CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211281Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA 505(b)(2)
Application Number(s)	211281
Priority or Standard	Standard
Submit Date(s)	November 21, 2018
Received Date(s)	November 21, 2018
PDUFA Goal Date	February 20, 2020 (due to major amendment)
Division/Office	OND / ODEIII / DGIEP
Review Completion Date	February 12, 2020
Established/Proper Name	Lactitol
(Proposed) Trade Name	Pizensy
Pharmacologic Class	Osmotic laxative
Applicant	Braintree Laboratories Inc.
Dosage Form	Powder for oral solution
Applicant Proposed Dosing Regimen	(b) (4)
Applicant Proposed Indication(s)/Population(s)	The treatment of chronic idiopathic constipation (CIC) in adults
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	82934008 chronic idiopathic constipation
Recommendation on Regulatory Action	Approval
Recommended Dosing Regimen	20 grams orally once daily, preferably with meals. Reduce the dosage to 10 grams once daily for persistent loose stools. Administer oral medications at least 2 hours before or 2 hours after Pizensy (lactitol).

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OPQ, Office of Pharmaceutical Quality
OPDP, Office of Prescription Drug Promotion
OSI, Office of Scientific Investigations
OSE, Office of Surveillance and Epidemiology
DEPI, Division of Epidemiology
DMEPA, Division of Medication Error Prevention and Analysis
DRISK, Division of Risk Management
DPMH, Division Of Pediatrics And Maternal Health
DPV, Division of Pharmacovigilance
DGIEP, Division of Gastroenterology and Inborn Errors Products
OB/DBIII, Office of Biostatics/Division of Biometrics III
OCP, Office of Clinical Pharmacology
ODEIII, Office of Drug Evaluation III

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BCSIII	Biopharmaceutical Classification System Class III
BLA	biologics license application
BP	blood pressure
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CIC	chronic idiopathic constipation
CMC	chemistry, manufacturing, and controls
CSBM	complete spontaneous bowel movement
CSR	clinical study report
DGIEP	Division of Gastroenterology and Inborn Errors Products
DPV	Division of Pharmacovigilance
ECG	electrocardiogram
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GD	gestation day
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ITT	intent to treat
mITT	modified intent to treat
MMRM	mixed model repeated measures
NDA	new drug application
NI	non-inferiority
NMT	not more than
NOAEL	no observed adverse effect level
OSE	Office of Surveillance and Epidemiology
PAC-QOL	Patient Assessment of Constipation Quality of Life
PAC-SYM	Patient Assessment of Constipation Symptom
PD	pharmacodynamics
PDE	permitted daily exposure
PK	pharmacokinetics
PMR	postmarketing requirement
PP	per protocol
PSUR	Periodic Safety Update Report
QT	qualification threshold
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The Applicant resubmitted NDA 211281 for Pizensy (lactitol) on November 21, 2018 to the Division of Gastroenterology and Inborn Errors Products (DGIEP) for the proposed indication of the treatment of chronic idiopathic constipation (CIC) in adults. The first submission for this NDA, dated June 29, 2018, was issued a refuse to file action due to lack of an agreed iPSP. This is a 505(b)(2) application that relies, in part, upon published nonclinical and clinical studies to support the safety of lactitol and supplement the submitted efficacy data, respectively.

Lactitol, an osmotic laxative, is a new chemical entity that is a synthetic derivative of lactose, and consists of galactose and sorbitol linked through a glycoside bond. Lactitol causes the influx of water into the small intestine leading to a laxative effect in the colon. It is a colonically metabolized polyol sugar and is minimally absorbed systemically following oral administration.

The recommended dosage and administration is as follows:

- The recommended adult dosage of Pizensy is 20 grams orally once daily, preferably with meals.
- Reduce the dosage to 10 grams once daily for persistent loose stools.
- Administer oral medications at least 2 hours before or 2 hours after Pizensy.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The data submitted for this NDA establish the clinical benefit of Pizensy (lactitol) for the treatment of adults with chronic idiopathic constipation (CIC). The effectiveness of Pizensy (lactitol) in CIC is supported by data from one large, multicenter, placebo-controlled trial (Study BLI400-302 or Study 302) plus supportive evidence from a non-inferiority (active-controlled) trial (Study BLI400-301 or Study 301) and published controlled clinical trials. Study 302, the placebo-controlled trial, demonstrated a significant lactitol-placebo treatment difference of 12% (95% CI: 6.0,18.5%). Study 301, the non-inferiority trial with Amitiza (lubiprostone) as an active comparator, could not be relied on as one of two adequate and well-controlled trials the Applicant submitted for this NDA. This is because the Applicant chose the non-inferiority margin based on a treatment difference between linaclotide (a drug from a different class) and placebo rather than using a comparison between Amitiza (lubiprostone) and placebo. Also, there is no historical data that can be used to derive an appropriate non-inferiority margin for Amitiza (lubiprostone) in this NDA because this NDA used a 12-week frequency of complete spontaneous bowel movements (CSBMs) as the primary endpoint but Amitiza (lubiprostone) was approved based on a 4-week frequency of spontaneous bowel movements (SBMs) primary endpoint. Since lactitol has been widely marketed in other countries for many years, we considered additional evidence to evaluate its effectiveness for CIC in adults. Therefore, upon our request, the Applicant submitted a comprehensive summary of published literature for lactitol trials and a meta-analysis comparing the data from the lactitol treatment group in Study 301 to historical placebo data from other recent CIC studies to provide additional support for efficacy. The additional trials in the published literature and the meta-analysis comparing the response rate from the lactitol treatment group in Study 301 to historical placebo data provided supportive evidence to show that lactitol improves stool frequency in adults with CIC. Overall,

the submitted evidence establishes the effectiveness of lactitol for the treatment of adults with CIC to support product approval and labeling.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The data submitted in this NDA establish a clinical benefit for lactitol for the treatment of adult patients with chronic idiopathic constipation (CIC). In support of this NDA, the Applicant conducted two randomized, controlled trials and an open-label, long-term safety trial. Study 301 was a 12-week, non-inferiority trial with Amitiza (lubiprostone) as the active comparator. Study 302 was a 6-month, placebo-controlled trial. Study 303 was a 12-month, open-label, long-term safety trial.

Patients were eligible for enrollment if they had an average <3 complete spontaneous bowel movements (CSBMs) per week during the 14 day screening period and met an adapted ROME II definition for a diagnosis of CIC, including the following criteria: fewer than 3 spontaneous defecations per week and at least one of the following symptoms for at least 12 weeks (which need not be consecutive) in the preceding 12 months:

a. Straining during >25% of defecations
b. Lumpy or hard stools in >25% of defecations
c. Sensation of incomplete evacuation for >25% of defecations

The primary endpoint was the same for both Studies 301 and 302 and the primary efficacy assessment for both trials occurred at 12 weeks. The primary endpoint was defined by the proportion of patients who were weekly responders for at least 9 weeks out of the first 12-week treatment period, with at least 3 of those weeks occurring in the last 4 weeks of the first 12 week treatment period. A weekly responder was defined as having ≥3 CSBMs and an increase from baseline of >1 CSBM for that given week. No secondary endpoints were adjusted for multiplicity. The exploratory secondary endpoints included change from baseline in mean CSBMs per week, overall response during weeks 13-24 of Study 302 (6-month trial duration), and rescue medication use.

Study 302, the placebo-controlled trial, demonstrated favorable efficacy results for lactitol. The efficacy responder rates for the primary endpoint were 25% in the lactitol arm and 13% in the placebo arm (12% treatment difference; 95% CI: 6.0 - 18.5). Additional exploratory analyses for the long-term treatment effect and change in number of CSBMs supported the results for the primary endpoint. A responder analysis based on Weeks 13 to 24 of the treatment period (i.e., the proportion of responders for at least 9 weeks of the last 12 weeks and at least 3 of the last 4 weeks) showed results similar to the responder analysis of the first 12 weeks. Improvements in the mean frequency of CSBMs/week were seen as early as Week 1 with improvement generally maintained through Week 12. Patients in the lactitol group had a mean increase of 0.8 CSBM/week from baseline to Week 12 over the placebo group. Rescue medication use was permitted during the trial and was accounted for in the primary endpoint analysis; a CSBM was defined as a BM that occurred with no rescue laxative use in the previous 24 hours and that was accompanied by a sense of complete evacuation. Patients in the lactitol group and patients in the placebo group took an estimated average of 1.7 and 1.8 bisacodyl doses per week, respectively, during the first 12 week treatment period. The use of rescue medication was generally similar between the groups and since the primary endpoint accounted for rescue medication use, any small differences are unlikely to impact the overall conclusions.

