- Prohibited concomitant medication use (11.6%, during Week 1).
- Less than 70 % study drug compliance (3.7% during Week 2, 3.3% during Week 3, and 2.5% during Week 4).
- Use of rescue medication within 48 hours prior to the first dose of study drug (2.1%).

10.1.4 Efficacy Results

Responder analysis:

In order to assess treatment response and to account for study dropout and rescue medication use, a trichotomous responder analysis was performed for each week. Responders and non-responders are defined below. The number and percent of non-responders, moderate responders, and full responders were summarized by treatment group at each week. A van Elteren test stratified by pooled center was used to analyze the responder rates at each week.

A **responder** was defined as any subject with an SBM frequency rate of ≥ 3 for a given week, who did not use rescue medication during or within 24 hours prior to the given week, and who did not drop out during or prior to the given week due to lack of efficacy.

A **full responder** was a subject with an SBM frequency of ≥ 4 per week.

A **moderate responder** was a subject with an SBM frequency rate ≥ 3 but < 4.

A **non-responder** was defined as any subject with an SBM frequency rate of < 3 for a given week, any subject who dropped out during or prior to the given week due to lack of efficacy, or any subject who used rescue medication during or within 24 hours prior to the given week.

Primary Efficacy Endpoint

The primary efficacy analysis was on the SBM frequency during Week 1. An SBM was defined as any bowel movement that did not occur within 24 hours after rescue medication use. In order to adjust for early withdrawals, weekly SBM frequency rates were calculated as follows:

[Number of SBMs / Number of days (based on 24-hour periods)] x 7

where the number of days was the number of days during the week that the subject was in the study. Weeks were calculated as 168-hour intervals starting with the exact time of the first intake of study drug. The number of days was generally 7 unless a subject dropped out during a treatment week. If the number of days during Week 1 was less than 4, then the rate was considered missing because of insufficient data.

For statistical analysis, 4 populations were derived: Intent to treat (ITT) subjects with last-observation-carried-forward (LOCF), ITT subjects, ITT subjects who were completers, and per protocol (PP) subjects.

The baseline mean and median SBM frequency rates were similar in the placebo and RU-0211 treated groups for the 4 populations derived for the primary efficacy analysis. For the ITT with LOCF subjects, the mean frequency at baseline was 1.47 for placebo and 1.37 for RU-0211 group; the median was 1.5 for both groups. At baseline, the range of mean SBM rates across populations was 1.37 to 1.47 in the placebo group and 1.34 to 1.37 in the RU-0211 group.

During Week 1, the mean and median SBM frequency rates were higher in the 48 mcg RU-0211 group in all 4 derived populations. In spite of the apparent placebo effect, Table 61 below shows a difference of a least 2 SBMs in the mean and median frequency of all four treatment groups during the first week of the treatment. A statistical analysis employing the van Elteren's test stratified by pooled center was used showing a significant difference ($p \leq 0.0002$) between groups in all 4 populations in favor of RU-0211 and for SBM frequency rate during Week 1. Based on this analysis, it is deduced that RU-0211 treatment in 48 mcg dose produces statistically significant improvement in SBM frequency in subjects with constipation.

Table 61: Spontaneous Bowel Movement Frequency During Week 1

Population	Placebo	48 mcg RU-0211*
	Mean (Std. Dev.)	**Mean (Std. Dev.)**
ITT Subjects with LOCF	**3.46 ± 2.285**	**5.69 ± 4.417**
ITT Subjects without LOCF	3.46 ± 2.285	5.69 ± 4.417
ITT Subjects – completers	3.49 ± 2.308	5.63 ± 4.432
Per Protocol Subjects	3.65 ± 2.062	6.03 ± 4.378
	Median (Std. Dev.)	**Median (Std. Dev.)**
ITT Subjects with LOCF	**3.0 (0.0, 12.0)**	**5.0 (0.0, 24,0)**
ITT Subjects without LOCF	3.0 (0.0, 12.0)	5.0 (0.0, 24,0)
ITT Subjects – completers	3.0 (0.0, 12.0)	5.0 (0.0, 24,0)
Per Protocol Subjects	3.0 (0.0, 11.0)	5.0 (0.0, 24,0)

*$p \leq 0.0002$ for all 4 populations compared to the respective placebo group data (van Elteren's test stratified by center)
Reviewer's table, modified from Clinical Study Report SC0131ver4.1, Table 11.3, page 44

Secondary Efficacy Analyses:

As shown below in Table 62, the mean and median frequencies during Week 2, Week 3, and Week 4 were always higher in the 48 mcg RU-0211 group in all 4 derived populations. Statistical analysis of the mean and median SBM frequency rates by van Elteren's test showed significant difference ($p \leq 0.0024$) between the 2 groups in all 4 populations for Week 2, Week 3, and Week 4.

Table 62: Spontaneous Bowel Movement Frequency During Week 2, Week 3, and Week 4

Week	Group	ITT with LOCF	ITT without LOCF	ITT Completers	Per protocol Subjects
		Mean ± Std. Dev.			
Week 2	Placebo	3.18 ± 2.530	3.20 ± 2.544	3.20 ± 2.561	3.18 ± 2.502
	RU-0211*	5.06 ± 4.076	5.04 ± 4.072	5.06 ± 3.957	5.13 ± 4.096
Week 3	Placebo	2.84 ± 2.231	2.87 ± 2.251	2.88 ± 2.254	2.83 ± 2.194
	RU-0211*	5.25 ± 4.875	5.37 ± 4.939	5.22 ± 4.308	5.51 ± 5.019
Week 4	Placebo	2.91 ± 2.357	2.96 ± 2.373	2.98 ± 2.376	3.02 ± 2.348
	RU-0211*	5.30 ± 4.735	5.27 ± 4.130	5.27 ± 4.130	5.32 ± 4.117
		Median (Min, Max)			
Week 2	Placebo	3.0 (0.0, 15.0)	3.0 (0.0, 15.0)	3.0 (0.0, 15.0)	3.0 (0.0, 15.0)
	RU-0211*	4.0 (0.0, 17.0)	4.0 (0.0, 17.0)	4.0 (0.0, 17.0)	4.0 (0.0, 17.0)
Week 3	Placebo	2.0 (0.0, 13.0)	2.0 (0.0, 13.0)	2.0 (0.0, 13.0)	2.0 (0.0, 13.0)
	RU-0211*	5.0 (0.0, 30.8)	5.0 (0.0, 30.8)	5.0 (0.0, 21.0)	5.0 (0.0, 30.8)
Week 4	Placebo	2.3 (0.0, 12.0)	2.3 (0.0, 12.0)	2.4 (0.0, 12.0)	3.0 (0.0, 12.0)
	RU-0211*	4.0 (0.0, 30.8)	4.0 (0.0, 20.0)	4.0 (0.0, 20.0)	4.1 (0.0, 20.0)

***p ≤ 0.0024** for all 4 populations compared to the respective placebo group data (van Elteren's test stratified by center)
Reviewer's table, modified from Clinical Study Report SC0131ver4.1, Table 11.4, page 45

Table 63: Bowel Movement Changes From Baseline During Week 1, Week 2, Week 3, and Week 4

Week	Group	ITT with LOCF	ITT without LOCF	ITT Completers	Per protocol Subjects
		Mean ± Std. Dev.			
Week 1	Placebo*	1.20 ± 2.269	1.20 ± 2.269	1.20 ± 2.243	1.20 ± 2.131
	RU-0211*	3.51 ± 4.347	3.51 ± 4.347	3.48 ± 4.353	3.61 ± 4.348
Week 2	Placebo*	1.24 ± 2.583	1.28 ± 2.580	1.31 ± 2.565	1.41 ± 2.486
	RU-0211*	3.30 ± 3.787	3.29 ± 3.790	3.31 ± 3.691	3.41 ± 3.812
Week 3	Placebo*	1.03 ± 2.497	1.11 ± 2.474	1.12 ± 2.480	1.16 ± 2.429
	RU-0211*	3.47 ± 4.598	3.61 ± 4.661	3.44 ± 4.019	3.73 ± 4.746
Week 4	Placebo*	1.08 ± 2.569	1.17 ± 2.554	1.18 ± 2.564	1.25± 2.440
	RU-0211*	3.73 ± 4.560	3.74 ± 3.971	3.74 ± 3.971	3.73 ± 3.990
		Median (Min, Max)			
Week 1	Placebo*	1.0 (-4.4, 9.0)	1.0 (-4.4, 9.0)	1.0 (-4.4, 9.0)	1.0 (-3.3, 9.0)
	RU-0211*	2.5 (-3.5, 22.0)	2.5 (-3.5, 22.0)	2.5 (-3.5, 22.0)	3.0 (-3.5, 22.0)
Week 2	Placebo*	1.0 (-6.3, 13.9)	1.3 (-6.3, 13.9)	1.3 (-6.3, 13.9)	1.4 (-5.4, 13.9)
	RU-0211*	2.3 (-3.5, 15.0)	2.3 (-3.5, 15.0)	2.0 (-3.0, 15.0)	2.3 (-3.0, 15.0)
Week 3	Placebo*	0.8 (-7.6, 11.9)	0.9 (-7.6, 11.9)	1.0 (-7.6, 11.9)	1.0 (-7.6, 11.9)
	RU-0211*	2.5 (-3.5, 28.8)	2.6 (-2.5, 28.8)	2.9 (-3.5, 20.0)	3.0 (-2.5, 28.8)
Week 4	Placebo*	0.5 (-5.3, 11.0)	0.5 (-5.3, 11.0)	0.9 (-5.3, 11.0)	1.0 (-5.3, 11.0)
	RU-0211*	3.0 (-3.5, 28.8)	3.2 (-2.5,18.8)	3.2 (-2.5, 18.8)	3.0 (-2.5, 18.8)

***p<0.0001** for all 4 populations compared to the respective placebo group data (Wilcoxon signed-rank test)
^ Change calculated as (follow-up – baseline)
Reviewer's table, modified from Clinical Study Report SC0131ver4.1, Table 11.8, page 50

Compared to the respective baseline values, frequencies of SBMs and BMs were significantly increased ($p<0.0001$) at all time points in the placebo and RU-0211 treated groups. The increase in frequency of SBMs and BMs was consistently higher in the RU-0211 than in the placebo treated group. These analyses suggest that, compared to baseline, the 48 mcg dose of RU-0211 demonstrates efficacy by week one with sustained improvement in SBM and BM frequencies in subjects with constipation throughout the duration of the four week trial.

APPEARS THIS WAY
ON ORIGINAL

Percentage of Subjects with a Spontaneous Bowel Movement Within 24 Hours of First Study Drug Administration

As shown below in Table 64, the ITT population, 36.9% of the subjects in the placebo group and 56.7% of the subjects in the RU-0211 group had a SBM during the 24 hours since the first intake of study drug. In the per protocol (PP) population, as shown in Table 65, 34.5% of the subjects in the placebo group and 53.2% of the subjects in the RU-0211 group had a SBM during the 24 since the first intake of study drug. It is unclear to the reviewer why there was such a large placebo effect for SBM in the first 24 hours. In both populations, however, the RU-0211 treated group had statistically significantly higher ($p \leq 0.01$) percentages of subjects who had SBMs within 24 hours after the first intake of study drug. This indicates that within 24 hours of RU-0211 treatment, efficacy is apparent with constipation.

Table 64: Summary of Subjects with SBMs within 24hrs after First Study Drug Administration ITT:

SBM Within 24 Hours	Placebo (N = 122)	RU-0211 48 mcg (N = 120)	P-value*
Yes (%)	45 (36.9)	68 (56.7)	0.0024
No (%)	77 (63.1)	52 (43.3)	

*P-value is based on a Cochran-Mantel-Haenszel (CMH) test for general association controlling for pooled center
Reviewer's table, modified from Clinical Study Report SC0131ver4.1, Table 14.2.5.1, page 206

Table 65: Summary of Subjects with SBMs within 24hrs after First Study Drug Administration Per Protocol:

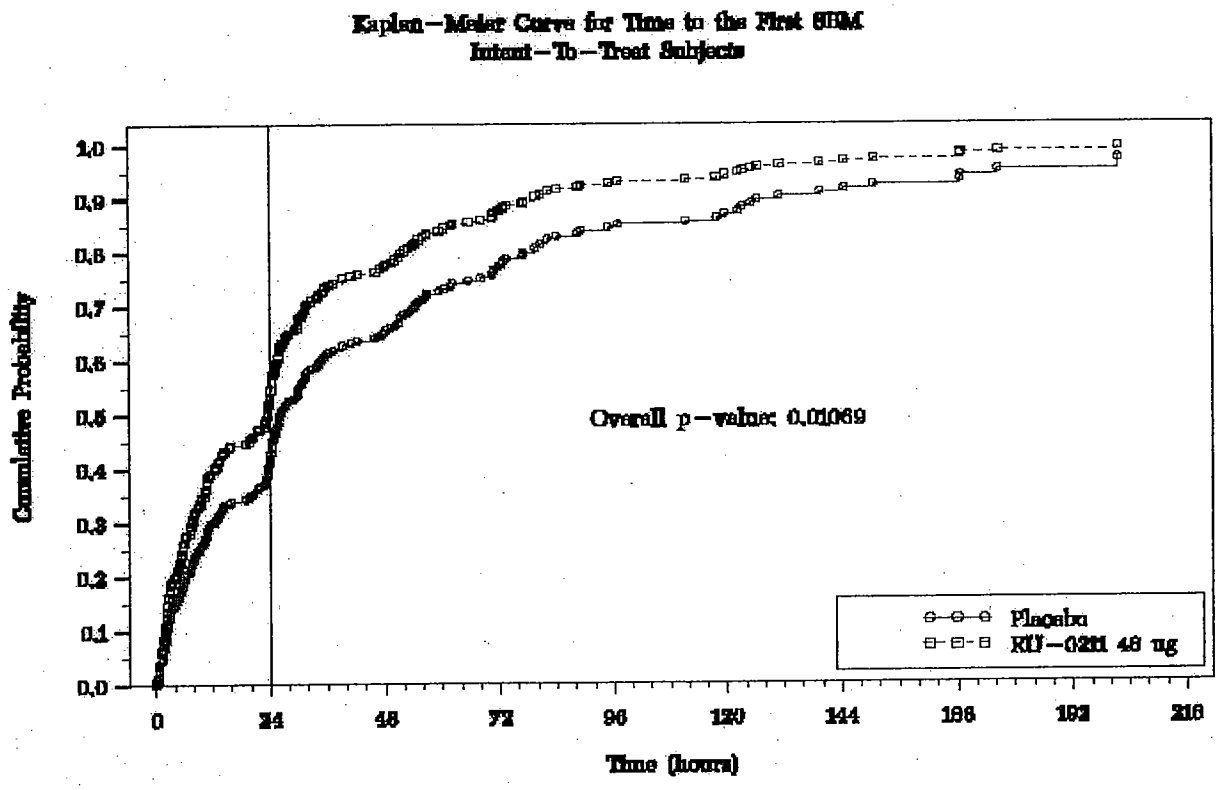
SBM Within 24 Hours	Placebo (N = 119)	RU-0211 48 mcg (N = 111)	P-value*
Yes (%)	41 (34.5)	59 (53.2)	0.0106
No (%)	59 (49.6)	42 (37.8)	