Study 301, the non-inferiority study with Amitiza (lubiprostone) as an active comparator, could not be relied on as one of two adequate, well-controlled trials after determining that the Applicant chose the non-inferiority margin based on results from a different drug (linaclotide), rather than on comparisons between the active comparator (lubiprostone) and placebo. There is no historical data for the active comparator that can be used to derive an appropriate margin for the primary endpoint. Furthermore, the study results were borderline with respect to the proposed margin. The 95% confidence interval (CI) for the treatment difference barely excluded the non-inferiority margin and the efficacy conclusions were not robust with respect to missing data. In addition, an analysis using another endpoint for which a historical comparison between the active comparator and placebo is available failed to reliably establish efficacy for lactitol. Since lactitol has been widely marketed in other countries for many years, we requested that the Applicant provide additional information to support the efficacy data submitted in the NDA.

The Applicant submit a comprehensive summary of published efficacy trials in adults with CIC, including both placebo- and active-controlled designs based on our recommendation. The summary of literature included one randomized placebo-controlled trial, four active-controlled trials (lactulose was the active comparator), and several single-arm and/or open-label trials. We focused on the controlled trials. Lactitol showed improvement compared to placebo, and the efficacy measures in patients treated with lactitol were either slightly better or similar to patients treated with lactulose. While the trials from the published literature do not have the same statistical rigor as Study 302, these trials provide supplemental evidence that lactitol improves stool frequency in patients with CIC.

In addition, we requested that the Applicant submit a meta-analysis comparing the response rate from the lactitol treatment group in Study 301 to historical placebo data from other recent CIC trials. Although the team had concerns about the robustness of Study 301, the efficacy data from the lactitol group was considered as part of the collective evidence to support product approval. The Applicant identified 12 placebo-controlled trials across three approved drugs that were included in the meta-analysis. Placebo response rates ranged from 2.9% to 13.0%. When comparing those placebo response rates to the placebo response rate in Study 302, only one of the trials (Study SP304203-03) had a higher placebo response rate than that observed in Study 302. Two other trials (Study SPD-555-302 and Study SPD-555-401) had similar placebo response rates to Study 302. We performed an additional meta-analysis analysis using those three trials. The lower bound of the 95% CI for the lactitol response rate in Study 302 was greater than the upper bound of the 95% CI for the placebo response rates from all meta-analyses conducted, which provides additional supportive evidence for the efficacy of lactitol. Despite the limitations of these historical control comparisons, including their post hoc nature and the possible impact of differences in design and conduct between Study 301 and the historical studies, these results provide additional supportive evidence for the efficacy of lactitol.

The safety database included data obtained from the three, phase 3 clinical trials. Study 302, the placebo-controlled trial, was the focus of the safety assessment and the safety data from Studies 301 and 303 were assessed separately. In Study 302, the most common adverse reactions occurring in >3% of patients and greater than placebo included upper respiratory tract infection, flatulence, diarrhea, increased blood creatinine phosphokinase, abdominal distension, and increased blood pressure. Severe diarrhea was reported in 2 (1%) patients in the lactitol arm and no patients in the placebo arm. Eleven of 291 (4%) patients in the lactitol arm discontinued due to adverse reactions, compared to 10/302 (3%) patients in the placebo group. The most common adverse reactions leading to discontinuation in lactitol-treated patients (1% each) were elevated creatine kinase, flatulence, diarrhea, and increased blood pressure. The safety profile of lactitol in Study 301 was similar to

Study 302. In Study 303, adverse reactions were generally consistent with those observed in the other two phase 3 trials and in addition, urinary tract infection and abdominal pain were observed in at least 3% of patients over the 12 month duration.

Of note, there were several data integrity concerns for this submission. Due to these issues, we defined new analysis populations for the efficacy and safety analyses. The "FDA primary analysis population" was used as the primary analysis population for efficacy analyses. Details are outlined in the subsequent sections of this multi-disciplinary review.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	CIC, also known as functional constipation, is characterized according to the Rome diagnostic criteria.[1] The prevalence of chronic constipation in adults in North America is estimated to vary between 2 to 27 percent (average of approximately 15 percent) depending on how the disease is defined. The prevalence of chronic constipation rises with age, most notably in patients 65 years of age or older.	CIC remains a considerable health issue and can have a profound impact on patient quality of life.
Current Treatment Options	The general goal of CIC treatment is to increase the frequency of bowel movements (BMs), improve stool consistency, and reduce straining associated with BMs. Several products are approved for the treatment of adults with CIC, including lubiprostone, linaclotide, plecanatide, and prucalopride. In addition, patients often use unapproved products, including probiotics, osmotic and stimulant laxatives, stool softeners, and fiber. At times, patients also use dietary and lifestyle modifications to treat their chronic constipation.	Not all patients will have an adequate response to available therapy; the response rates for other products approved for CIC, using similar efficacy endpoints, approximately range from 8 to 17% higher for treatment arms compared to placebo arms. Therefore, additional treatment options are needed.
Benefit	Study 302, the placebo-controlled trial, demonstrated favorable efficacy results for lactitol. The efficacy responder rates for the primary endpoint were 25% in the lactitol arm and 13% in the placebo arm (12% treatment difference; 95% CI: 6.0 - 18.5). Additional exploratory analyses for the long-term treatment effect and change in number of CSBMs supported results for the	Study 302, the placebo-controlled trial, demonstrated favorable and robust results in favor of lactitol.

[1] Drossman, D., Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features, and Rome IV. Gastroenterology 2016; 150;1262-1279.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	primary endpoint. A responder analysis based on Weeks 13 to 24 of the treatment period (i.e., the proportion of responders for at least 9 weeks of the last 12 weeks and at least 3 of the last 4 weeks) showed results similar to the responder analysis of the first 12 weeks. Improvements in the mean frequency of CSBMs/week were seen as early as Week 1 with improvement generally maintained through Week 12. Patients in the lactitol group had a mean increase of 0.8 CSBM/week from baseline to Week 12 over the placebo group.	
	Study 301, the non-inferiority study with Amitiza (lubiprostone) as an active comparator, could not be relied on as one of the adequate, well-controlled trials after determining that the Applicant chose the non-inferiority margin based on results from a different drug (linaclotide), rather than on comparisons between the active comparator (lubiprostone) and placebo. Furthermore, there is no historical data for lubiprostone that can be used to derive an appropriate margin for the primary endpoint. The study results were also borderline with respect to the proposed margin. The 95% CI for the treatment difference barely excluded the non-inferiority margin and the efficacy conclusions were not robust with respect to missing data. In addition, an analysis using another endpoint for which a historical comparison between lubiprostone and placebo is available failed to reliably establish efficacy for lactitol.	Study 301, the non-inferiority study with Amitiza (lubiprostone) as an active comparator, could not be relied on as one of the adequate, well-controlled trials. To help address the concerns with Study 301, the Applicant submitted a comprehensive summary of published literature for lactitol trials and a meta-analysis of placebo response rates for recent CIC trials to provide additional support for efficacy.
	To address the limitations of relying on Study 301, the review team requested that the Applicant submit a comprehensive summary of published literature for lactitol trials and a meta-analysis of placebo response rates for recent CIC trials to provide additional support for efficacy. The summary of literature included one randomized placebo-controlled trial, four active-comparator controlled trials (lactulose was the active comparator), and several single-arm and/or open-label trials. The placebo-controlled and active comparator-controlled trials show that treatment with lactitol resulted in improvements in BM frequency and consistency compared to patients' baseline status. Lactitol showed improvement compared to placebo, and the efficacy measures in patients treated with lactitol were generally slightly better or similar to patients	Given the lack of robustness of the non-inferiority trial with lubiprostone (Study 301) and since lactitol has been widely marketed in other countries for many years, the review team considered additional evidence that could supplement the data submitted in the NDA to establish effectiveness of lactitol for CIC. This included comparisons of outcomes on lactitol in Study 301 to a historical placebo control, as well as additional trials in the published literature. While these data sources do not