*P-value is based on a Cochran-Mantel-Haenszel (CMH) test for general association controlling for pooled center
Reviewer's table, modified from Clinical Study Report SC0131ver4.1, Table 14.2.5.2, page 207

Time to First Spontaneous Bowel Movement

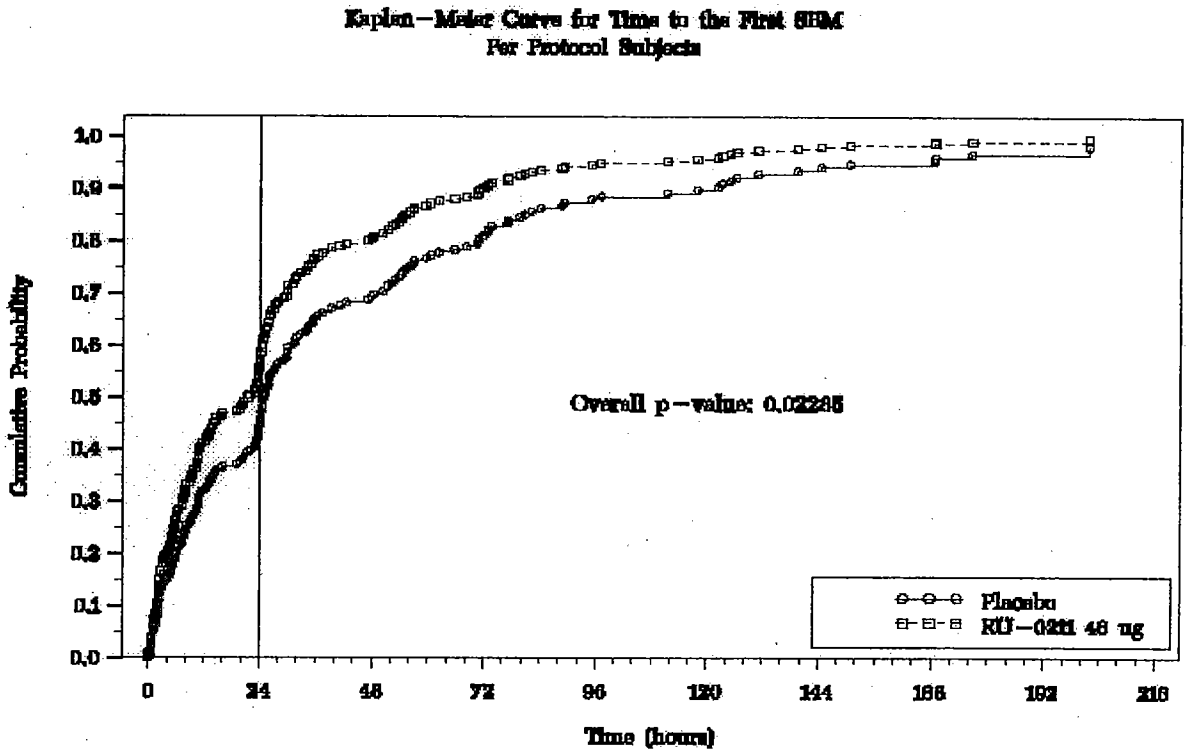
Time-to-event analysis was used to evaluate between treatment group differences in time to the first SBM. Data from subjects who used rescue medication or who dropped out of the study before the first SBM were censored at the time of rescue medication use or early termination. Cox proportional hazards regression was used in this analysis. Pooled center and treatment were considered and tested at an alpha level of 0.10 in the saturated model. The number of hours since the most recent BM prior to the start of study drug was used as a covariate. The reverse stepwise modeling process eliminated pooled center at the first step. For the ITT population, Figure 8, presents the cumulative probability comparison between treatment groups graphically with Kaplan-Meier curves. For the PP population a similar display is presented in Figure 9.

Figure 8: Kaplan-Meier Curve For Time to First SBM: ITT Population



Sponsor's Figure, Figure 14.2.5.3, Clinical Study Report SC0131ver4.1, page 208

Figure 9: Kaplan-Meier Curve for Time to First SBM: Per Protocol Subjects



Sponsor's Figure, Figure 14.2.5.4, Clinical Study Report SC0131ver4.1, page 209

In both the ITT and PP populations, the statistically significant test of the coefficient of the treatment effect ($p<0.023$) suggests that an early onset of relief, namely in the form of the first SBM, was much faster in subjects treated with RU-0211 than among placebo subjects. In both figures, the line denoting the 24-hour mark is only to illustrate that mark as a point of interest, and is not to be construed as being related to the Cox proportional hazard p-value. This analysis confirms the findings of the primary efficacy variable in this study.

Average Stool Consistency

Stool consistency was recorded by each subject in a daily diary after each bowel movement, and was scored as Very Loose (0), Loose (1), Normal (2), Hard (3) or Very Hard (4). The average was calculated by summing the scores for the week and dividing by the number of SBMs in that week. The average stool consistency at Week 1, Week 2, Week 3, and Week 4 was analyzed by van Elteren's test stratified by pooled center. If there were no SBMs during the week or if there were SBMs but all ratings were missing, then the LOCF method imputed the average.

Change in stool consistency compared to the respective baseline was always statistically significant ($p<0.001$) in the RU-0211 group in all 4 populations, but not for the placebo group. The van Elteren's test, stratified by center, showed that during Week 1, Week 2, Week 3, and Week 4 in placebo and RU-0211 treated groups, the differences between the groups were

consistently significant ($p<0.0001$) in all 4 populations. This analysis suggests that treatment with RU-0211 significantly softens the stool consistency in subjects with constipation.

Average Degree of Straining

The degree of straining was recorded in the daily diary after each bowel movement, and was scored as Absent (0), Mild (1), Moderate (2), Severe (3), or Very Severe (4). The average was calculated by summing the scores for the week and dividing by the number of SBMs in that week. The average straining at Week 1, Week 2, Week 3, and Week 4 was analyzed by van Elteren's test stratified by center. If there were no SBMs during the week, or if there were SBMs but all ratings were missing, the LOCF method imputed the average. Statistical comparisons did not reveal differences ($p \geq 0.30$) between the 2 groups in the baseline straining in any of the 4 populations.

In Week 1, Week 2, Week 3, and Week 4, the mean change in straining was always lower in the RU-0211 group than in the placebo group in all 4 populations derived for this secondary efficacy analysis. This analysis indicates RU-0211 treatment consistently decreases the straining in subjects with constipation.

Average Degree of Severity of Constipation

For all randomized subjects, severity of constipation was recorded using a 5-point scale; Absent (0), Mild (1), Moderate (2), Severe (3), Very Severe (4) at baseline, and Week 1 through Week 6 (Follow-up). The severity of constipation score was analyzed by the van Elteren's test, stratified by pooled center. The Wilcoxon signed-rank test was used for analysis of the change from baseline, for each treatment group at the end of each week and follow-up.

Between groups comparison did not show any differences ($p>0.5$) in constipation severity at baseline and at follow-up visit in any of the 4 populations. However, during treatment at Week 1, Week 2, Week 3, and Week 4, severity of constipation was always significantly ($p \leq 0.0007$) lower than baseline in the RU-0211 group in all 4 populations.

Global Assessment of Treatment Effectiveness

Global assessment of treatment effectiveness for all randomized subjects was recorded using a 5-point scale; Not At All Effective (0), A Little Bit Effective (1), Moderately Effective (2), Quite a Bit Effective (3), Extremely Effective (4) at Week 1, Week 2, Week 3, Week 4, and at the Follow-up Visit. In the RU-0211 group, global assessment of treatment effectiveness was always higher than in the placebo group in all 4 populations. The van Elteren's test, stratified by pooled center showed the differences between the groups were consistently significant ($p<0.0001$) during Week 1, Week 2, Week 3, Week 4, and at the Follow-up Visit in all 4 populations. This analysis indicates that subjects suffering from chronic idiopathic constipation consistently had better scores for treatment effectiveness with RU-0211 treatment than with placebo.

Abdominal Symptoms (Bloating and Discomfort)

At Week 1, Week 2, Week 3, Week 4, and at the Follow-up Visit, all randomized subjects rated their abdominal bloating and discomfort upon waking, using a 5 point scale; Absent (0), Mild (1), Moderate (2), Severe (3), and Very Severe (4). In all 4 populations, compared to baseline, the mean rating of abdominal bloating was lower in the RU-0211 group than in the placebo group during Week 1, Week 2, Week 3, and Week 4. Abdominal bloating had a statistically significant ($p \leq 0.05$) difference between the groups in Week 2 and Week 3 in ITT subjects with LOCF and in ITT subjects who were completers. In ITT subjects without LOCF, a statistically significant ($p<0.05$) difference between the groups for this variable was seen in Week 3 only. Statistically significant ($p<0.05$) differences in abdominal bloating were seen between the groups in Week 2, Week 3, and Week 4 in the PP population. In all 4 populations, subjects with abdominal discomfort had statistically significant ($p \leq 0.05$) differences between the groups in Week 2, Week 3, and Week 4.

With the exception of abdominal bloating in the placebo group in ITT without LOCF, ITT completers, and PP population, all other changes from the baseline in abdominal bloating and discomfort were statistically significant ($p \leq 0.05$) in all 4 populations in both the placebo and RU-0211 treated groups.

While statistical significance varies between populations, the trend exhibited in the per protocol population indicates RU-0211 treatment is effective in relieving abdominal bloating. Additionally, RU-0211 treatment showed consistent efficacy in relieving abdominal discomfort in subjects with constipation.

Use of Rescue Medication

Of the 242 participating subjects, over the 4 weeks of the study, 11.6% to 67.8% took rescue medications. In the placebo group, 67.2%, 13.9%, 33.3%, 47.1%, and 50.8% of subjects used rescue medication at baseline, Week 1, Week 2, Week 3, and Week 4, respectively. In the RU-0211 group, 68.3%, 9.2%, 24.6%, 33.3%, and 35.6% of subjects used rescue medication during the same weeks. Except at baseline, the percent of subjects using rescue medication was always lower in the RU-0211 group. This was found to be significantly lower ($p=0.0357$) at Week 4. The van Elteren test was employed to determine the cumulative use and exposure to rescue medication over time. Analysis of the weekly use of rescue medication and cumulative exposure to rescue medication computed as total and daily use did not show any obvious trend or statistical significance in this study. However, after the baseline, the percent of subjects using rescue medication was always lower in the RU-0211 group.

10.1.5 Reviewer's summary and comments on study SC0131

The total number of subjects enrolled in this study (n = 242) was adequate for evaluation. No significant difference ($p > 0.05$) was seen among the two treatment groups with respect to demographics (age, height, gender, race, history of constipation, history of medical procedures, history of Irritable Bowel Syndrome, or history of Gastroesophageal Reflux Disease).

The primary efficacy analysis was based on the SBM frequency during Week 1. Study SC0131 demonstrated a statistically significant difference between the placebo group and the RU-0211 treatment group in SBM frequency during Week 1. The mean and median SBM frequency rates were significantly higher ($p \leq 0.0002$) in the 48 mcg RU-0211 group in all 4 patient populations during the first week of treatment compared to the placebo group.

Results of the secondary efficacy analyses also revealed statistical significance in favor of RU-0211. Significant improvements for RU-0211 48 mcg subjects over placebo subjects were observed in the following efficacy variables: frequency of SBMs at Weeks 2, 3, and 4; weekly responder rates (at each week and all weeks); percentage of subjects with a spontaneous bowel movement within 24 hours after first dose of study drug; time to first SBM; average stool consistency; average degree of straining; constipation severity; and treatment effectiveness.

At least one adverse event was reported by 70.0% of the subjects in the RU-0211 group and 50.8% of the subjects in the placebo group. The difference between the RU-0211 group and placebo group was statistically significant ($p = 0.0026$). A total of 15 subjects (6.2 %) had AEs that were considered as severe, 6 (4.9%) in the placebo group and 9 (7.5%) in the RU-0211 group. This was not found to be statistically significant.

The most frequent severe AEs, at the Systems Order Class (SOC) level, were gastrointestinal disorders in 10 subjects (4.1%), and nervous system disorders in 7 subjects (2.9%).