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treated with lactulose. The meta-analysis compared the lactitol treatment group in Study 301 to historical placebo data from 12 placebo-controlled trials across three approved drugs; the placebo response rates range from 2.9% to 13.0%. Only one of the included trials (Study SP304203-03) had a higher placebo response rate than Study 302. Two other trials (Study SPD-555-302 and Study SPD-555-401) had placebo response rates similar to Study 302. An additional meta-analysis was performed by the review team using those three studies. The lower bound of the 95% CI for the lactitol response rate is greater than the upper bound of the 95% CI for the placebo response rates from all meta-analyses conducted.	have the same statistical rigor as Study 302, they provided supportive evidence that lactitol improves stool frequency in adult patients with CIC. Although the label will primarily describe the efficacy and safety data from Study 302 (placebo-controlled trial), the collective evidence support approval and product labeling for lactitol for the treatment of adults with CIC.
Risk and Risk Management	The safety database included data obtained from the three, phase 3 clinical trials. Study 302, the placebo-controlled trial, was the focus of the safety assessment and the safety data from Studies 302 and 303 were assessed separately. In Study 302, the most common adverse reactions occurring in >3% of patients and greater than placebo included upper respiratory tract infection, flatulence, diarrhea, increased blood creatinine phosphokinase, abdominal distension, and increased blood pressure. Severe diarrhea was reported in 2 (1%) patients in the lactitol arm and no patients in the placebo arm. Eleven of 291 (4%) patients in the lactitol arm discontinued due to adverse reactions, compared to 10/302 (3%) patients in the placebo group. The most common adverse reactions leading to discontinuation in lactitol-treated patients (1% each) were elevated creatine kinase, flatulence, diarrhea, and increased blood pressure. The safety profile of lactitol in Study 301 was similar to Study 302. In Study 303, adverse reactions were consistent with those observed in the other two phase 3 trials and in addition, urinary tract infection and abdominal pain were observed in at least 3% of patients over the 12 month duration. The Applicant has not conducted in vitro or in vivo studies to evaluate the drug interaction potential for lactitol. Although the absolute bioavailability of lactitol	The product labeling will describe the common adverse reactions reported in Study 302 with descriptive information on Studies 301 and 303 noting that the safety profile was similar. Post-marketing studies will be required under the Pediatric Research Equity Act to collect information on the safety and efficacy of lactitol in the pediatric population with functional constipation. In vitro studies to evaluate the drug interaction potential for lactitol will be required post-marketing under the Food and Drug Administration Amendments Act of 2007

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	is expected to be low following oral administration, considerably high plasma concentrations were observed at the recommended oral dose of 21 g lactitol monohydrate. For example, individual plasma C_{max} concentrations ranging from 922 to 6,300 ng/mL in fasted condition and from 439 to 1,330 ng/mL in fed condition were observed following a single oral dose administration in healthy adult subjects. Currently, there is no information to adequately address the drug interaction potential for lactitol at these observed systemic concentrations.	(FDAAA). The results of the in vitro studies will be reviewed to determine whether in vivo drug interaction studies are needed.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO) – Bowel movement diary, rescue bisacodyl diary	Efficacy
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

CIC, also known as functional constipation, is characterized according to the Rome diagnostic criteria, and is based upon the presence of the following symptoms for the last three months with symptom onset at least six months prior to diagnosis:[2,3]

1. Must include two or more of the following:
   - Straining during more than 25% of defecations
   - Lumpy or hard stools (Bristol Stool Scale Form 1-2) more than 25% of defecations
   - Sensation of incomplete evacuation more than 25% of defecations
   - Sensation of anorectal obstruction/blockage more than 25% of defecations
   - Manual maneuvers to facilitate more than 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
   - Fewer than 3 spontaneous bowel movements per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

The prevalence of chronic constipation in adults in North America is estimated to vary between 2 to 27 percent (average of approximately 15 percent) depending on how the disease is defined.[4,5] A systematic review, published in 2004, estimated that 63 million people in North America fulfilled the Rome II criteria for constipation.[6] The prevalence of chronic constipation rises with age, most notably in patients 65 years of age or older.[7,8,9] In this older age group, 26% of women and 16% of men report constipation.[10] Ultimately, CIC remains a considerable health issue and can have a profound impact on patient quality of life.

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[2] Longstreth, GF, WG Thompson, WD Chey, LA Houghton, F Mearin, and RC Spiller, 2006, Functional bowel disorders, Gastroenterology, 130(5):1480-1491.
[3] Mearin, F, BE Lacy, L Chang, WD Chey, AJ Lembo, M Simren, and R Spiller, 2016, Bowel Disorders, Gastroenterology.
[4] Higgins, PD and JF Johanson, 2004, Epidemiology of constipation in North America: a systematic review, Am J Gastroenterol, 99(4):750-759.
[5] Suares, NC and AC Ford, 2011, Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis, Am J Gastroenterol, 106(9):1582-1591; quiz 1581, 1592.
[6] Higgins, PD and JF Johanson, 2004, Epidemiology of constipation in North America: a systematic review, Am J Gastroenterol, 99(4):750-759.
[7] Sonnenberg, A and TR Koch, 1989, Physician visits in the United States for constipation: 1958 to 1986, Dig Dis Sci, 34(4):606-611.
[8] Talley, NJ, KC Fleming, JM Evans, EA O'Keefe, AL Weaver, AR Zinsmeister, and LJ Melton, 3rd, 1996, Constipation in an elderly community: a study of prevalence and potential risk factors, Am J Gastroenterol, 91(1):19-25.
[9] Higgins, PD and JF Johanson, 2004, Epidemiology of constipation in North America: a systematic review, Am J Gastroenterol, 99(4):750-759.
[10] Gallegos-Orozco, JF, Foxx-Orenstein, AE, Sterler, SM, and Stoa, JM. Chronic constipation in the elderly. Am J Gastroenterol 2012; 107:18–25.

2.2. Analysis of Current Treatment Options

The general goal of CIC treatment is to increase the frequency of bowel movements (BMs), improve stool consistency, and reduce straining associated with BMs. The currently approved therapies for CIC are summarized in Table 1 below. Unapproved products patients often use for treatment of chronic constipation include probiotics, osmotic and stimulant laxatives, stool softeners, and fiber. At times, patients also use dietary and lifestyle modifications to treat their chronic constipation. Not all patients will have an adequate response to available therapy; therefore, additional treatment options are needed.

Table 1: Currently Approved Treatments for CIC

Drug	Indications	Dosing/ Administration	Mechanism of Action	Contraindications and Common AEs	Year Approved
Lubiprostone (Amitiza)	CIC (adults) OIC (adults) IBS-C in women ≥18 years of age	CIC: 24 mcg oral twice daily OIC: 24 mcg oral twice daily IBS-C: 8 mcg oral twice daily	Apical chloride-2 channel activator	Contraindicated in known or suspected mechanical GI obstruction. Common AEs: nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence	CIC: 2006 IBS-C: 2008 OIC: 2013
Linaclotide (Linzess)	CIC (adults) IBS-C (adults)	CIC: 145 mcg oral once daily, 72 mcg once daily may be used based on individual presentation or tolerability. IBS-C: 290 mcg oral once daily	Guanylate cyclase-C agonist	Contraindicated in known or suspected mechanical GI obstruction, patients less than 6 y/o due to the risk of serious dehydration Common AEs: diarrhea, abdominal pain, flatulence, abdominal distension, viral gastroenteritis, and headache	CIC: 2012 IBS-C: 2012
Plecanatide (Trulance)	CIC (adults) IBS-C (adults)	CIC: 3 mg oral once daily IBS-C: 3 mg oral once daily	Guanylate cyclase-C agonist	Contraindicated in known or suspected mechanical GI obstruction, patients less than 6 years of age due to the risk of serious dehydration. Most Common AE: diarrhea	CIC: 2017 IBS-C: 2018
Prucalopride (Motegrity)	CIC (adults)	CIC: 2 mg oral once daily Patients with severe renal impairment CrCL less than 30 mL/min: 1 mg oral once daily	Serotonin-4 (5-HT4) receptor agonist	Contraindicated in patients with hypersensitivity to prucalopride, intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract such as Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum. Common AEs: headache, abdominal pain, nausea, diarrhea, abdominal distension, dizziness, vomiting, flatulence, and fatigue.	CIC: 2018

Abbreviations: AE, adverse event; CIC, chronic idiopathic constipation; CrCL, creatinine clearance; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome – constipation; OIC, opioid-induced constipation; y/o, year-old
Source: Reviewer's Table

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lactitol is not currently marketed in the United States. Lactitol has been marketed in countries outside of the United States since 1985 for the treatment of constipation and for the treatment of hyperammonemia associated with hepatic encephalopathy. Lactitol is marketed under various tradenames in different countries, and two of the largest distributors are Danisco/Dupont and Novartis who market lactitol as Osmoaid and Imported, respectively.