Of the total 24 AEs that occurred in subjects who discontinued the study from the RU-0211 group, 5 were severe events (2 events of headache and 1 each of nausea, anxiety, and diarrhea NOS), and 18 were moderate events (5 events of nausea, 2 events of flatulence, and 1 each of diarrhea NOS, edema lower limb, edema upper limb, dry throat, dizziness excluding vertigo, palpitations, dyspnea NOS, esophageal pain, abdominal pain NOS, rash NOS, headache NOS), and 1 mild (dry mouth). Of the total 24 AEs, 12 events were considered as possibly related to the drug treatment, 12 events each were considered as probably related to the drug treatment. The AEs possibly related to RU-0211 were: flatulence (2 events), headache NOS (2 events), edema lower limb, edema upper limb, dry mouth, dry throat, nausea, dizziness (excluding vertigo), esophageal pain, and rash NOS (each 1 event). The AEs probably related to RU-0211 were: nausea (5 events), diarrhea NOS (2 events), and palpitations, anxiety NEC, dyspnea NOS, abdominal pain NOS, and headache NOS (each 1 event).

Overall, most of the AEs reported in this study were rated as mild or moderate.

STUDY RTU/0211SC0232

Title: Multi-Center, Double-Blind, Randomized, Placebo-Controlled Phase III Study of the Efficacy and Safety of Oral RU-0211 for the Treatment of Occasional Constipation.

10.1.6 Objectives

The objectives of this study were to assess the efficacy and safety of oral 48 mcg RU-0211 compared to placebo for the treatment of constipation. Constipation was defined in this study as, on average, less than 3 spontaneous bowel movements (SBMs) per week. An SBM was defined as any bowel movement (BM) that did not occur within 24 hours after rescue medication use.

Study Design

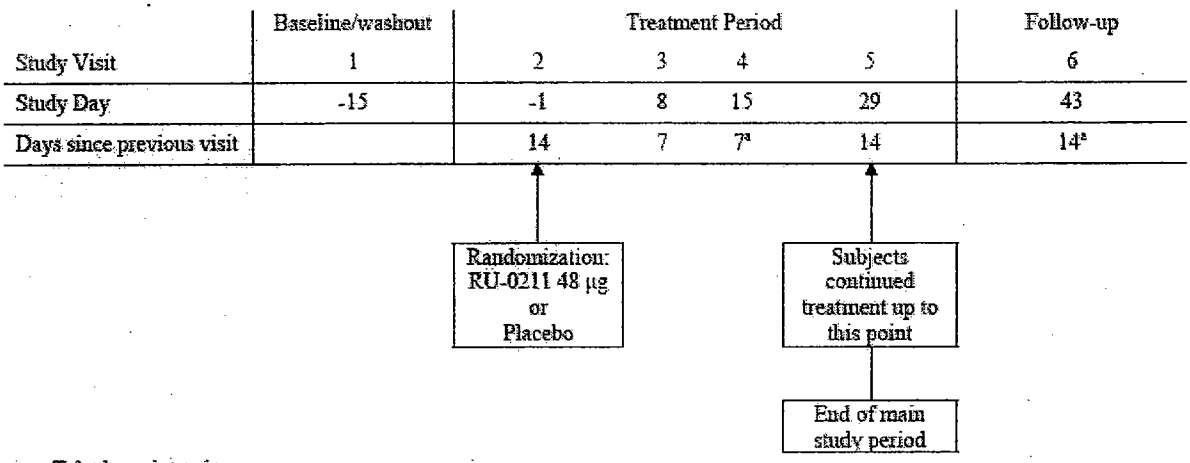
This was a multi-center, parallel-group, double-blind, placebo-controlled study consisting of approximately 57 days duration including follow-up. Two-hundred-thirty-seven subjects (119 subjects in the RU-0211 treatment arm and 118 in the placebo group) were enrolled at up to 20 centers in the United States. Following initial assessments, including a 2-week baseline/washout period, subjects received 4 weeks of double-blind medication. The study consisted of a screening visit (Visit 1), an enrollment visit (Visit 2), 2 interim visits (Visit 3 and 4; these occurred after 1 and 2 weeks of treatment), an end of treatment visit (Visit 5), and a follow-up evaluation (Visit 6) approximately 2 weeks after Visit 5.

In order to qualify for randomization into the double-blind treatment phase, evidence of constipation (defined as less than 3 SBMs per week, on average) must have been demonstrated and recorded in the daily diary during the washout period. Study drug was self-administered orally for a total treatment period of 4 weeks; it was taken at breakfast and dinner with food and at least 8 ounces of water. Subjects documented bowel activity and symptoms in a daily diary. The frequency of SBMs during Week 1, Week 2, Week 3, and Week 4, responder rates at each week, the percentage of subjects with an SBM during the 24 hours since the first intake of study drug, the time to the first SBM, average degree of straining, average stool consistency, assessments of abdominal symptoms (bloating and discomfort upon waking in the morning), global assessments (treatment effectiveness and severity of constipation) and the safety and tolerability of administered doses relative to placebo were evaluated to determine the efficacy and safety of RU-0211. The study ran between October 2002 and September 2003. Treatment medication was given in one of the following combinations:

2. Two placebo capsules (one 0 mcg capsule taken b.i.d.) with food (breakfast and dinner) and with at least 8 ounces of water

3. Two RU-0211 capsules (one 24 mcg capsule taken b.i.d.) with food (breakfast and dinner) and with at least 8 ounces of water

Figure 10: A graphic depiction of Study SC0232



a Telephone interview

Sponsor's figure, Clinical Study Report-SC0131ver2.3, page 15

Statistical Methods of Analysis:

The primary efficacy variable is the frequency rate of SBMs during Week 1. A spontaneous bowel movement was defined as any bowel movement that does not occur within 24 hours after rescue medication use. Since rescue medication use was disallowed during Week 1, the SBM rate equaled the BM rate. In the case of protocol violators, the analysis was based on SBMs. In order to adjust for early withdrawals, weekly SBM frequency rates were calculated as follows:

$$7 \times \text{Number of SBMs} / \text{Number of days}$$

where the number of days in the denominator is the number of days during the week that the subject was in the study. Weeks were calculated as 168-hour intervals starting with the exact time of the first intake of study drug. The number of days in the week was generally 7 unless a subject dropped out during a treatment week. If the number of days was less than 4, then the data was considered insufficient and the rate was missing. Results were analyzed by a van Elteren test stratified by center. Small centers (i.e., those that enrolled $\leq$ 8 subjects) were pooled.

Frequency rate of SBMs at Weeks 2, 3, and 4 were analyzed as discussed above for Week 1. However, if the number of days in the week was less than 4, then the most recent data from days during the previous week were combined with data from the current week in order to bring the number of days up to 4. If the number of days for a given week was 0, then the LOCF method was used to impute the frequency rate from the rate for the most recent week.

A longitudinal analysis of the frequency rates of SBMs and of all BMs was performed in order to assess the treatment effect over time. Missing values were not imputed for this analysis. The model included terms for treatment, time, center, and baseline. The time variable was defined by

treatment Weeks 1, 2, 3, and 4. Treatment-by-time, treatment-by-center, and treatment-by-baseline interactions were included in the model and tested one at a time at the alpha=0.10 level.

The analysis of the primary and secondary efficacy variables was based on 4 subsets: ITT subjects with LOCF, ITT subjects without LOCF, ITT completers, and PP subjects. No interim analysis was performed. To assess improvement from baseline, the Wilcoxon signed-rank test was performed for each treatment group for each study week. All tests for treatment effects were two-tailed, at a significance level of 5%. For all inferential analyses of efficacy, pooled center was used as a stratification variable.

Demographic data (age, gender, weight, height, and race) and constipation history were summarized for each treatment group using descriptive statistics. The descriptive statistics included the mean for continuous variables and numbers and percentages for categorical variables. Baseline disease status was assessed for constipation history, BM frequency, and stool quality data from the diary for the screening period. The comparability between the treatment groups was evaluated by t-tests for age and height, van Elteren tests for ordinal scale baseline disease status variables, and chi-square tests for nominal categorical variables. The comparability of demographic and baseline variables between pooled centers was evaluated by analysis of variance (ANOVA) for continuous variables, Kruskal-Wallis tests for ordinal scale variables, and chi-square tests for categorical variables. These analyses were for the intent-to-treat subjects (ITT). Physical examination, medical history, and surgical history were summarized by treatment group and overall, but no inferential statistical comparisons were done.

The "last observation carried forward" (LOCF) technique was used to impute missing values. For a given subject, the most recent non-missing treatment-period data point was carried forward to subsequent weeks where data was missing.

Adjustments for multiple efficacy variables were not used since the primary variable was clearly identified.

Table 66: Study SC0232; Study Schedule

	Baseline/Washout	Treatment Period				Follow-up
Visit #	1	2	3	4	5	6
Study Day	-15	-1	8	15	29	43
Location	Office	Office	Office	Phone	Office	Phone
Informed Consent	X					
Medical History	X[b]				X[b]	
Inclusion/Exclusion	X	X				
Randomization		X				
Barium enema and/or flex Sigmoidoscopy or colonoscopy	X[c]					
Physical exam	X				X	
Vital signs[d] and wt.	X	X	X		X	
Lab tests[e]	X				X	
Serum pregnancy[f]	X				X	
Subject eligibility		X				
Concomitant meds recorded	X	X	X		X	
Abdominal assessments[g]	X	X	X	X	X	X
Global assessments		X	X	X	X	X
Adverse events			X	X	X	X
Diary dispensed	X	X	X			
Diary collected and checked		X	X		X	
Study drug dispensed		X[a]				
Study drug compliance			X	X	X	
Study drug returned					X	

a Subjects were to begin treatment on the day following Visit 2 (Day -1), which, for purposes of this study was considered Day 1
b Subjects with IBS and/or GERD were asked to rate the severity of their disease(s) at the time of the medical history (Visit 1) and (Visit 5)
c If a Flexible Sigmoidoscopy, with or without barium enema, or colonoscopy was performed at Visit 1, subjects were to wait at least 1 week, or until bowel habits returned to those noted prior to the procedure, before starting to fill out the daily diary.
d Vital signs measures were respiration rate, pulse, and regularity
e Tests consisted of hematology, chemistry, and urinalysis
f Performed for females of childbearing potential
g Assessment was based on perceptions of bloating and discomfort upon walking in the morning
Reviewer's table, modified from Clinical Study Report-SC0131ver4.1, page 14

As noted above in Table 66, subjects were screened at Visit 1 to determine their eligibility to enroll in the trial. This visit took place approximately 14 days prior to the subject entering the treatment period and receiving study drug. Subjects were instructed to stop all prescription and over-the-counter laxative intake and not to change their diet or lifestyle. Subjects who had been routinely taking a daily fiber supplement, such as Metamucil® or PerDiem®, etc., for at least the 3 months preceding Visit 1 were allowed to remain on the supplement throughout the study and were instructed not to change dosage or schedule. The sponsor did not provide rescue medications. However, after 3 consecutive days of not having an SBM, if a subject needed relief, the Investigator could prescribe a 10-mg bisacodyl (Dulcolax®) suppository. If this was not effective, a Fleet® enema was prescribed. Any global and abdominal assessment must have been completed before taking rescue medications. If both rescue medications failed, additional rescue medications were prescribed after further discussion with the Investigator. All global and abdominal assessments were completed before taking rescue medications.

Subjects were instructed to return 2 weeks after the first day of the baseline/washout period for the Visit 2 evaluation. Subjects were instructed to return the completed daily diary. Visit 2 took place approximately 14 days after the Baseline/Washout Visit. Before any assessments were performed, subjects were asked to complete the abdominal and global assessments.

Subjects were instructed to return after approximately 1 week of double-blind treatment for the Visit 3 evaluation (Study Day 8). Subjects were instructed to complete the daily diary and return it to the clinic at Visit 3, along with the study drug container. Visit 3 took place after the subject had completed 1 week of double-blind treatment. Subjects were asked to fill out the abdominal and global assessments before any other assessments were performed.

Subjects were reminded that the next visit was a telephone interview that would take place approximately at the end of the second week of double-blind treatment (Visit 4; Study Day 15), and were instructed to continue dosing study drug, and return after the completion of the double-blind treatment for the End-of-Treatment evaluation (Visit 5; Study Day 29). Subjects were instructed to complete the daily diaries and return them to the clinic at Visit 5, along with the study drug containers. Visit 4 took place approximately 7 days after Visit 3, after approximately 2 weeks of double-blind treatment had been completed, and it was conducted as a telephone interview.

Visit 5 took place approximately 14 days after Visit 4, after approximately 4 weeks of double-blind treatment.

Visit 6 was a follow-up telephone interview that took place approximately 14 days after the completion of Visit 5 (Day 43).

Inclusion/Exclusion Criteria

For **inclusion criteria** in this study, the patient must:

- be a male or a non-pregnant (as per negative serum pregnancy test), non-breast-feeding female subject 18 years of age or over.
- have a history of constipation, defined as, on average, <3 SBMs per week as confirmed during the 2-week baseline/washout period.
- have 1 or more of the following symptoms relating to bowel movements for at least 6 months before the Baseline/Washout Visit:

    - very hard (little balls) and/or hard stools for at least a quarter of the bowel movements;
    - sensation of incomplete evacuation following at least a quarter of the bowel movements;
    - straining at defecation at least a quarter of the time.

- be willing and able to fill out his/her own diary and questionnaires.
- have read and understood the IRB-approved Informed Consent Form.

Exclusion criteria for this study encompassed patients who:

- had a documented mechanical obstruction (e.g., bowel obstruction due to tumor, hernia, etc.), with a megacolon/megarectum, or with a diagnosis of pseudo-obstruction.
- had known or suspected organic disorders of the large or small bowel; i.e., ulcerative colitis, Crohn's Disease, etc. Subjects under 50 years of age were to have the results of a flexible sigmoidoscopy or colonoscopy within the last 5 years. If the subject was age 50 or over, results of a barium enema with flexible sigmoidoscopy or a colonoscopy were required. Additionally, if there was evidence of weight loss, anemia, or rectal bleeding since any subject's last evaluative procedure, a flexible sigmoidoscopy with barium enema or colonoscopy was required.
- had suffered from secondary causes of constipation, was hospitalized for any gastrointestinal or abdominal surgical procedure during the 3 months before the start of the study, or ever had any bowel resection.
- had, per Investigator's discretion, clinically significant cardiovascular, liver, or lung disease, neurologic or psychiatric disorders (including active alcohol or drug abuse), other systemic disease, impaired renal function (i.e., serum creatinine concentration greater than 1.8 mg/dL) or was known to be human immunodeficiency virus positive or had acquired immune deficiency syndrome.
- had clinically significant abnormalities: hematology, urinalysis, or blood chemistry, per Investigator discretion.
- had clinically significant cancer within the last 5 years.
- was unwilling to stop administration of disallowed medications during the baseline/washout and treatment periods.
- had received antibiotic therapy during 4 weeks prior to randomization visit (Visit 2).
- was a female of childbearing potential without adequate contraceptive protection during the trial. Oral contraceptives, Depo Provera® or Norplant® must have been used for at least 3 months prior to randomization; intra uterine device, sterilization or a double barrier

method or other acceptable methods of birth control were to be used during the trial.
- had history of any medical/surgical condition that might significantly interfere with the absorption, distribution, metabolism, or excretion of the study drug.
- had received an investigational drug during the 30 days preceding the washout/baseline phase of the study.
- had demonstrated a potential for non-compliance with study protocol (i.e., dosing schedule, visit schedule, or study procedures).
- Prescription and OTC laxatives (e.g., MiraLax®, ExLax®, etc.) other than those prescribed as a rescue medication by the Investigator.
- Rescue medications were not allowed during Week 1 of the treatment period or within 48 hours of the first dose, but they were allowed during the baseline/washout period and Weeks 2, 3, and 4 of the treatment period per Investigator discretion.

Demography and Disease History

A total of 237 patients were enrolled in this study to receive either 24 mcg of RU-0211 b.i.d. or placebo b.i.d. at 20 centers in the United States. Overall, the study population was predominantly female (209 of 237 subjects, 88.2%) and Caucasian (179 of 237, 75.5%). The mean age of subjects was 45.8 years (range: 20-81 years) and most subjects (236 of 237, 99.6%) had a confirmed history of constipation.

In general, variables like age, height, gender, ethnic distribution, constipation history, history of medical procedures like flexible sigmoidoscopy, barium enema, and colonoscopy did not differ significantly ($p > 0.05$) between the two treatment groups. Forty-seven subjects (19.8%) received a flexible sigmoidoscopy before study entry, 6 subjects (2.5%) received a barium enema before study entry, and 192 subjects (81.0%) received a colonoscopy before study entry. Thirty-three subjects (13.9%) reported a history of irritable bowel syndrome (IBS): 20 placebo subjects (16.9%) and 13 RU-0211 48 µg subjects (10.9%); 68 subjects (28.7%) reported a history of gastroesophageal reflux disease (GERD): 34 placebo subjects (28.8%) and 34 RU-0211 48 µg subjects (28.6%). There were no statistically significant differences ($p < 0.05$) between the treatment groups for any constipation history category. Table 67 below graphically depicts subject demographics and disease history.

Table 67: Summary of Demographics and disease history (Intent-to-Treat Subjects)

	Placebo (N = 122)	RU-0211 48 mcg (N = 120)	Total (N = 242)	P-value
Mean Age (years)	45.4	46.2	45.8	0.6559
Mean Height (inches)	64.4	65.1	64.8	0.1548
Gender (%) Male/Female	13/105 (11.0/89.0)	15/104 (12.6/87.4)	28/209 (11.8/88.2)	0.8409
Race (%)				
Caucasian	89 (75.4)	90 (75.6)	179 (75.5)	0.6933
Black	12 (10.2)	13 (10.9)	25 (10.5)	-
Asian	1 (0.8)	4 (3.4)	5 (2.1)	-
Hispanic	14 (11.9)	11 (9.2)	25 (10.5)	-
Other	2 (1.7)	1 (0.8)	3 (1.3)	-
Constipation Hx Yes/No (%)	117/0 (99.2)	119/0 (100)	236/0 (99.6)	-
Flex. Sigmoidoscopy Yes/No (%)	27/91 (22.9/77.1)	20/99 (16.8/83.2)	47/190 (19.8/80.2)	0.2580
Barium Enema Yes/No (%)	3/115 (2.5/97.5)	3/116 (2.5/97.5)	6/231 (2.5/97.5)	1.0000
Colonoscopy Yes/No	25/93 (21.2/78.8)	20/99 (16.8/83.2)	45/192 (19.0/81.0)	0.4120
Irritable Bowel Syndrome Yes/No	20/98 (16.9/83.1)	13/106 (10.9/89.1)	33 (13.9/86.1)	0.1942
Absent	4 (3.4)	1 (0.8)	5 (2.1)	-
Mild	2 (1.7)	4 (3.4)	6 (2.5)	-
Moderate	7 (5.9)	4 (3.4)	11 (4.6)	-
Severe	5 (4.2)	4 (3.4)	9 (3.8)	-
Very Severe	2 (1.7)	0 (0.0)	2 (0.8)	-
Gastroesophageal Reflux Disease Yes/No	34/84 (28.8/71.2)	34/85 (28.6/71.4)	68/169 (28.7/71.3)	1.0000
Absent	10 (8.5)	7 (5.9)	17 (28.7)	-
Mild	12 (10.2)	15 (12.6)	27 (7.2)	-
Moderate	12 (10.2)	7 (5.9)	19 (8.0)	-
Severe	0 (0.0)	1 (0.8)	1 (0.4)	-
Very Severe	0 (0.0)	2 (1.7)	2 (0.8)	-

Reviewer's table, modified from Clinical Study Report SC0232ver4.1, Table 11-1, pages 44-45

10.1.7 Adverse Events

An adverse event (AE) was any undesirable event occurring to a subject during the clinical study, whether or not it was considered related to the study product(s). Events that were absent at baseline and developed after the initiation of double-blind treatment and events that were present at baseline and worsened after initiation of double-blind treatment were to be recorded as AEs. Events with onset within 7 days after the last day of treatment were included in the AE tabulations and analysis. Events with onset more than 7 days and within 14 days after the last day of treatment were considered as falling outside of the treatment period and were excluded from the tabulations but are included in the listings.

The Principal Investigator was required to assess the severity of the event and the relationship to study drug for all AEs, according to the criteria below.

Severity:

- **Mild:** Transient symptoms, no interference with the subject's daily activities; acceptable.
- **Moderate:** Marked symptoms, moderate interference with the subject's daily activities, but still acceptable.
- **Severe:** Considerable interference with the subject's daily activities; unacceptable.

Relationship to Study Drug:

- **Unrelated:** Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, **OR** based upon available information regarding subject history, disease process, relationship of the AE to dosing and drug pharmacology, a relationship between the study drug and the AE is unlikely.
- **Possible:** The AE follows a reasonable sequence from the time of study drug administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- **Probable:** The AE follows a reasonable sequence from the time of study drug administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the study drug, and the suspect drug is the most likely of all causes.
- **Definite:** The AE follows a reasonable sequence from the time of study drug administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the drug, and no other reasonable cause exists.

A serious adverse event (SAE) was any experience that suggested a medical hazard, including any event that:

- was fatal;
- was life-threatening (an event in which the subject was at risk of death at the time of the event; it did not refer to an event that might have caused death had it been more severe);
- required hospitalization or prolonged the existing hospitalization;
- resulted in persistent or significant disability/incapacity;
- was a congenital anomaly; or
- was an important medical event (an event that may not fit the other criteria for an SAE listed above, but based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes listed above).

All SAEs that occurred on or after the day of the first dose of study drug until 7 days after the final dosing with double-blind study drug were to be reported immediately to PRA International.

The original terms used in the case report form by investigators to identify AEs were coded to MedDRA preferred terms. Any verbatim AE that could not be coded was assigned "UNCODED" as the body system and the verbatim AE was used as the preferred term, so that these AEs could be included in the summary tables. The incidence of an AE was defined as the number of subjects who experienced at least 1 episode during the study. AEs with onset dates before randomization or more than 7 days after the last day of treatment were considered as falling outside of the treatment period, and were excluded from the summaries. Events with completely or partially missing onset dates were included in the tabulations, unless the partial date information available clearly indicated that the event happened out of the treatment period.

Study SC0232

Of the 237 subjects in Study SC0232, 106 (44.7%) experienced at least one adverse event during the course of the study. Of these subjects, 41 were in the placebo group and 65 were in the RU-0211 48 µg group. This difference was statistically significant (p=0.0026).

Seventy subjects overall (29.5%) reported at least 1 treatment-related AE; of these subjects, 19 were in the placebo group and 51 were in the RU-0211 48 µg group. These treatment-related adverse event difference were also statistically significant (p=0.0001).

Sixteen subjects (6.8%) withdrew from the study because of an AE. Of those subjects who withdrew, one was in the placebo group and 15 were in the RU-0211 48 mcg group. This was statistically significant (p = 0.0003).

No subjects died during this study.

Overall, 16 subjects (1 placebo; 15 RU-0211 48 mcg) experienced a total of 42 AEs for which the study drug was permanently discontinued. Upper abdominal pain caused 1 placebo subject to discontinue the study. Adverse events that led to permanent drug discontinuation in the RU-0211 group were reported generally sporadic with most being reported by only 1 or 2 subjects.

The exceptions were nausea (6 RU-0211 48 mcg subjects, 6 events), dyspnea NOS (4 RU-0211 48 mcg subjects, 5 events), and abdominal pain NOS (3 RU-0211 48 mcg subjects, 3 events).

The most common body system for AEs was gastrointestinal disorders (overall 69 subjects, 29.1%); no other body system had AEs reported for more than 10% of subjects. Of the 69 subjects reporting AEs in the gastrointestinal body system, 22 were placebo subjects and 47 were RU-0211 48 μg subjects. This difference was statistically significant (p=0.0006). There were no statistically significant differences between the treatment groups for the number of subjects reporting AEs in any other body system.

The overall frequency of most AEs was low and the frequencies across treatment groups for most AEs were similar. The only AEs reported by at least 5% of subjects overall were nausea (37 subjects, 15.6%) and headache not otherwise specified (13 subjects, 5.5%). The frequency of nausea was higher among the RU-0211 compared to placebo (24.4 % versus 6.8%) respectively, and the frequency of headache NOS was similar in both groups (4.2% for placebo and 6.7% for RU-0211 48 mcg).

Fourteen subjects (5.9%) had at least 1 severe AE and no severe AE was reported by more that 2 subjects overall. The frequencies of severe AEs were similar in both treatment groups.

There were no clinically significant trends in the assessment of laboratory values, vital signs, or physical examination, nor were there any statistically significant differences between the treatment groups for any laboratory or vital sign value.

10.1.8 Withdrawals, Compliance, and Protocol Violations

Subject Disposition/Withdrawals

A total of 237 patients were randomized into the study: 118 subjects into the placebo group and 119 subjects into the 48 mcg RU-0211 group. Two subjects (0512 and 0609) in the placebo group were randomized but not treated, making a total of 122 subjects who were treated with the placebo and 120 subjects treated with RU-0211. A total of 206 subjects completed the study. The percentage of subjects completing the study in the placebo group was 90.7% and was 83.2% in the 48 mcg RU-0211 group. The mean number of days the subjects were on the study drug was 28.1 in the placebo group and 25.4 in the RU-0211 group. A total of 31 subjects (13.1%; 20 RU-0211; 11 placebos) discontinued the study. The most common reasons for discontinuation were AE (16 subjects, 6.8%), lack of efficacy (7 subjects, 3.0%), and lost to follow-up (5 subjects, 2.1%). Subjects in the RU-0211 48 μg discontinued more frequently (16.8% of subjects) than placebo subjects (9.3%). Nineteen of 20 RU-0211 48 μg subjects who discontinued did so because of AEs (15 subjects) or being lost to follow-up (4 subjects); the most common reason for placebo subjects discontinuing was lack of efficacy (6 of 11 subjects). Overall, the frequency of early discontinuation was highest during Week 1 (5.5%) and decreased in subsequent weeks: 3.8% in Week 2; 1.7% in Week 3; 1.3% in Week 4; and no subjects after Week 4. In general, subjects in the RU-0211 48 μg group appeared more likely to discontinue

during Weeks 1 and 2, while placebo subjects discontinued more frequently during Weeks 3 and 4.

Table 68: Summary of Subject Disposition: All Randomized Subjects

Variable	Placebo N = 118 n (%)	RU-0211 48 mcg N = 119 n (%)	Total N = 237 n (%)
Subjects Treated	118 (100.0)	119 (100.0)	237 (100.0)
Subjects Completed	107 (90.7)	99 (83.2)	206 (86.9)
Subjects Discontinued	11 (9.3)	20 (16.8)	31 (13.1)
Reason for Discontinuation			
Adverse Event	1 (0.8)	15 (12.6)	16 (6.8)
Protocol Violation	0 (0.0)	0 (0.0)	0 (0.0)
Subject Voluntary Withdrawal	1 (0.8)	0 (0.0)	1 (0.4)
Lack of Efficacy	6 (5.1)	1 (0.8)	7 (3.0)
Lost to Follow-up	1 (0.8)	4 (3.4)	5 (2.1)
Other	2 (1.7)	0 (0.0)	2 (0.8)
Timing of Early Discontinuation			
Week 1	2 (1.7)	11 (9.2)	13 (5.5)
Week 2	2 (1.7)	7 (5.9)	9 (3.8)
Week 3	3 (2.5)	1 (0.8)	4 (1.7)
Week 4	3 (2.5)	0 (0.0)	3 (1.3)
After Week 4	0 (0.0)	0 (0.0)	0 (0.0)
Number of Days on Study Drug (mean)	28.1 (4.78)	25.4 (8.65)	26.8 (7.12)

Reviewer's table, modified from Clinical Study Report SC0232ver4.1, Table 14.1.2, pages 85

Compliance

Treatment compliance was estimated by using the study drug administration record in the subject's daily diary. Percent compliance was assessed by the actual cumulative exposure (in capsules) divided by the exposure the subject should have received based on the number of days the subject was under double-blind medication [i.e., (number of days of double-blind treatment) x 2]. Study medication was dispensed at Visit 2; unused study medication was collected, counted, and verified at Visit 5 in order to provide drug accountability. Mean compliance was 94.1%, and median compliance was 96.7%. Both mean and median compliance were slightly higher among placebo subjects than among RU-0211 subjects (mean: 95.5% vs. 92.6%; median: 98.2% vs. 96.7%). Of the 233 subjects for whom treatment compliance data were available, 224 were at least 70% compliant and 9 were less than 70% compliant. Of the 9 subjects who were less than 70% compliant, 7 were RU-0211 48 mcg subjects and 2 were placebo subjects.