3.2. Summary of Presubmission/Submission Regulatory Activity

The regulatory history below describes the relevant history of the development program in the U.S. for the indication of CIC. Recommendations and discussions that are relevant to the adequacy of the efficacy and safety analyses are summarized below.

- June 14, 2013: Investigational new drug (IND) 118906 was submitted to the FDA by Braintree Laboratories Inc (the Applicant).

- December 12, 2013: Applicant's response to FDA Advice Letter, dated October 15, 2013. The Applicant's response was submitted as part of the End of Phase 2 (EOP2) meeting information package.
    - Applicant communicated that upward dose titrations will no longer be allowed in studies BLI400-301 and BLI400-302. All patients will be maintained on a dose of 21g for the duration of each study, which is the dose supported by the literature as being safe and effective for chronic idiopathic constipation. Dose reductions will be allowed in patients that experience prolonged diarrhea.
    - Applicant agreed that baseline ECGs will be performed at Visit 1 in studies BLI400-301 and BLI400-302, in addition to each follow-up visit.
    - Applicant clarified rescue bisacodyl use, including the maximum bisacodyl doses and total mg allowed per week and a plan if the patient does not respond to bisacodyl.
    - FDA advised and the Applicant agreed that in compliance with the Food and Drug Administration Safety and Innovation Act, a Pediatric Study Plan will be submitted no later than 60 days after the End of Phase 2 meeting.

- January 14, 2014: Type B EOP2 meeting
    - FDA agreed that the proposed dose of lactitol appears to be within the range previously assessed in published studies.
    - FDA communicated that the 6-month placebo-controlled trial would be the primary basis of efficacy evidence in support of lactitol for the proposed CIC indication. Of note, at that time the Applicant proposed Study BLI400-301 as this placebo-controlled trial; however, Study BLI400-301 is a non-inferiority trial in the current NDA submission. The data from published studies of lactitol cited in the Applicant's meeting package may be considered supportive, but none of these studies represent an adequate, well-controlled clinical trial to evaluate the safety or efficacy of lactitol for treatment of CIC.
    - FDA agreed with the proposed primary endpoint for the 6-month placebo-controlled trial, defined as the proportion of subjects who are weekly responders

for 9 out of the first 12 weeks, with at least 3 of these weeks occurring in weeks 9 to 12. A weekly responder was defined as a subject who has an average of ≥3 complete spontaneous bowel movements (CSBM)/week and an average increase from baseline of >1 CSBM/week for that week.
    - FDA agreed with the proposed plan for bisacodyl rescue treatment.
    - The Applicant also proposed to evaluate the safety of long term dosing of lactitol for up to one year in a separate single-arm trial. Note that at the time, the Applicant proposed Study BLI400-302 as this single-arm, 52 week trial; however, Study BLI400-302 in the current NDA submission is a 6 month placebo-controlled trial. FDA agreed that the proposed study duration of one year may be adequate, provided the drug data base adequately characterizes and quantifies the safety profile of lactitol. However, FDA communicated that if adverse events differ between the controlled and uncontrolled trials, it may be more difficult to assess the causality relationship between adverse events observed and the study drug in the absence of a concurrent control.
    - FDA communicated that there is inadequate information from the published literature studies to evaluate the carcinogenicity and reproductive toxicity of lactitol. To support the NDA, FDA stated that the Applicant should conduct the required carcinogenicity and reproductive toxicity nonclinical studies. These studies were submitted and reviewed by Tamal Chakraborti, PhD. Refer to Dr. Chakraborti's reviews in DARRTS, dated September 21, 2016 and November 4, 2016 for further discussion.
    - The Applicant clarified and FDA agreed with the use of "regular" (i.e., not digestion-resistant) maltodextrin for the clinical trials.

- March 14, 2014: iPSP submitted; however, on April 11, 2014 DGIEP informed the Applicant that the iPSP submission was materially incomplete and could not be reviewed. The Division recommended that the Applicant submit a revised iPSP within 30 days.

- May 8, 2014: Revised iPSP submitted.
    - Due to submission coding error, this submission was not received by the appropriate reviewers.

- August 20, 2015: Study BLI400-301, originally designed as a placebo-controlled study, was amended to a double-blind, active-controlled design (lactitol versus lubiprostone).

- May 2, 2016: Study BLI400-302, originally designed as a 12 month open-label study, was amended to a double-blind, placebo-controlled design. Protocol BLI400-303 was submitted and designed as a 12 month open-label safety study.

- June 9, 2016: DGIEP sent an Advice Letter/IR requesting information on the adult program and an update on the status of the iPSP.

- August 8, 2016: Applicant responded to the Advice Letter/IR dated June 9, 2016 and acknowledged that no further comment had been received from FDA since the May 2014 submission of the revised iPSP. Applicant confirmed that Study BLI400-302 is intended to be a second pivotal trial (in addition to BLI400-301) to support an approval.

- February 14, 2018: PPSR submitted.
    - During the team's review of the PPSR, the team identified that there was no agreed iPSP; therefore, the team requested that the Applicant submit a revised iPSP in accordance with the most recent iPSP Guidance.

- May 24, 2018: Revised iPSP submitted.

- June 7, 2018: DGIEP issued an Inadequate Letter for the PPSR.
    - The team had concerns with the intended patient population, dosing, treatment duration, and endpoints.

- June 29, 2018: The Applicant submitted NDA 211281 (no pre-NDA meeting was held prior to submission)

- August 1, 2018: The Division's assessment of the May 24, 2018 iPSP submission was presented to the Pediatric Review Committee (PeRC), who agreed that the iPSP required substantial revisions, and that a refuse-to-file action is warranted based on the lack of agreed iPSP at the time of filing. Specifically, the following deficiencies were identified within the submitted iPSP:
    - Justification to support the proposed [redacted] (b) (4) is insufficient
    - Proposed timelines are not acceptable (no justification for a need to wait until adult approval to initiate studies in pediatric patients, based on safety or concerns of prospect of direct benefit)
    - Required juvenile toxicology studies needed to support the study of patients less than 6 years of age were not proposed
    - Proposed study population (inclusion and exclusion criteria) and primary study endpoint are not consistent with current FDA recommendations
    - Proposed duration of trial is not sufficient to support the planned chronic administration

  August 21, 2018: DGIEP issued a written response to the iPSP, reiterating the comments from the inadequate PPSR letter as well as additional comments specific to the iPSP.

- August 27, 2018: The Applicant submitted a proposed Agreed iPSP; however, the submission could not be agreed upon due to deficiencies. Additional negotiations with the Applicant were needed during the 30-day review cycle and presented to PeRC for concurrence prior to reaching agreement.

- August 28, 2018: Refusal to file action due to lack of agreed iPSP.

- September 20, 2018: Agreed iPSP issued.

- November 21, 2018: Resubmission of NDA 211281.