Protocol Deviations

Intent-to-treat subjects with protocol violations were summarized by treatment group, study week, and type of violation. The following criteria were used to determine protocol violations after database freeze and before database lock and un-blinding. Subjects who violated any of these criteria were considered protocol violators for the applicable weeks and were removed from the per-protocol subset at these weeks.

- Any subject who took at least 1 of the prohibited concomitant medications listed in the protocol (laxatives, e.g., MiraLax®, ExLax®, etc.), that was not prescribed as a rescue medication by the Investigator, was a protocol violator during the week(s) in which the medication was taken.
- A subject who was mis-randomized by being assigned an incorrect subject number and/or box of study medication.
- A subject who took rescue medications (e.g., Dulcolax® suppository, a Fleet® enema) during Week 1 of the treatment period was considered a protocol violator for Week 1.
- A subject who took fewer than 70% of the required double-blind doses for a given week was considered a protocol violator for that week.
- Any subject who took rescue medication prior to 72 hours since the last SBM was considered a protocol violator for the week during which the medication was taken and for the following week if the medication was taken within 24 hours of the start of the following week.
- A subject with any other clear violation of inclusion/exclusion criteria who was mistakenly enrolled into the study.

Overall, the most common protocol deviations noted in each double-blind treatment week were use of prohibited concomitant medication and study drug compliance that was < 70%.

- Prohibited concomitant medication use was generally similar for both treatment groups throughout all four weeks.
- Subjects in the RU-0211 48 mcg group were more likely than placebo subjects to have study drug compliance < 70% during Weeks 1, 2, and 4, whereas the proportion of placebo subjects was higher during Week 3. Thirteen (10.9%) of RU-0211 subjects had < 70% compliance versus 4 (3.4%) subjects in the placebo group at Week 1. Similarly, 13 (10.9%) versus 6 (5.1%) at Week 2, 3 (2.5%) versus 6 (5.1%) at Week 3, and 7 (5.9%) versus 3 (2.5%).

10.1.9 Efficacy Results

Responder analysis:

In order to assess treatment response and to account for study dropout and rescue medication use, a trichotomous responder analysis was performed for each week. Responders and non-responders are defined below. The number and percent of non-responders, moderate responders, and full responders were summarized by treatment group at each week. A van Elteren test stratified by pooled center was used to analyze the responder rates at each week.

A **responder** was defined as any subject with an SBM frequency rate of $\geq$ 3 for a given week, who did not use rescue medication during or within 24 hours prior to the given week, and who did not drop out during or prior to the given week due to lack of efficacy.

A **full responder** was a subject with an SBM frequency of $\geq$ 4 per week.

A **moderate responder** was a subject with an SBM frequency rate $\geq$ 3 but $<$ 4.

A **non-responder** was defined as any subject with an SBM frequency rate of $<$ 3 for a given week, any subject who dropped out during or prior to the given week due to lack of efficacy, or any subject who used rescue medication during or within 24 hours prior to the given week.

Primary Efficacy Endpoint

The primary efficacy analysis was on the SBM frequency during Week 1. A spontaneous bowel movement (SBM) was defined as any bowel movement that did not occur within 24 hours after rescue medication use. In order to adjust for early withdrawals, weekly SBM frequency rates were calculated as follows:

[Number of SBMs / Number of days (based on 24-hour periods)] x 7

where the number of days was the number of days during the week that the subject was in the study. Weeks were calculated as 168-hour intervals starting with the exact time of the first intake of study drug. The number of days was generally 7 unless a subject dropped out during a treatment week. If the number of days during Week 1 was less than 4, then the rate was considered missing because of insufficient data.

For statistical analysis, 4 populations were derived: Intent to treat (ITT) subjects with last-observation-carried-forward (LOCF), ITT subjects, ITT subjects who were completers, and per protocol (PP) subjects.

Overall, the mean baseline number of SBMs per week was 1.4, the mean baseline average stool consistency was 2.7, the mean baseline average degree of straining was 2.4, the mean baseline severity of constipation was 3.0, mean baseline abdominal bloating was 2.2, and mean baseline abdominal discomfort was 1.9. Placebo subjects and RU-0211 48 mcg subjects were generally similar in the assessments of baseline constipation status, although there was a

statistically significant difference between the groups in mean baseline number of SBMs (1.52 for placebo, 1.28 for RU-0211 48 mcg; p=0.0126).

At Week 1, the mean SBM frequency rates in the placebo and RU-0211 48 mcg groups were 3.99 and 5.89, respectively; the corresponding median values were 3.5 and 5.0. The difference between the groups was statistically significant (p<0.0001), indicating that subjects treated with RU-0211 48 mcg experienced better constipation relief during their first week of treatment than did placebo subjects, despite the fact that RU-02211 48 mcg subjects were significantly more constipated at baseline. Additionally, the test for overall treatment effect revealed a statistically significant difference (p<0.0001) in favor of treatment with RU-0211 48 mcg.

Table 69: Summary of Spontaneous Bowel Movement Frequency Rates[1] for Intent-to Treat (ITT) Subjects with Last-Observation-Carried-Forward (LOCF)

Week	Placebo (N=118)	RU-0211 48 mcg (N=119)	P-Value[2]	Overall P-Value[3]
Baseline				
Mean (Std. Dev.)	1.52 (0.801)	1.28 (0.881)	0.0126	
Week 1				
Mean (Std. Dev.)	**3.99** (2.706)	**5.89** (4.022)	**<0.0001**	**<0.0001**
Week 2				
Mean (Std. Dev.)	3.55 (2.670)	4.96 (4.208)	0.0487	
Week 3				
Mean (Std. Dev.)	3.36 (2.755)	5.56 (4.560)	0.0004	
Week 4				
Mean (Std. Dev.)	3.46 (2.861)	5.37 (4.804)	0.0068	

1 SBM Frequency Rate: (Number of SBMs/Number of days) x 7.
2 P-values are based on van Elteren tests adjusted for pooled center.
3 Overall p-value is based on the final mixed model testing for overall treatment effect.
Reviewer's table, modified from Clinical Study Report SC0232ver2.3, Table 11.3, page 49

As noted below in Table 70, SBM frequency rate results were similar for ITT subjects without LOCF, ITT subjects who completed the study, and PP subjects as they were for intent-to-treat subjects with the last-observation-carried-forward population.

Table 70: Spontaneous Bowel Movement Frequency During Week 1[1] for all Populations

Population	Placebo	48 mcg RU-0211	P-Value[2]	Overall P-value[3]
Group	Mean (Std. Dev.)	Mean (Std. Dev.)	Week 1	Week 1
ITT Subjects with LOCF	3.99 (2.706)	5.89 (4.022)	<0.0001	<0.0001
ITT Subjects without LOCF	3.99 (2.706)	5.89 (4.022)	<0.0001	<0.0001
ITT Subjects – completers	4.05 (2.661)	5.78 (3.669)	0.0003	<0.0001
Per Protocol Subjects	4.05 (2.684)	6.07 (4.059)	0.0002	<0.0001

1 SBM Frequency Rate: (Number of SBMs/Number of days) x 7.
2 P-values are based on van Elteren tests adjusted for pooled center.
3 Overall p-value is based on the final mixed model testing for overall treatment effect.
Reviewer's table, modified from Clinical Study Report SC0232ver2.3, Table 11.4, page 51

Secondary Efficacy Analyses:

At all post-baseline evaluation time points, the mean and median SBM frequency rates in the RU-0211 48 mcg group were higher than the corresponding rates in the placebo group. This difference was statistically significant for each individual week. At Week 2, the mean SBM frequency rate in the placebo group was 3.55, and the mean SBM frequency rate in the RU-0211 48 mcg group was 4.96 (p=0.0487); at Week 3 the values were 3.36 and 5.56 (p=0.0004), and at Week 4, the values were 3.46 and 5.37 (p=0.0068). At each of Weeks 2, 3, and 4, the median SBM frequency rates in the placebo group was 3.0; in the RU-0211 48 mcg group, the median rates were 4.0, 5.0, and 4.3, respectively. Similar results were also observed for ITT subjects without LOCF, ITT subjects who completed the study, and PP subjects

Table 71: Spontaneous Bowel Movement Frequency During Week 2, Week 3, and Week 4[1]

Week	Group	ITT with LOCF	ITT without LOCF	ITT Completers	Per protocol Subjects
		Mean ± Std. Dev.			
Week 2	Placebo	3.55 (2.670)	3.56 (2.659)	3.65 (2.678)	3.68 (2.676)
	RU-0211	4.96 (4.208)	4.98 (4.224)	4.93 (4.003)	4.97 (4.028)
	P-value[2]	**0.0487**	**0.0559**	**0.1227**	**0.1219**
Week 3	Placebo	3.36 (2.755)	3.38 (2.767)	3.48 (2.774)	3.45 (2.781)
	RU-0211	5.56 (4.560)	5.54 (4.428)	5.60 (4.415)	5.55 (4.400)
	P-value[2]	**0.0004**	**0.0011**	**0.0014**	**0.0012**
Week 4	Placebo	3.46 (2.861)	3.61 (2.881)	3.63 (2.889)	3.62 (2.900)
	RU-0211	5.37 (4.804)	5.39 (4.698)	5.39 (4.698)	5.41 (4.618)
	P-value[2]	**0.0068**	**0.0368**	**0.0411**	**0.0246**

1 SBM Frequency Rate: (Number of SBMs/Number of days) x 7.
2 P-values are based on van Elteren tests adjusted for pooled center.
Reviewer's table, modified from Clinical Study Report SC0232ver2.3, Table 11.4, page 51

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Table 72: Change From Baseline in Spontaneous Bowel Movement and Bowel Movement Frequency Rates* During Week 1, Week 2, Week 3, and Week 4

Week	Group	ITT with LOCF	ITT without LOCF	ITT Completers	Per protocol Subjects
		Mean ± Std. Dev.			
Week 1	Placebo+	2.47 (2.609)	2.47 (2.609)	2.53 (2.605)	2.49 (2.603)
	RU-0211+	4.64 (4.079)	4.64 (4.079)	4.53 (3.704)	4.84 (4.197)
Week 2	Placebo+	2.04 (2.551)	2.05 (2.556)	2.14 (2.585)	2.16 (2.590)
	RU-0211+	3.69 (4.239)	3.70 (4.258)	3.67 (4.023)	3.76 (4.022)
Week 3	Placebo+	1.85 (2.642)	1.87 (2.670)	1.97 (2.668)	1.95 (2.678)
	RU-0211+	4.27 (4.609)	4.28 (4.452)	4.32 (4.454)	4.28 (4.457)
Week 4	Placebo+	1.94 (2.702)	2.09 (2.737)	2.10 (2.747)	2.09 (2.759)
	RU-0211+	4.09 (4.844)	4.12 (4.728)	4.12 (4.728)	4.19 (4.693)
		Median (Min, Max)			
Week 1	Placebo+	1.5 (-5.5, 9.5)	1.5 (-1.5, 10.5)	1.5 (-1.5, 10.5)	1.5 (-1.5, 10.5)
	RU-0211+	3.8 (-2.0, 25.0)	3.8 (-2.0, 25.0)	4.0 (-2.0, 17.0)	4.0 (-2.0, 25.0)
Week 2	Placebo+	1.5 (-1.6,12.5)	1.5 (-1.6, 12.5)	1.5 (-1.6, 12.5)	2.0 (-1.6, 12.5)
	RU-0211+	2.8 (-2.2, 21.0)	2.9 (-2.2, 21.0)	3.0 (-2.2, 18.5)	3.0 (-2.0, 18.5)
Week 3	Placebo+	1.5 (-2.5, 17.5)	1.5 (-2.5, 15.5)	1.5 (-2.5, 15.5)	1.5 (-2.5,15.5)
	RU-0211+	3.1 (-2.7, 21.0)	3.5 (-2.7, 20.5)	3.5 (-2.7, 20.5)	3.2 (-2.7, 20.5)
Week 4	Placebo+	1.5 (-2.5, 17.5)	1.5 (-2.0, 17.5)	1.5 (-2.0, 17.5)	1.5 (-2.0,17.5)
	RU-0211+	3.0 (-2.0, 25.5)	3.0 (-2.0, 25.5)	3.0 (-2.0, 25.5)	3.0 (-2.0, 25.5)

* BM (SBM) Frequency Rate: (Number of BMs (SBMs) / Number of days) x 7.
+**p<0.0001** for all 4 populations compared to the respective placebo group data (Wilcoxon signed-rank test)
Reviewer's table, modified from Clinical Study Report SC0232ver2.3, Table 14.2.3.1, pages 175 - 182

Compared to the respective baseline values, frequencies of SBMs and BMs were significantly increased ($p<0.0001$) at all time points in the placebo and RU-0211 treated groups. The increase in frequency of SBMs and BMs was consistently higher in the RU-0211 than in the placebo treated group. These analyses suggest that, compared to baseline, the 48 mcg dose of RU-0211 demonstrates efficacy by week one with sustained improvement in SBM and BM frequencies in subjects with constipation throughout the duration of the four week trial.