- June 14, 2019: Major amendment to this application due to the Applicant's May 21, 2019 submission. This submission included a meta-analysis comparing the response rate of the lactitol group from Study 301 to placebo response rates from published trials, as well as responses to the Information Request sent on May 7, 2019 and to FDA requests included in the agenda of the Mid-Cycle Communication meeting held on May 8, 2019. The Division communicated to the Applicant that the new goal date is February 20, 2020.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Compliance with Good Clinical Practices

The Applicant stated that Studies 301, 302, and 303 were conducted in compliance with Good Clinical Practices, including the archiving of essential documents. The studies were conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, and all of the applicable US Code of Federal Regulations (CFR), 21 CFR Parts 50 and 312. Informed consent was mandatory for participation in the trials. In obtaining and documenting informed consent, the investigator was instructed to comply with the applicable regulatory requirement(s), and was to adhere to Good Clinical Practices and to the ethical principles that have their origin in the Declaration of Helsinki.

Inspections for this NDA were conducted at four clinical investigator (CI) sites and the Applicant. Although inspectional observations were noted at the two clinical investigator sites (Drs. Idalia Acosta and M.A. Mahmud), the findings are unlikely to have an impact on overall results. At Dr. Acosta's site, 4/26 patients were noted to have incomplete daily diary entries, specifically the date of the last bowel movement (efficacy data) entry was at least four months prior to the date of the last visit, as noted in the source documentation. Three of these patients were randomized to the placebo group and one to the lactitol group. The missing values were reported in the NDA submission and 3 of the 4 patients were identified by the Applicant as having participated in the trial but had not been compliant with data entry. At Dr. Mahmud's site, one patient was randomized and completed the trial but did not meet the enrollment criterion for <3 CSBMs per week during the screening period. In the NDA submission, the Applicant noted that this patient was randomized in error and was excluded from the modified intent to treat (mITT) and per-protocol (PP) populations. No substantial regulatory findings or data integrity issues were noted. The study data generated by these sites and the sponsor are acceptable in support of the application. See OSI review by Dr. Susan Leibenhaut, dated June 21, 2019 for full details.

Data Integrity Concerns Identified by the Review Team

Upon review of the submission, the review team discovered that several patients had enrolled in both Study 301 and Study 302. The Division previously communicated in the Refuse to File letter (08/28/2018) that although it was not a refuse to file issue, the future resubmission of the NDA should ensure that patients who had enrolled in both studies should be only included in the efficacy for the first study in which they enrolled. The NDA resubmission following refusal to file (11/21/2018) added newly defined analysis populations, which excluded subjects that had previously enrolled in Study 301. Upon further review, the review team determined that the newly defined efficacy analysis population included a randomized patient that had enrolled in two study sites and excluded two randomized patients enrolling in "multiple" (per the Applicant) investigational studies. In addition, the primary efficacy analysis population excluded subjects without post-baseline diary entries; however, these patients should have been included based on the definition in the statistical analysis plan (SAP). Due to these issues, the review team defined a new study population, 'the FDA primary analysis population", which was used as the primary analysis population for efficacy results.

In addition, the review team was alerted during the review of this NDA that Sami Anwar has been under investigation for falsifying data and has now been convicted of various crimes relating to the falsification of data in clinical trials. He is the owner of Mid Columbia Research LLC and Zain Research LLC. The review team carefully evaluated the submission to determine whether any investigators were associated with Mid Columbia and Zain Research for the three, phase 3 trials submitted to support this NDA.

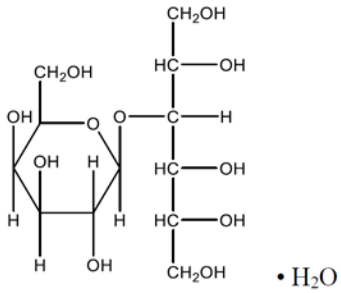
The review team identified one investigator, Cheta Nand, who was associated with Zain Research. He enrolled 8 patients in Study 301 at site 33: 4 in the lactitol arm and 4 in the Amitiza arm. Excluding these patients from the analysis does not change the results. Mid Columbia and Zain and Mid-Columbia Research groups do not appear to have been involved with the other phase 3 trials (Studies 302 and 303).

Financial Disclosure

The Applicant provided a signed copy of FDA Form 3454 with an attached list of investigators from each study. This certified that they have not entered into any financial arrangement with the listed 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). Refer to the Appendix 15.2 Financial Disclosure for details.

4.2. Product Quality

The drug substance in lactitol for oral solution is lactitol monohydrate. It is a synthetic monosaccharide sugar derivative of lactose. It is very soluble in water but poorly absorbed Biopharmaceutical Classification System Class III (BCSIII) compound. It is a chiral compound with no known polymorphs. Its molecular formula is $C_{12}H_{24}O_{11}.H_2O$ and its molecular weight is 362.33.



Lactitol Monohydrate

Lactitol monohydrate is manufactured by (b) (4) (DMF (b) (4)) and by (b) (4) (DMF (b) (4)). The complete CMC information including raw materials, manufacturing process, (b) (4) characterization, stability, storage and container closure is provided in these DMFs. The overall quality of lactitol monohydrate is controlled by its specification. Based on the stability studies of multiple lactitol monohydrate batches a re-test period of (b) (4) months was granted.

The drug product, lactitol for oral solution, is supplied as lactitol powder in 10 g single-dose (b) (4) 280 g multi-dose HDPE bottle and 560 g multi-dose HDPE bottle. Ten grams of lactitol

is equivalent to 10.5 g of lactitol monohydrate. There are no preservatives or anti-oxidants in the drug product. The cap of the multi-dose bottle is used to measure 10 g of lactitol. The drug product is dissolved in 4 oz to 8 oz of water, juice or beverage for oral administration.

The drug product is manufactured by Braintree Laboratories, Inc.; MA. A 5 g desiccant packet is added to each bottle. The drug product manufacturing process includes (b) (4) . The proposed commercial batch size is approximately (b) (4) kg. The overall control strategy for the drug product's identity, strength, purity and quality deemed adequate based on raw material controls and drug product specification. The microbial limits tests are performed on each of batch of the bulk drug substance. Therefore, the applicant's proposal for not testing microbial purity of the finished drug product deemed acceptable.

Based on satisfactory stability studies of the drug product, 24 months of expiration dating period is granted when stored at room temperature in the proposed container closure system.

The applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.

The Office of Process and Facilities has made an "Approval" recommendation for all manufacturing and testing facilities involved in this NDA.

The claim of a categorical exclusion from the requirements of an environmental assessment (EA) is granted.

The label/labeling is satisfactory form the CMC perspective.

Therefore, from the Office of Pharmaceutical Quality perspective, this NDA is recommended for approval.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

In pharmacology studies in rats, following oral administration, lactitol increased the weight of the contents of the small intestine and fermentation was not necessary for lactitol-induced osmotic effects in the small intestine.

The Applicant has conducted a 28- and 91-day oral (gavage) toxicity studies in Tg.rasH2 mice and rats, respectively, with lactitol at 125, 500 and 2000 mg/kg/day. These studies were conducted to inform the dose selection of the carcinogenicity studies. Target organs could not be identified in the absence of significant treatment-related histopathological changes in any organ or tissue in either species. The No Observed Adverse Effect Level (NOAEL) was 2000 mg/kg/day for both mice and rats. The Applicant did not conduct any chronic toxicity, fertility and early embryonic development and genotoxicity studies per the agreement with the Agency (FDA meeting minutes dated 1/21/2014) and relied on the published literature for chronic toxicity, fertility and early embryonic development and genotoxicity studies. The published studies are considered adequate to support the safety of lactitol for the proposed indication. In a 13-week oral gavage study in rats with lactitol at 625, 2500 or 10000 mg/kg/day, the NOAEL was 625 mg/kg/day. In a combined oral dietary chronic toxicity/carcinogenicity study, Swiss mice were fed diets containing 0, 2, 5, and 10% lactitol monohydrate for 104 weeks. The high dose resulted in a mean daily intake of approximately 11000 mg/kg and 7500 mg/kg of lactitol for male and female mice, respectively. These doses are approximately 31- and 21-fold higher, respectively, than the recommended dose in humans (21g). Lactitol was generally well tolerated. The incidence of nonneoplastic, preneoplastic and neoplastic lesions was similar across the groups.