As shown below in Table 73, the ITT without LOCF population, 31.4% of the subjects in the placebo group and 66.9% of the subjects in the RU-0211 group had a SBM during the 24 hours since the first intake of study drug. In the per protocol (PP) population, as shown in Table 74, 28.8% of the subjects in the placebo group and 61.1% of the subjects in the RU-0211 group had a SBM during the 24 since the first intake of study drug. It is unclear to the reviewer why there was such a large placebo effect for SBM in the first 24 hours. The difference in SBM occurrence during the 24 hours after the first study drug administration between the treatment groups and two populations was statistically significant ($p<0.0001$) and ($p=0.0002$), respectively.

Table 73: Summary of Subjects with SBMs within 24hrs after First Study Drug Administration ITT without LOCF:

SBM Within 24 Hours	Placebo (N = 118)	RU-0211 48 mcg (N = 119)	P-value*
Yes (%)	37 (31.4)	73 (61.3)	<0.0001
No (%)	79 (66.9)	43 (36.1)	

*P-value is based on a Cochran-Mantel-Haenszel (CMH) test for general association controlling for pooled center
Reviewer's table, modified from Clinical Study Report SC0232ver2.3, Table 14.2.5.1, page 191

Table 74: Summary of Subjects with SBMs within 24hrs after First Study Drug Administration Per Protocol:

SBM Within 24 Hours	Placebo (N = 118)	RU-0211 48 mcg (N = 119)	P-value*
Yes (%)	34 (28.8)	60 (50.4)	0.0002
No (%)	72 (61.0)	39 (32.8)	

*P-value is based on a Cochran-Mantel-Haenszel (CMH) test for general association controlling for pooled center
Reviewer's table, modified from Clinical Study Report SC0232ver2.3, Table 14.2.5.1, page 192

Time to First Spontaneous Bowel Movement

Time-to-event analysis was used to evaluate between treatment group differences in time to first SBM. Data from subjects who used rescue medication or who dropped out of the study before the first SBM were censored at the time of rescue medication use or early termination. Cox proportional hazards regression was used in this analysis. Pooled center and treatment were considered and tested at an alpha level of 0.10 in the saturated model. The number of hours since the most recent BM prior to the start of study drug was used as a covariate. The reverse stepwise modeling process eliminated pooled center at the first step. Figure 11 presents graphically with Kaplan-Meier curves, the cumulative probability comparison between treatment groups for the ITT population without LOCF. Figure 12 presents a similar display for the PP population.

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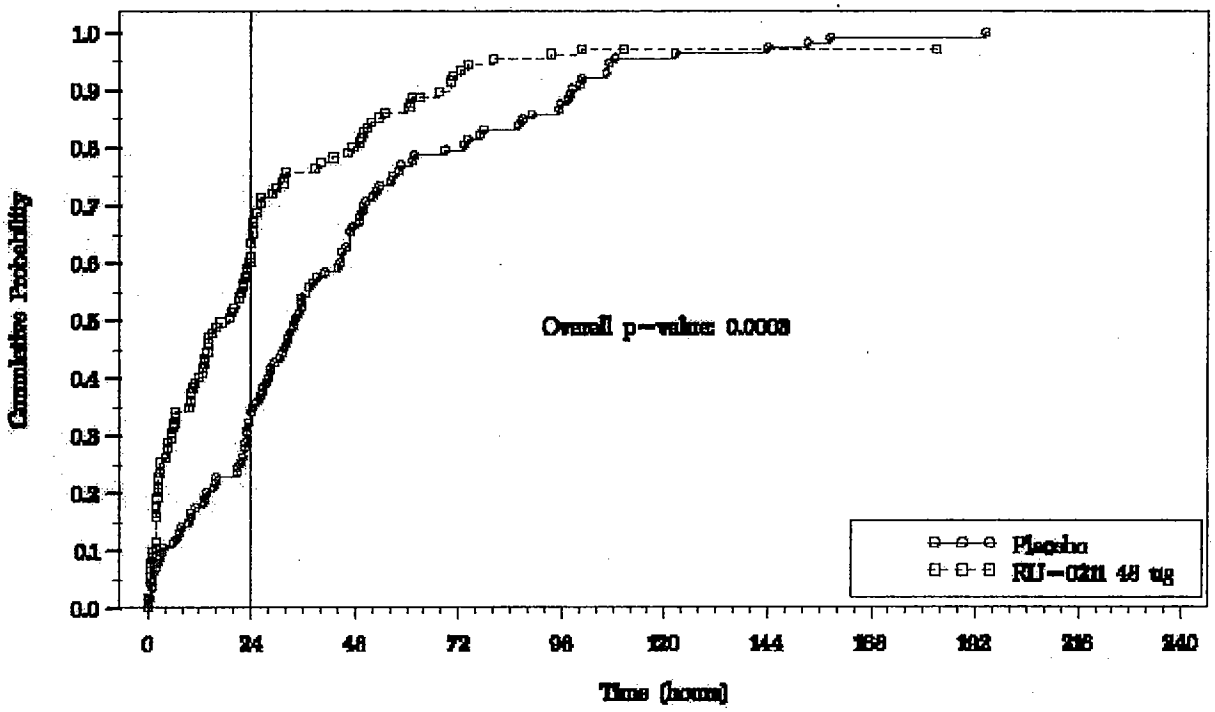
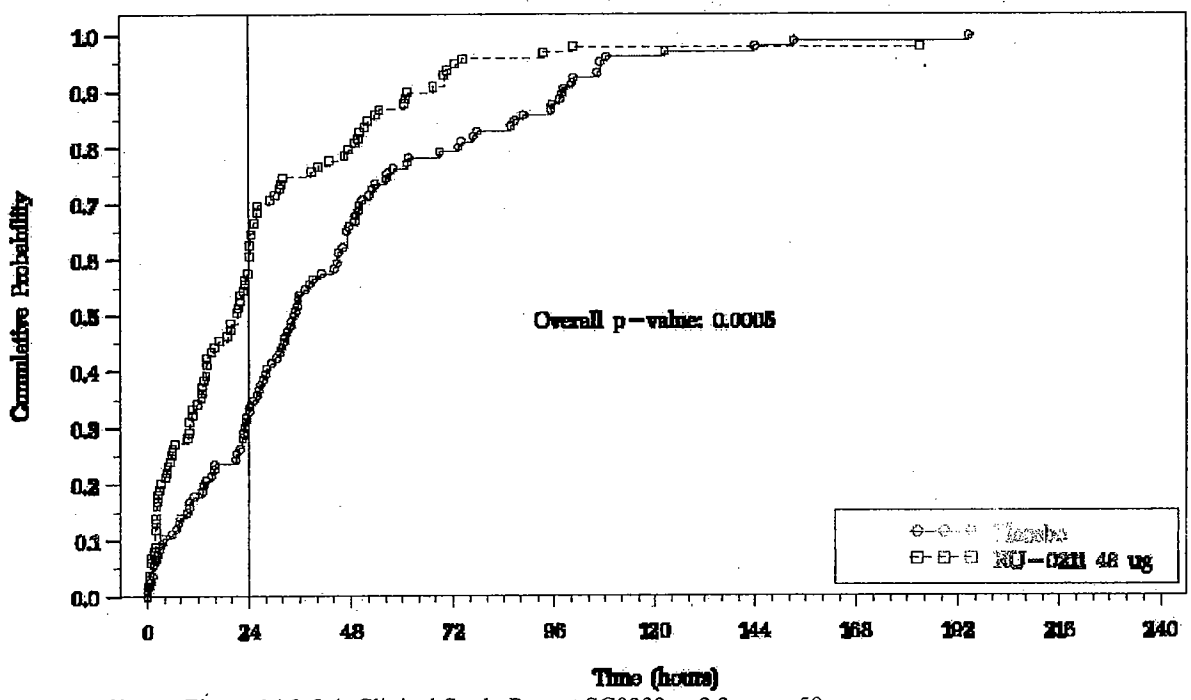
Figure 11: Kaplan-Meier Curve for Time to First SBM (Intent-to-Treat Subjects without LOCF



Sponsor's Figure, Figure 14.2.5.3, Clinical Study Report SC0232ver2.3, page 57

APPEARS THIS WAY
ON ORIGINAL

Figure 12: Kaplan-Meier Curve for Time to First SBM: Per Protocol Subjects



Sponsor's Figure, Figure 14.2.5.4, Clinical Study Report SC0232ver2.3, page 59

For both populations, adjusting for the time since the last BM before dosing, the time to first SBM was significantly shorter for RU-0211 48 mcg subjects (p=0.0003 for ITT subjects without LOCF; p=0.0005 for PP subjects). This suggests an early onset of beneficial effects of RU-0211 in subjects with constipation. In both figures, the line denoting the 24-hour mark is only to illustrate that mark as a point of interest, and is not to be construed as being related to the Cox proportional hazard p-value. This analysis confirms the findings of the primary efficacy variable in this study.

Average Stool Consistency

Stool consistency was recorded by each subject in a daily diary after each bowel movement, and was scored as Very Loose (0), Loose (1), Normal (2), Hard (3) or Very Hard (4). The average was calculated by summing the scores for the week and dividing by the number of SBMs in that week. The average stool consistency at Week 1, Week 2, Week 3, and Week 4 was analyzed by van Elteren's test stratified by pooled center. If there were no SBMs during the week or if there were SBMs but all ratings were missing, then the LOCF method imputed the average.

For ITT subjects with LOCF, mean baseline stool consistency was similar in both treatment groups (2.78 for placebo; 2.69 for RU-0211 48 mcg). At all post-baseline evaluation time points, the mean stool consistency reported in the RU-0211 48 mcg group (range: 1.74-1.83) was lower than that in the placebo group (2.45-2.55). The difference between the two groups was statistically significant at all time points (p<0.0001). The lower mean stool consistency represents an overall softening of the stool in subjects taking RU-0211. Similar results of

statistical significance were observed for the mean average degree of stool consistency among the ITT subjects without LOCF, the ITT subjects who completed the study, and the PP subjects.

Average Degree of Straining

The degree of straining was recorded in the daily diary after each bowel movement, and it was scored as Absent (0), Mild (1), Moderate (2), Severe (3), or Very Severe (4). The average was calculated by summing the scores for the week and dividing by the number of SBMs in that week. The average straining at Week 1, Week 2, Week 3, and Week 4 was analyzed by van Elteren's test stratified by center. If there were no SBMs during the week, or if there were SBMs but all ratings were missing, the LOCF method imputed the average.

For ITT subjects with LOCF, the mean average degree of straining at baseline was similar in both treatment groups (2.36 for placebo; 2.34 for RU-0211 48 mcg). At all post-baseline evaluation time points, the mean weekly degree of straining reported in the RU-0211 48 mcg group (range: 1.33-1.48) was lower than that in the placebo group (1.79-1.96). The difference was statistically significant at all time points ($p<0.002$). Similar results for the mean average degree of straining were observed for ITT subjects without LOCF, ITT subjects who completed the study, and PP subjects. Notable differences were observed at Week 3: for ITT subjects without LOCF, the mean average degree of straining was 1.79 for placebo subjects and 1.43 for RU-0211 48 mcg subjects ($p=0.0529$); and for ITT subjects who completed the study, the mean values were 1.76 and 1.43 ($p=0.0673$).

In general, despite the aforementioned differences noted at Week 3 which were non-significant yet showed a positive trend, the secondary efficacy analysis indicate that RU-0211 treatment consistently decreases the straining in subjects with constipation.

Average Degree of Severity of Constipation

For all randomized subjects, severity of constipation was recorded using a 5-point scale, Absent (0), Mild (1), Moderate (2), Severe (3), Very Severe (4) at baseline, and Week 1 through Week 6 (Follow-up). The severity of constipation was analyzed by the van Elteren's test, stratified by pooled center, at Week 1, Week 2, Week 3, and Week 4, and follow-up. The Wilcoxon signed-rank test was used for analysis of the change from baseline, for each treatment group at the end of each week and follow-up.

For ITT subjects with LOCF, mean baseline constipation severity was similar in both treatment groups (2.99 for placebo; 3.00 for RU-0211 48 mcg). At all post-baseline evaluation time points including follow-up, the mean stool consistency reported in the RU-0211 48 mcg group (range: 1.64-2.21) was lower than that in the placebo group (1.99-2.31), and the difference was statistically significant at Week 1 ($p=0.0061$), Week 2 ($p=0.0243$), Week 3 ($p=0.0265$), and Week 4 ($p=0.0022$). At the follow-up visit, the mean severity of constipation among placebo subjects was 2.26, and the mean severity among RU-0211 48 mcg subjects was 2.21 ($p=0.7858$). Generally similar results for the mean average severity of constipation were observed for ITT subjects without LOCF, ITT subjects who completed the study, and PP subjects. One notable difference was at Week 2 for the ITT subject population who completed the study. At this time

point, the mean average severity of constipation was 1.95 for placebo subjects and 1.63 for RU-0211 48 mcg subjects. Although this result was not statistically significant (p=0.0544), it still trended in favor of RU-0211.

Global Assessment of Treatment Effectiveness

Global assessment of treatment effectiveness for all randomized subjects was recorded using a 5-point scale, Not At All Effective (0), A Little Bit Effective (1), Moderately Effective (2), Quite a Bit Effective (3), Extremely Effective (4) at Week 1, Week 2, Week 3, Week 4, and at the Follow-up Visit. For ITT subjects with LOCF, at all post-baseline evaluation time points, including follow-up, the mean treatment effectiveness was higher in the RU-0211 48 mcg group than in the placebo group. In the placebo group, mean effectiveness remained more or less constant over Weeks 1-4 (range: 1.17-1.22) and increased slightly at follow-up (1.44). In the RU -0211 48 mcg group, mean effectiveness was 1.88 at Week 1, 1.95 at Week 2, 1.86 at Week 3, 1.97 at Week 4, and 2.14 at follow-up. At all time points, the difference in mean effectiveness between the treatment groups was statistically significant ($p<0.0005$). Similar results were observed for ITT subjects without LOCF, ITT subjects who completed the study, and PP subjects. This analysis indicates subjects with constipation consistently had better global assessment of treatment effectiveness for RU-0211 treatment.