The Applicant did not conduct any fertility and early embryonic development study. The Applicant relied on published literature, which indicated that lactitol did not cause any adverse effect on fertility and early embryonic development in rats at doses up to 10000 mg/kg/day (about 4.6 times the recommended daily human dose based on body surface area). Embryofetal development studies have been performed in pregnant rats at oral doses of lactitol up to 2000 mg/kg/day (about 0.93 times the recommended daily human dose based on body surface area) and in pregnant rabbits at oral doses up to 1000 mg/kg/day (about 0.93 times the recommended daily human dose based on body surface area) administered during the period of organogenesis. These studies did not reveal any evidence of adverse effects on embryofetal development due to lactitol. In a pre-and postnatal development study in rats, lactitol, administered from gestation day 6 to lactation day 20, did not cause any adverse effect on pre and postnatal development at doses up to 2000 mg/kg/day (about 0.93 times the recommended daily human dose based on body surface area).

Published studies (referenced in Section 5.5.1/General toxicology; additional studies) indicated that lactitol was negative in the Ames test, chromosome aberration test with cultured mammalian cells, and in vivo mouse micronucleus test.

In a 26-week oral (gavage) carcinogenicity study in Tg.rasH2 mice at 225, 675 and 2000 mg/kg/day, there were no drug-related neoplasms in either males or females. The 104-week oral carcinogenicity study in rats was initiated in February 2017, and the study report will be submitted post approval, as per agreement with the Agency.

The NOAELs of 2000 mg/kg/day in mice and rats are about 5.7-fold higher than the maximum human dose proposed in this NDA (21 g/60 kg person, or 0.35 g/kg). Based on the AUC at the NOAEL, the exposure multiples in animals compared to humans ranged from 0.7 to 1.5-fold (compared to fasted healthy humans, $AUC_{0\text{-}24h}$ = 14827 ng.h/mL from clinical study BLI400-101) to approximately 3.7 to 1.8-fold (compared to fed healthy humans, $AUC_{0\text{-}24h}$ = 5842 ng.h/mL from clinical study BLI400-101).

From the nonclinical perspective, there are no approvability issues.

5.2. Referenced NDAs, BLAs, DMFs

IND 118906 (Lactitol, Braintree Laboratories)

5.3. Pharmacology

Primary Pharmacology
Potential acute gastrointestinal (GI) effects of lactitol was examined in Sprague Dawley rats following a single oral (gavage) dose (4000 mg/kg). Lactitol decreased GI motility (29% below control values) and increased small intestine and colon content weight (62% and 73% above control values, respectively).

Potential acute GI effects of a single oral gavage administration of lactitol in Sprague Dawley rats was examined following a 20-day pretreatment period with antibiotics. Lactitol at 4000 mg/kg increased the tissue weights or contents of all the intestinal tissues except the ileum when compared to control. Antibiotic pretreatment further enhanced the effect of lactitol in all tissues except the stomach. Total excreted fecal pellet weights appeared to be higher for the antibiotic pretreated groups relative to the non-pretreated groups. Bacterial content of the GI tract for antibiotic pretreated animals was reduced by 10^6 (aerobic bacteria) to 10^8 (anaerobic bacteria). Overall, there was no meaningful difference in tissue weight, tissue contents, or tissue lactitol content between animals that were not pretreated versus those that were pretreated with antibiotics prior to administration of lactitol.

Secondary Pharmacology
The potential of lactitol to release guanosine 3′,5′-cyclic monophosphate (cGMP) was examined using Caco-2 cells. In the pilot study, lactitol appeared to stimulate the release of cGMP from the Caco-2 cells. The subsequent follow-up study showed cGMP was not released after incubation with lactitol.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Determination of the Pharmacokinetics and Relative Bioavailability of Lactitol Following Oral or Intravenous Administration to Rats (2062-030)	Following a single intravenous bolus injection (100 mg/kg) of lactitol to fed male rats, mean $AUC_{0\text{-}24hr}$, and AUC_{NF} values were 151000 ng.hr/mL and 152000 ng.hr/mL, respectively. Following a single oral administration of lactitol (750 mg/kg) to fed male rats, mean C_{max}, $AUC_{0\text{-}24hr}$, and AUC_{INF} values were 2980 ng/mL, 8990 ng.hr/mL, and 9830 ng.h/mL, respectively. Following a single oral administration of lactitol at 750 mg/kg to fasted male rats, mean C_{max}, $AUC_{0\text{-}24hr}$, and AUC_{INF} values were 3480 ng/mL, 8760 ng.hr/mL, and 8780 ng.hr/mL. respectively. There was no apparent difference in systemic exposure ($AUC_{0\text{-}24hr}$ and AUC_{INF} values) between fed and fasted animals; however, there was an apparent extended absorption from 4 hours to 8 hours for animals in the fed state when compared to animals in the fasted state indicating a potential food-effect. Oral bioavailability calculated using $AUC_{0\text{-}24hr}$/dose was approximately 0.795% and 0.775% for fed and fasted animals, respectively. Oral bioavailability calculated using AUC_{INF}/dose was approximately 0.862% and 0.770% for fed and fasted animals, respectively.
Distribution	
	Distribution study was not performed. However, GI distribution of lactitol was examined in a pharmacology study in rats after an oral dose of 4 g/kg. Lactitol reached in mg/g levels in all intestinal components including the colon. The drug level peaked in the duodenum in 10 minutes, while levels in the jejunum, cecum and colon were still rising at 90 minutes post-dose.
Metabolism	
	Metabolism studies were not performed. Published studies indicated that lactitol is not degraded by the galactosidase enzymes of the small intestine. In rats, colonic microflora degrades lactitol extensively so that approximately 50% of an administered dose of ^{14}C-labeled lactitol appeared in expired air at 24 hours post-dose while a minor proportion of the administered radioactivity appeared in the urine (6.8%) or feces (11%) at 24 hours post-dose (WHO Food Additives Series, 1983). Lactitol increased proportions of acetic acid and decreased proportions of butyric acid in the hindgut of rats (Nilsson U and Nyman M, 2005, Br J Nutr, 94:705-713).
Excretion	
	Excretion study was not performed. However, GI distribution of lactitol was examined in a pharmacology study in rats after an oral dose of 4 g/kg. As discussed above, lactitol reached mg/g levels in all intestinal components including the colon. Lactitol was detected in the feces of rats 10 minutes postdose in µg/g levels. Overall, 0.15% of the administered dose was excreted in the feces.

TK data from general toxicology studies

28-Day Toxicity Study in TgrasH2 Mouse (Study No. 2062-015)

Mouse

Study 2062-015

Group; Dose	Day	Sex	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng.hr/mL)	AUC_{0-24h} (ng.hr/mL)	$t_{1/2}$ (hr)
Group 6;	1	M	468	1	518	674	Nc*
125 mg/kg		F	414	1	522	756	Nc*
		F/M	0.885		1.01	1.12	
Group 6;	28	M	631	1	724	756	Nc*
125 mg/kg		F	506	1	614	861	Nc*
		F/M	0.802		0.849	1.14	
Group 7;	1	M	1,920	1	2,361	2,420	Nc*
500 mg/kg		F	1,390	1	2,069	2,119	Nc*
		F/M	0.724		0.876	0.876	
Group 7;	28	M	2,000	1	3,011	3,381	1.72
500 mg/kg		F	2,450	1	4,323	4,462	1.02
		F/M	1.23		1.44	1.32	
Group 8;	1	M	4,547	1	7,934	8,053	0.838
2,000		F	3,217	2	7,625	9,001	Nc*
		F/M	0.707		0.961	1.12	
Group 8;	28	M	5,413	1	12,566	13,176	1.05
2,000		F	2,863	1	7,397	8,102	1.38
		F/M	0.529		0.589	0.615	

*Nc: Not calculable

Rat

90-Day Oral Toxicity Study in Rats (Study No. 2062-013)