Abdominal Symptoms (Bloating and Discomfort)

At Week 1, Week 2, Week 3, Week 4, and at the Follow-up Visit, all randomized subjects rated their abdominal bloating and discomfort upon waking during the week, using a 5 point scale, Absent (0), Mild (1), Moderate (2), Severe (3), and Very Severe (4).

For ITT subjects with LOCF, mean baseline abdominal bloating was similar in both treatment groups (2.18 for placebo; 2.25 for RU-0211 48 mcg). At all post-baseline evaluation time points including follow-up, the mean level of abdominal bloating reported in the RU-0211 48 mcg group (range: 1.39-1.59) was lower than that in the placebo group (1.49-1.71), but the difference was statistically significant only at Week 1 ($p=0.0380$); no other results approached statistical significance. Similar results were generally observed for ITT subjects without LOCF, ITT subjects who completed the study, and PP subjects. Of note, there were no significant differences at any time point for ITT subjects who completed the study.

Compared with baseline, mean weekly abdominal bloating assessments were decreased at all post-baseline evaluation time points for subjects in both treatment groups. In both treatment groups, all observed mean changes from baseline were statistically different from zero ($p<0.0001$ for placebo and RU-0211 48 mcg subjects). In all cases, the mean decreases observed among RU-0211 48 mcg subjects were larger than those observed among placebo subjects. Similar results were observed for ITT subjects without LOCF, ITT subjects who completed the study, and PP subjects.

For ITT subjects with LOCF, mean baseline abdominal discomfort was similar in both treatment groups (1.84 for placebo; 1.88 for RU-0211 48 mcg). At most post-baseline evaluation time points including follow-up, the mean level of abdominal discomfort reported in the RU-0211 48

mcg group (range: 1.16-1.36) was lower than that in the placebo group (1.14-1.47), however the difference was not statistically significant at any time point. Similar results were observed for ITT subjects without LOCF, ITT subjects who completed the study, and PP subjects.

Compared with baseline, mean weekly abdominal assessments were decreased at all post-baseline evaluation time points for subjects in both treatment groups. In each case, all observed mean changes from baseline were statistically different from zero ($p \leq 0.0009$ in all cases for placebo subjects; $p<0.0001$ for RU-0211 48 mcg subjects). In all cases, the mean decreases observed among RU-0211 48 mcg subjects were larger than those observed among placebo subjects. Similar results were observed for ITT subjects without LOCF, ITT subjects who completed the study, and PP subjects.

While statistical significance varied between populations, the RU-0211 data exhibited a positive trend in relieving abdominal bloating and discomfort in subjects with constipation.

Use of Rescue Medication

Of the 237 participating subjects, over the 4 weeks of the study, 5.5% to 49.8% took rescue medication. In the placebo group, 44.9%, 5.9%, 24.1%, 28.9%, and 22.0% of subjects used rescue medication at baseline, Week 1, Week 2, Week 3, and Week 4, respectively. In the RU-0211 group, 54.6%, 5.0%, 18.5%, 18.8%, and 17.7% of subjects used rescue medication during the same weeks. Except at baseline, the percent of subjects using rescue medication was always lower in the RU-0211 group. The van Elteren test was employed to determine the cumulative use and exposure to rescue medication over time. In both treatment groups and overall, the use of rescue medications was lowest during Week 1 (5.5% overall; per protocol, rescue medications were not to be taken during Week 1) and increased at Week 2 (21.4% overall) and Week 3 (24.2% overall) before decreasing slightly during Week 4 (20.0% overall). At all post-baseline evaluation time points, rescue medication use was higher among placebo subjects; however, this difference did not reach statistical significance at any time point ($p \geq 0.0966$).

10.1.10 Reviewer's summary and comments on study SC0232

The total number of subjects enrolled in this study (n = 237) was adequate for evaluation. No significant difference ($p > 0.05$) was seen among the two treatment groups with respect to demographics (age, height, gender, race, history of constipation, history of medical procedures, history of Irritable Bowel Syndrome, or history of Gastroesophageal Reflux Disease).

The primary efficacy analysis was based on the SBM frequency during Week 1. Study SC0232 demonstrated a statistically significant difference between the placebo group and the RU-0211 treatment group in SBM frequency during Week 1. The overall mean SBM frequency rates were significantly higher ($p \leq 0.0001$) in the 48 mcg RU-0211 group in all 4 patient populations during the first week of treatment compared to the placebo group.

Results of the secondary efficacy analyses also revealed statistical significance in favor of RU-0211. Significant improvements for RU-0211 48 mcg subjects over placebo subjects were

observed in the following efficacy variables: frequency of SBMs at Weeks 2, 3, and 4; the proportion of full responders at all post-baseline time points, the percentage of subjects with an SBM within 24 hours after taking the first dose of study drug, the time to first SBM, and overall effectiveness of the treatment.

Overall, 106 subjects (44.7%) reported at least one adverse event during the study. Of these subjects, 41 (34.7%) were in the placebo group, and 65 (54.6%) were in the RU-0211 48 mcg group. This difference between the RU-0211 group and placebo group was statistically significant (p=0.0026). Seventy subjects overall (29.5%) reported at least one treatment-related AE; of these subjects, 19 (16.1%) were in the placebo group and 51 (42.9%) were in the RU-0211 48 mcg group. This difference was statistically significant (p=0.0001).

A total of 14 subjects (5.9 %) had AEs that were considered as severe, 6 (5.1%) were in the placebo group and 8 (6.7%) were in the RU-0211 group. This was not found to be statistically significant, (p = 0.7841).

The most frequent severe AEs, at the Systems Order Class (SOC) level were gastrointestinal disorders (overall 69 subjects, 29.1%). No other body system had AEs reported for more than 10% of subjects. Of the 69 subjects reporting AEs in the gastrointestinal body system, 22 were placebo subjects and 47 were RU-0211 48 mcg subjects. This difference was statistically significant (p = 0.0006). Most notably, statistical significance was demonstrated in the frequency of nausea (6.8% for placebo, 24.4% for RU-0211 48 mcg), diarrhea (0.8% vs. 4.2%), and dyspepsia (2.5% vs. 5.0%). There were no statistically significant differences between the treatment groups for the number of subjects reporting AEs in any other body system.

In terms of severity of AEs, 16 subjects (1 placebo; 15 RU-0211 48 mcg) experienced a total of 42 AEs for which the study drug was permanently discontinued. Thirty-two of the 42 AEs were considered treatment-related by the Investigator. Upper abdominal pain caused 1 placebo subject to discontinue the study. For subjects in the RU-0211 48 mcg group, the AEs that led to permanent drug discontinuation were generally infrequent, with most being reported by only 1 or 2 subjects. The exceptions were nausea (6 RU-0211 48 mcg subjects, 6 events), dyspnea NOS (4 RU-0211 48 mcg subjects, 5 events), and abdominal pain NOS (3 RU-0211 48 mcg subjects, 3 events).

No subjects died during the study, and there was only one serious adverse event; a skull fracture that was not considered treatment-related in a placebo subject.

There were no clinically important trends identified in the evaluation of laboratory parameters, vital signs, or physical examinations.

SYNOPSIS OF LONG-TERM SAFETY STUDIES:

Studies SC01S1, SC01S2 – SP2 portion, and SC02S3 were all Phase III, open-label, long-term safety studies that were designed to capture safety data during treatment with oral RU-0211 at a dose of 48 mcg/day (24 mcg/b.i.d.), administered for 24 weeks (6 months) [SC01S1] or 48 weeks (SP2 of SC01S2 and SC02S3), as needed. Efficacy data collected in these studies were

subjective in nature; however, the same subjective assessments were also performed as part of the double-blind, randomized, placebo-controlled studies. Therefore, these results contributed to the overall evaluation of RU-0211 efficacy by providing a comparison of results of the same efficacy assessments as in the double-blind studies and by demonstrating the persistence of efficacy over time, specifically at 6 and 12 months.

STUDY RTU/0211SC01S1

Title: Multi-Center, Open-Label, Safety Study of Oral RU-0211 for the Treatment of Occasional Constipation.

This was the first of three multi-center, open-label, Phase III safety studies which enrolled 306 subjects at 22 centers in the United States. This study ran from November 2001 through May 2003. The study consisted of a 2-week baseline/washout period, a 24-week open-label treatment period, and follow-up 1 week after the end of treatment. During the open-label treatment period, subjects administered 24 mcg RU-0211 b.i.d. as needed, based on the subject's perceived severity of constipation and need for relief. The study population included follow-on subjects who had completed Study SC0131 and newly enrolled subjects. For new subjects, evidence of constipation (defined as, on average, < 3 SBMs per week and at least 1 protocol-defined associated symptom) must have been demonstrated and recorded in the daily diary during the 2-week baseline/washout period in order for a subject to be enrolled into the 24-week treatment period; for follow-on subjects, evidence of constipation was documented during the baseline/washout period at the beginning of Study SC0131. Efficacy endpoints for this study included assessments for abdominal bloating and discomfort, constipation severity, and treatment effectiveness.

Safety Summary: SC01S1

Most subjects (76%) experienced at least 1 AE during the study. The most common AEs were nausea, headache NOS, diarrhea NOS, abdominal pain NOS, and flatulence. Most subjects reported AEs that were mild to moderate in intensity, and most AEs that were reported with a severe intensity were reported by a very small number of subjects. No subjects died during the study, 7 subjects experienced 8 SAEs (no SAEs were considered treatment-related). Given that the preferred terms for the SAEs in this study included thrombosis NOS, gastroenteritis NOS, bronchitis NOS, dehydration, diverticulitis NOS, renal cell carcinoma, lower limb fracture NOS, and cerebrovascular accident NOS, it may be possible to conclude that treatment with RU-0211 is not responsible for any systemic effect. Sixty subjects (35 of which were newly enrolled subjects) discontinued the study because of adverse events. Overall, there were some clinically significant changes observed in the laboratory parameters of some subjects, however; for the subject population as a whole, these results do not give evidence of any clinically adverse trends in subjects being treated with lubiprostone 48 mcg/day. Evaluation of vital signs, physical examination results, and bilateral hand X-rays did not indicate any additional safety concerns for subjects treated with RU-0211.

The results of this study demonstrate that RU-0211 48 mcg appears safe and tolerable in subjects with constipation, when administered on an as-needed basis, as determined by the subject's perceived need for constipation relief.

Efficacy Summary: SC01S1

For all three enrollment groups the mean improvement from baseline to each visit up to Week 24 and to the end of study assessment was statistically significant ($p < 0.0001$) with respect to constipation severity, abdominal bloating, and abdominal discomfort.

The mean overall change from baseline to Visit 3 (Week 1) for abdominal bloating was -0.73 ($p<0.0001$; n=299). The mean improvement overall and for all 3 enrollment groups from baseline in abdominal bloating at all post-baseline time points was statistically different from zero (overall range: -0.71 at Visits 4 and 9 to -1.28 at Visit 7; $p<0.0005$ in all cases), indicating sustained relief of constipation.

The mean overall change from baseline to Visit 3 (Week 1) for abdominal discomfort was -0.83 ($p<0.0001$; n=299). The mean improvement overall and for all 3 enrollment groups from baseline in abdominal discomfort at all post-baseline time points was statistically different from zero (overall range: -0.70 at end of study to -1.11 at Visit 7; $p<0.0025$ in all cases), indicating sustained relief of constipation.

Overall, mean treatment effectiveness increased from 1.86 at Visit 3 (Week 1; n=297) to 2.35 at Visit 8 (Week 24; n=171). Mean treatment effectiveness was generally similar among all 3 enrollment groups. From Visit 5 through Visit 8, the overall mean effectiveness score was greater than 2 (moderately effective), indicating that those subjects who remained on study were experiencing constipation relief over the 6-month treatment period.

The main efficacy conclusion to be drawn from this study is that treatment with RU-0211 at a dose of 48 mcg, when treatment was dictated by the subject's perceived need for relief, produced statistically significant improvements from baseline in constipation severity, abdominal bloating, and abdominal discomfort at all post-baseline time points in the 3 enrollment groups and for the overall subject population. As subjects were not asked to assess global treatment effectiveness at baseline, no inferential testing of this subjective parameter was performed. There appeared to be, however; improvement in treatment effectiveness over the course of the 24-week treatment period. The efficacy results reported at Week 4 in the current study (i.e., mean values of constipation severity, abdominal bloating, abdominal discomfort, and treatment effectiveness) were similar to or better than those reported at the same time point for the same efficacy variables in the earlier, double-blind, randomized, placebo-controlled Phase III studies.

STUDY RTU/0211SC01S2/SP2

Title: A Phase III, Multi-Center, 7-Week Randomized Withdrawal and 48-Week Open-Label Safety Study of Oral RU-0211 for the Treatment of Occasional Constipation. Integrated Clinical Study Report for Study Period 2: 48-Week Open-Label Study.

This was a multi-center, open-label, Phase III long-term safety trial that enrolled and treated 248 subjects at 20 centers in the United States. The study ran from December 2001 through January 2003. Study SC0121/SP2 consisted of a 2-week baseline/washout period, a treatment phase made up of 2 study periods, and a follow-up visit 2 weeks after the end of treatment. The 2 study periods that made up the treatment phase are as follows:

- **SP1** consisted of a 4-week active treatment (AT) period followed by a 3-week randomized withdrawal (RW) treatment period, during which time subjects were randomized to either active (48 mcg RU-0211) or placebo treatment. At the completion of SP1, subjects entered into SP2.

- **SP2** consisted of a 48-week open-label treatment period.

Two hundred and forty-eight subjects were enrolled and treated in SP2, of which 168 were subjects enrolled directly into SP2, 39 were follow-on subjects who received placebo during the randomized withdrawal period, and 41 were follow-on subjects who received 48 mcg RU-0211 during the randomized withdrawal period. During SP2, all subjects administered 24 mcg RU-0211 b.i.d. as needed, based on the subject's perceived severity of constipation and need for relief. Evidence of constipation (defined as, on average, less than 3 SBMs per week) must have been demonstrated and recorded in the daily diary during the 2-week washout period in order for SP1 subjects to continue into the 4-week AT period, and for SP2-only subjects to continue into the 48-week open-label period. Efficacy endpoints for this study included assessments for abdominal bloating and discomfort, constipation severity, and treatment effectiveness.

Safety Summary: SC01S2/SP2

Overall, 187 of the 248 subjects (75.4%) reported at least one adverse event during SP2, including 105 subjects (42.3%) who experienced at least one treatment-related adverse event. Eleven subjects (4.4%) reported serious adverse events during this study; 10 open-label only subjects and 1 RU-0211 48 mcg follow-on subject. One SAE was considered possibly related to study drug:

- **Subject 18-1804** (open-label only) became pregnant during the study and gave birth to a child with bilateral club feet. Subject 18-1804 was a 30-year old Caucasian female with a history of constipation since 2000. Concomitant medications included Benadryl, Paxil, Bisacodyl, cortisone, Vistaril, and Dulcolax. The subject became pregnant during the study, and discontinued the study on Day 241 because of the pregnancy. On Day 438, she gave birth to a child with bilateral club feet. The club feet event was reported as an SAE because it was a congenital anomaly to the offspring of a study participant.

The mean 48-week average daily exposure of subjects was 342.3 days for placebo, 345.5 days for open label subjects, and 342.0 days for RU-0211 48 mcg subjects.

The incidence of clubfoot is approximately 1 case per 1000 live births in the United States with a male-to-female ratio of 2:1. Incidence in first-degree relations is approximately 2% and the incidence in second-degree relations is approximately 0.6%. Bilateral involvement has been found in 30-50% of cases and the etiology of clubfeet has been attributed to such causes as

teratogenic agents (drugs) oligohydramnios, and genetics.[3] Given the lack of information about this case, the reviewer cannot conclude with certainty that RU-0211 is not responsible for this serious adverse event.

The most common reasons for discontinuation during SP2 were lack of efficacy (44 subjects, 17.6%), AE (33 subjects, 13.2%), and voluntary subject withdrawal (23 subjects, 9.2%). Of the 33 subjects (13.2%) that discontinued the study because of adverse events during SP2, 27 subjects were open-label only, 3 were placebo follow-on, and 3 were RU-0211 48 mcg follow-on. The most common adverse events that led to study discontinuation were nausea, headache NOS, abdominal distension, abdominal pain NOS, diarrhea NOS, and vomiting NOS. No subjects died during SP2. The most common body system for AEs was gastrointestinal disorders (49.6% of subjects overall; 51.2% of open-label only subjects; 51.3% of placebo follow-on subjects; 41.5% of RU-0211 48 mcg follow-on subjects). Other body systems with at least 10% subjects reporting adverse events during SP2 were infections and infestations (26.6%), nervous system disorders (13.3%), and musculoskeletal and connective tissue disorders (12.9%). Overall, 27 subjects (10.9%) had at least one AE for which the maximum intensity was severe. Of these 27 subjects, 16 were open-label only, 6 were placebo follow-on, and 5 were RU-0211 48 mcg follow-on.

The frequencies of the most common treatment-related AEs including nausea (24.4%) and abdominal pain NOS (7.1%) were higher for open-label only subjects than for follow-on subjects (10.3% and 9.8% for nausea; 0% and 2.4% for abdominal pain NOS). The frequencies of the most common SAEs, and discontinuations were also higher among open-label only subjects than among the follow-on subjects. The preferred terms for the SAEs in this study included syncope, ventral hernia, chest pain, compression fracture, atrial fibrillation, appendicitis, cervical disc lesion, neck pain, pseudoarthrosis, arthropathy NOS, congenital clubfoot, pyelonephritis NOS, dehydration, pneumonia NOS, abdominal adhesions, and oophorectomy NOS.

There were no clinically significant trends in the assessment of laboratory values (hematology, biochemistry, and urinalysis), vital signs, physical examinations, and hand X-rays.

The results of this study demonstrate that RU-0211 48 mcg appears safe and tolerable in subjects with constipation, when administered on an as-needed basis, as determined by the subject's perceived need for constipation relief.

Efficacy Summary: SC01S2/SP2

Though not a stated objective for SP2, evidence of the efficacy of RU-0211 provided statistically significant improvements from baseline in constipation severity, abdominal bloating, and abdominal discomfort at all post-baseline time points in all enrollment groups and for the overall subject population. As the assessment of global treatment effectiveness does not apply at baseline, no inferential testing of the post-baseline results was performed for this subjective parameter. There did appear to be however, an overall increase in treatment effectiveness over the course of the 48-week treatment period.

For all three enrollment groups the mean improvement from baseline to each visit up to Week 48 and to the end of study assessment was statistically significant ($p < 0.0001$) with respect to constipation severity, abdominal bloating, and abdominal discomfort.

Overall, there was a decrease in mean severity of constipation for efficacy evaluable subjects from 2.94 at Visit 2 (baseline; n=246) to 1.42 at Visit 10 (Week 48; n=129). The mean severity of constipation was 1.66 at the end of study visit, (n=243), based on the last recorded measurement. After Visit 2, no mean severity value at any visit was greater than 2 (moderate) indicating that relief of severity occurred very soon after taking RU-0211 for open-label only subjects and was sustained from SP1 for the follow-on subjects. Overall, and for all 3 enrollment groups, the mean decrease from baseline in constipation severity at all post baseline time points was statistically different from zero; $p<0.0015$ in all cases).

There was an overall decrease in mean abdominal bloating for all efficacy evaluable subjects from 2.10 at Visit 2 (baseline; n=246) to 0.92 at Visit 10 (Week 48; n=130). The mean abdominal bloating was 1.15 at the end of study visit, (n=243), an overall decrease of 0.95 ($p<0.0001$). At all post-baseline time points mean abdominal bloating was less than 2 (moderate) in all enrollment groups; at Visits 5, 7, 8, 9, and 10, overall mean abdominal bloating was less than 1 (mild). Overall and for all 3 enrollment groups, the mean decrease from baseline in abdominal bloating at all post baseline time points was statistically different from zero; $p \leq 0.0106$ in all cases).

There was a decrease in mean abdominal discomfort from 1.88 at Visit 2 (baseline; n=246) to 0.85 at Visit 10 (Week 24; n=130). The mean abdominal discomfort was 0.98 at the end of study visit, (n=243). Overall and for all 3 enrollment groups, the mean decrease from baseline in abdominal bloating at all post-baseline time points was statistically different from zero (overall range: 0.59 for open-label only subjects at Visit 11 to 1.38 for placebo follow-on subjects at Visit 10; $p<0.01$ in all cases).

Overall, mean treatment effectiveness increased from 2.13 at Visit 3 (Week 6; n=241) to 2.48 at Visit 10 (Week 48; n=130). The mean treatment effectiveness 2.02 at the end of study visit (n=243) and 2.36 at the follow up visit (Visit 11); (n=172). Mean treatment effectiveness was generally similar among all 3 enrollment groups, although the values were slightly higher for follow-on subjects in all cases. No inferential tests were performed on these results.

Subject ratings on the SF36 Quality of Life Assessment questionnaire did not change appreciably from baseline after receiving open-label treatment. There was, however; a statistically significant increase in the mean Bodily Pain component score ($p=0.0281$), from baseline to Visit 6 (Week 24) after receiving open-label treatment. This score represented a worsening for this component. No other changes from baseline were statistically significant.

Study SC01S2/SP2 produced significant improvements from baseline in constipation severity and abdominal symptoms overall and for all 3 enrollment groups evaluated during SP2 when treatment with RU-0211 at a dose of 48 mcg was dictated by the subject's perceived need for relief. Symptomatic relief was sustained throughout the study period, as shown by

improvements that were statistically significantly different from zero at all post-baseline time points.

10.1.11 Study RTU/0211SC02S3

Title: A Phase III, 48-Week Open-Label Safety Study of Oral RU-0211 for the Treatment of Occasional Constipation.

This was a multi-center, open-label, Phase III, long-term safety trial that enrolled and treated 324 subjects at 22 centers in the United States. The study ran from February 2003 through August 2004. Study SC02S3 consisted of a 2-week baseline/washout period, a 48-week treatment phase, and a follow-up visit 2 weeks after the end of treatment. The study was a single-group study, with no randomization, and dose intake was determined by individual subjects based on perceived need but did not exceed 48 µg within a 24-hour period. "Subject need" was defined as perceived severity of constipation and need for relief. Subjects could then remain on a daily dosing schedule or stop the study drug if the perceived need decreased or ceased. Subjects could also return to study drug when needed, but were to begin dosing again at 24 mcg RU-0211 b.i.d. Investigators could adjust the daily dose in response to exaggerated pharmacodynamic events (e.g., diarrhea) or treatment-related adverse events (e.g., nausea). Efficacy endpoints for this study included assessments for abdominal bloating and discomfort, constipation severity, and treatment effectiveness.

Safety Summary: SC02S3

Two hundred and seventy four of the 324 subjects (84.6%) reported at least one adverse event during the study, including 217 subjects (67.0%) who experienced at least one treatment-related adverse event. Thirteen subjects (4.0%) reported serious adverse events during this study. One SAE was considered possibly related to study drug:

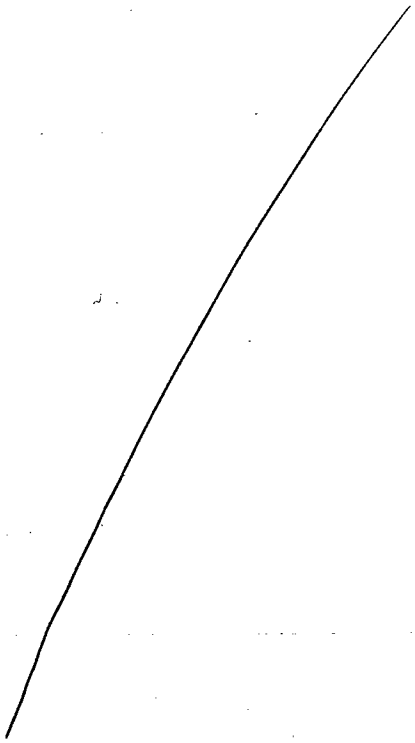
- **Subject 05-0507** was a 64-year old Caucasian female with a past medical history of gastroesophageal reflux disease (no constipation history). Relevant concomitant medications included Robaxin, Albuterol, zinc, Premarin, progesterone, BuSpar, Aldactone, Lasix, vitamin B, Vicodin, Celebrex, Aciphex, Aristocort, Benadryl, Bactrim DS, Atarax, Depo-Medrol, influenza vaccine, loperamide hydrochloride, promethazine, Lisinopril, Verapamil, and Peri-Colace. On Day 272, the subject experienced severe diarrhea, moderate diverticulitis with questionable rectal bleeding, which resolved on Day 273. The investigator considered these events to be possibly related to the study drug. The subject completed the study.

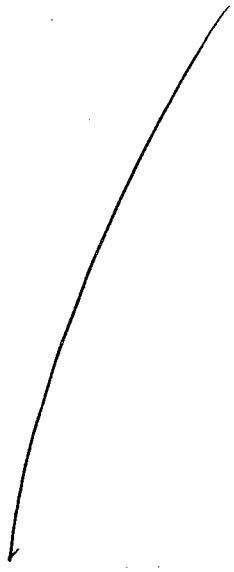
Sixty-eight subjects (21.0%) experienced a total of 132 adverse events that led to study drug discontinuation. The most common adverse events that led to study drug discontinuation included nausea (29 subjects, 9.0%; 29 events), headache NOS (11 subjects, 3.4%; 11 events), diarrhea NOS (7 subjects, 2.2%; 7 events), peripheral swelling (5 subjects, 1.5%; 7 events), abdominal pain NOS (5 subjects, 1.5%; 6 events), abdominal distension (5 subjects, 1.5%; 5 events), vomiting NOS (5 subjects, 1.5%; 5 events), and flatulence (4 subjects, 1.2%; 4 events).

Of the 324 subjects treated with RU-0211, 239 (74%) did not require a dose decrease, and 85 (26%) did require a dose decrease. No statistically significant differences in age, weight, gender, or race were observed between those subjects who required a dose decrease and those who did not ($p>0.25$). No subjects died during the study. Most AEs were reported with similar frequencies by gender and by race. The most common body system for AEs were gastrointestinal disorders (67.3%), infections and infestations (28.4%), nervous system disorders (22.5%), musculoskeletal and connective tissue disorders (17.0%), general disorders and administrative site conditions (11.7%), and skin and subcutaneous tissue disorders (10.5%). Eighty-two subjects (25.3%) had at least one severe AE. Most severe AEs were reported by less than 1% of subjects; exceptions were diarrhea NOS (5.2% of subjects), abdominal pain NOS (2.8%), nausea (2.8%), abdominal distension (2.5%), and dizziness (excluding vertigo) (1.2%).

Evaluation of laboratory measures, vital signs, and physical examination results did not reveal any clinically significant trends in subjects with lubiprostone.

Efficacy Summary: SC02S3





Line-by-Line Labeling Review

Medical Officer Comments:
Given that an acceptable tradename for lubiprostone has not been established by the Office of Drug Safety; Division of Medication Errors and Technical Support at this stage of the review process, all uses of a proprietary name throughout this labeling review will be substituted with the word 'TRADENAME'.

The medical officer has the following comments and recommendations for the INDICATIONS AND USAGE section of the lubiprostone capsule label. The medical officer recommends that the INDICATIONS AND USAGE section follow the CLINICAL STUDIES section. Additionally, to be consistent with other approved drugs which were evaluated in similar populations, the medical officer recommends the indication be changed to the treatment of idiopathic constipation. See added text below.

16 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

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

/s/

Kristen Buck
12/19/2005 12:32:31 PM
MEDICAL OFFICER

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12/19/2005 04:25:36 PM
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