Study 2062-013

Group; Dose	Day	Sex	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng.hr/mL)	AUC_{0-24h} (ng.hr/mL)	$t_{1/2}$ (hr)
Group 6; 125 mg/kg	1	M	532	1	1,324	1,544	nc
		F	413	2	1,493	1,771	nc
		F/M	0.776		1.13	1.15	
Group 6; 125 mg/kg	91	M	506	1	1,317	1,401	1.15
		F	761	1	1,184	1,219	nc
		F/M	1.50		0.899	0.870	
Group 7; 500 mg/kg	1	M	2,230	1	5,505	6,126	1.47
		F	1,670	1	3,654	4,004	1.42
		F/M	0.749		0.664	0.654	

Type of Study	Major Findings							
	Group 7; 500 mg/kg	91	M	2,545	2	5,916	6,182	nc
			F	1,653	1	3,324	3,505	1.12
			F/M	0.650		0.562	0.567	
	Group 8; 2,000 mg/kg	1	M	3,847	1	13,722	18,674	2.58
			F	3,303	1	10,691	13,339	2.13
			F/M	0.859		0.779	0.714	
	Group 8; 2,000 mg/kg	91	M	2,917	1	14,052	21,244	3.64
			F	3,647	1	17,822	21,990	2.07
			F/M	1.25		1.27	1.04	

Type of Study: **TK data from reproductive toxicology studies**

Pilot Prenatal Developmental Toxicity Study in Rats with a Toxicokinetic Evaluation (Study No. 2062-021)

Pilot Prenatal Developmental Toxicity Study in New Zealand White Rabbits with a Toxicokinetic Evaluation (Study No. 2062-022)

Major Findings

Rat

Study 2062-21

Group	Dose (mg/kg/day)	Day	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24h} (ng.hr/mL)	$t_{1/2}$ (hr)
7	125	GD6	744	1	1,566	Nc*
		GD17	559	1	1,420	Nc*
		% Change	-25%		-9%	
8	500	GD6	2,230	1	5,045	0.891
		GD17	2,853	2	8,245	Nc*
		% Change	28%		63%	
9	750	GD6	2,203	1	6,584	1.54
		GD17	1,867	1	8,529	3.28
		% Change	-15%		30%	
10	2,000	GD6	3,530	1	13,576	2.15
		GD17	2,557	1	19,330	2.87
		% Change	-28%		42%	

Rabbit

Study 2062-022

Dose Normalized Toxicokinetic Parameters

Parameter	Group	Day	Mean	N
NC_{max} (ng/mL) /(mg/kg)	7	GD6	18.1	4
		GD18	13.6	3
	8	GD6	9.75	4
		GD18	13.2	4
	9	GD6	5.99	4
		GD18	7.48	4
	10	GD6	5.56	4
		GD18	8.53	4
$NAUC_{last}$ (ng.hr/mL) /(mg/kg)	7	GD6	41.5	4
		GD18	26.0	3
	8	GD6	28.2	4
		GD18	33.7	4
	9	GD6	21.6	4
		GD18	18.9	4
	10	GD6	30.7	4
		GD18	25.6	4

Abbreviations: C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; AUC_{0-24h}, area under the curve from time zero to 24 hours; AUC_{0-t}, area under the curve from time zero to time t; $T_{1/2}$, half-life; $NAUC_{last}$, dose-normalized area under the curve from time zero to the time of the last quantifiable concentration and calculated as AUC_{last}/dose; NC_{max}, dose-normalized maximum plasma concentration and calculated as C_{max}/dose
Note: N: Dose normalized

5.5. Toxicology

5.5.1. General Toxicology

GLP compliant chronic toxicity studies with lactitol were not required because of the Generally Recognized as Safe food additive status of lactitol and extensive ex-US experience with the drug.

Study title/number: 28-Day Toxicity Study in TgrasH2 Mice (Study No. 2062-015)

Key Study Findings:

- There were no significant treatment-related effects on clinical pathology parameters and organ weights.
- There was no significant treatment related gross or histopathology findings.
- The No Observed Adverse Effect Level (NOAEL) was determined to be the highest tested dose of 2000 mg/kg/day.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 125, 500, 2000 mg/kg/day ; once daily
Route of administration:	Oral (gavage)
Formulation/Vehicle:	Water
Species/Strain:	CByB6F1-Tg(HRAS)2Jic (-/-homozygous c-Ha-ras) transgenic hybrid mice
Number/Sex/Group:	10/sex/group
Age:	5 Weeks
Satellite groups/ unique design:	Toxicokinetics (38/sex/dose; 8/sex in control
Deviation from study protocol affecting interpretation of results:	None

Observations and Results:

Parameters	**Major findings**
Mortality	None
Clinical Signs	None
Body Weights	There were no significant treatment related effects.
Hematology	There were no significant treatment related effects.
Clinical Chemistry	There were no significant treatment related effects.
Urinalysis	There were no significant treatment related effects.
Gross Pathology	There were no significant treatment related findings.
Organ Weights	There were no significant treatment related effects.
Histopathology Adequate battery: Yes/No	Yes. There were no significant treatment-related histopathological findings in any organ or tissue.
[Other evaluations]	None

Study title/number: 91-Day Toxicity Study in Sprague Dawley Rat (Study No. 2062-013)

Key Study Findings:

- There were no significant treatment-related effects on clinical pathology parameters and organ weights.
- There were no significant treatment-related gross or histopathology findings.
- The NOAEL was determined to be the highest tested dose of 2000 mg/kg/day.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 125, 500, 2000 mg/kg/day; once daily
Route of administration:	Oral (gavage)
Formulation/Vehicle:	Water
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	10/sex/group
Age/Weight:	6 Weeks/ Male: 231-268 g; Female: 175-206 g
Satellite groups/ unique design:	Toxicokinetics (9/sex/dose)
Deviation from study protocol affecting interpretation of results:	None

Observations and Results:

Parameters	Major findings
Mortality	Three animals (one main study female at LD, one main study female at MD, and one TK male at MD) were found dead between Days 20 and 81. The cause of death for both main study animals was attributed to lymphoma. Spontaneous lymphoma in Sprague Dawley rats, although rare, has been previously reported (Matsushima K, et al., 2010, Spontaneous Malignant T-Cell Lymphoma in a Young Adult Crl:CD (SD) Rat, J Toxicol Pathol, 23(1):49-52). Due to the sporadic and low occurrence only in the lower dose females and the lack of evidence for neoplastic process in males in the low dose groups and/or males and females at the high dose, this finding was considered to be incidental and unrelated to the test article. Microscopic examination of the TK animal was not conducted, per the protocol. Deaths were not considered treatment related.
Clinical Signs	None
Body Weights	There were no significant treatment related effects.
Ophthalmoscopy	There were no significant treatment related effects.
Hematology	There were no significant treatment related effects.
Clinical Chemistry	There were no significant treatment related effects.
Urinalysis	There were no significant treatment related effects.
Gross Pathology	Enlarged spleen, adrenal glands, and lymph nodes (iliac and mandibular) and red foci of the brain and glandular stomach in one main study female at MD were secondary to lymphoma and considered unrelated to the test article.

Organ Weights	Increase in absolute mean weight and organ-to-body/brain weight ratios of the cecum and colon in males and females, respectively, at HD compared to controls. Due to lack of microscopic correlates, absence of related clinical observations, and/or lack of similar trend in the opposite sex, these findings were considered incidental and unrelated to the test article.
Histopathology Adequate battery: Yes/No	Yes. An incidental neoplasm (lymphoma) was observed in one main study female each at LD and MD.
Other evaluations	None

Abbreviations: LD, low dose; MD, mid dose; HD, high dose

General toxicology; additional studies

Published Toxicity Studies

Single Dose Studies		
Mouse		Rat
Dose	LD_{50} values were 20-30 g/kg (Okazaki S, et al, 1994)	LD_{50} values were >30 g/kg (Okazaki S, et al, 1994)
Repeat Dose Studies		
Mouse		Rat
Oral (Diet)		Oral
Dose (mg/kg/day)	2, 5, 10% HD ~ 11 and 7.5 g/kg in males and females, respectively (Til HP, et al 1992)	0.625, 2.5 or 10 g/kg/day (Gavage) (Nishiguchi Y, et al., 1994)
Duration	104 Weeks	13 Weeks
Adverse Findings	Lactitol was generally well tolerated, without affecting body weights or survival. Urinalysis was unremarkable. Mean organ weights were not affected, except that the filled or empty cecum was heavier at the MD and HD compared to control. The incidence of nonneoplastic, preneoplastic and neoplastic lesions was similar across the groups.	At MD and HD, decreased food consumption and diarrhea. At the HD, decreased urine volume and K^+ excretion, decreased alkaline phosphate (ALP), total cholesterol, triglycerides, glucose, Ca^{++}, Na^+, Cl^- and total protein. Cecal weight was increased in all dose groups while at MD and HD, cecum was distended and showed mucosal hyperplasia. Adrenal weight was increased at HD and hypertrophy of zona fasciculata was seen at MD and HD. Thymus weight was decreased at HD. Except the cecum, the above-mentioned changes were reversed after the 5-weeek recovery period. The NOAEL was 0.625 g/kg-day.
Dose (mg/kg/day)		5, 10, or 20% (13 -13.8 g/kg) lactitol (Diet) (Sinkeldam EJ, et al., 1992)
Duration		13 Weeks
Adverse Findings		Weanling Rats: Lactitol was generally well tolerated except for diarrhea/soft stool, related to the pharmacological actions of the drug. Increased serum ALP was seen at all doses. Relative weights of the kidney, liver, brains and testes were increased at HD and relative weight of

		the thyroid was increased in males at MD and HD. Dose-related cecal enlargement was observed at all doses. Histological examinations revealed swollen liver cells with an opaque cytoplasm and a loss of granularity at MD (male) and HD (both sexes). Bile duct proliferation was observed in treated animals. Adult Rats (10% and 20% lactitol): Doses were well tolerated. Relative liver weights were not affected except at HD. Dose-related increases in cecal weight were observed. Unlike the results in the 13-week feeding study in weanling rats, there were no histopathology findings in the liver.
Dog		
Dose (mg/kg/day)	250, 1250 and 6250	
Duration	52 Weeks	
Findings	In a 52-week oral toxicity study with 9-week recovery period in beagle dogs, animals were administered lactitol at 250, 1250 and 6250 mg/kg/day (Onishi M, et al., 1994). There were no treatment-related effects on survival, body weight gain and food consumption. Clinical signs included soft stool and diarrhea at the mid- and high dose. At the high dose, bloody stool, increased water consumption and increased urine volume were also observed. Cecum weight was increased at the high dose group without any gross pathology changes. There were no significant treatment-related effects on ophthalmoscopy, hematology, clinical chemistry and electrocardiography. The above changes were reversible. The NOAEL was determined to be 250 mg/kg/day.	

Abbreviations: LD, low dose; MD, mid dose; HD, high dose; NOAEL, No Observed Adverse Effect Level
Okazaki S, et al, 1994, J Toxicol Sci, 19 Suppl 3:295-299)
Til HP, et al 1992, J Am Coll Toxicol, 11(2):209-217
Nishiguchi Y, et al., 1994, J Toxicol Sci, 19 Suppl 3:305-326
Sinkeldam EJ, et al., 1992, J Am Coll Toxicol, 11(2):165-188
Onishi M, et al., 1994, Lactitol, J Toxicol Sci, 19, 405-427

5.5.2. Genetic Toxicology

The Applicant did not conduct genotoxicity studies with lactitol and relied on the published literature. Lactitol was examined for potential mutagenicity in the Ames test, chromosome aberration test with cultured mammalian cells, and in vivo mouse micronucleus test. The results showed that lactitol has no mutagenicity potential (Iwakura K, et al., 1994, J Toxicol Sci, 19 Suppl 3:487-497).

5.5.3. Carcinogenicity

A 26-week oral (gavage) carcinogenicity study (Study No. 2062-014) in Tg.rasH2 mice was conducted with lactitol monohydrate at 225, 675 and 2000 mg/kg/day (0.1, 0.3 and 0.93 times the recommended daily human dose, respectively, based on body surface area). There were no drug-related neoplasms in either males or females. Please see Appendix 15.3 for the review of the carcinogenicity study in TgrasH2 mice.

The 104-week oral carcinogenicity study (Study No. 2062-026) in rats was initiated in February 2017 and the Applicant stated that the final report will be submitted to the Agency in December

2019. The report is pending. The 104-week rat carcinogenicity study will not be required prior to NDA approval.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The Applicant did not conduct any fertility and early embryonic development studies with lactitol and relied on the published literature. Published study (Ninomiya H et al., 1994, J Toxicol Sci, 19 Suppl 3: 429-439) indicated that lactitol did not cause any adverse effect on fertility and early embryonic development in rats at doses up to 10 g/kg/day (about 4.6 times the recommended daily human dose based on body surface area).

Embryo-Fetal Development

Study title/number: Study for the Effects on Embryofetal Development in Rats (Study No. 2062-023)

Key Study Findings

- There were no significant treatment-related effects of lactitol up to 2000 mg/kg/day on maternal survival, clinical findings, gestation body weights and body weight change, food consumption, macroscopic findings, uterine parameters (number of implantation sites, viable fetuses, resorption sites, preimplantation loss, and post-implantation loss), fetal sex ratios, fetal body weights or fetal external, visceral, and skeletal examinations.
- The NOAEL for maternal and developmental toxicity was determined to be 2000 mg/kg/day.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	125, 500 and 2000 mg/kg/day/Once daily
Route of administration:	Oral (Gavage)
Formulation/Vehicle:	Water
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	25/Group
Satellite groups:	
Study design:	Pregnant female rats were treated from gestation day (GD) 6 through GD 17 at a dose volume of 6 mL/kg
Deviation from study protocol affecting interpretation of results:	None

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	There were no significant treatment-related clinical signs.
Body Weights	Body weights were recorded on GD 6, 9, 12, 15, 18, and 20. There were no significant treatment-related effects on gestational body weights.
Necropsy findings Cesarean Section Data	There were no significant treatment-related effects on uterine parameters. Mean number of corpora lutea, uterine implantation sites, viable fetuses, litter size, resorption sites (live, dead and total), preimplantation loss and post-implantation loss per dam in the lactitol-treated groups was comparable to mean control values. Likewise, mean gravid uterine weights were comparable to mean control values. There were no significant treatment-related effects on fetal sex ratios. Mean fetal sex ratios in the lactitol-treated groups ranged from 50.7% to 58.0% and were comparable to the 51.2% in controls.
Necropsy findings Offspring	There were no significant treatment-related fetal external, visceral and skeletal abnormalities (malformation or aberration).

Abbreviations: LD, low dose; MD, mid dose; HD, high dose

Study title/number: Study for the Effects on Embryofetal Development in Rabbits (Study No. 2062-024)

Key Study Findings

- There were no significant treatment-related effects of lactitol up to 2000 mg/kg/day on maternal survival, clinical findings, gestation body weights and body weight change, food consumption, macroscopic findings, uterine parameters (number of implantation sites, viable fetuses, resorption sites, preimplantation loss, and post-implantation loss), fetal sex ratios, fetal body weights or fetal external, visceral, and skeletal examinations.
- The NOAEL for maternal and developmental toxicity was determined to be 1000 mg/kg/day.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	100, 500 and 1000 mg/kg/day/Once daily
Route of administration:	Oral (Gavage)
Formulation/Vehicle:	Water
Species/Strain:	New Zealand white rabbits
Number/Sex/Group:	23/Group
Satellite groups:	
Study design:	Pregnant female rabbits were treated from GD 6 through GD 18 at a dose volume of 6 mL/kg
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	There were no significant treatment-related clinical signs.
Body Weights	Body weights were recorded on GD 0, 6, 10, 13, 16, 19, 21, 25, and 29. There were no significant treatment-related effects on gestational body weights.
Necropsy findings Cesarean Section Data	There were no significant treatment-related effects on uterine parameters. Mean number of corpora lutea, uterine implantation sites, viable fetuses, litter size, resorption sites (live, dead and total), preimplantation loss and post-implantation loss per dam in the lactitol-treated groups were comparable to mean control values. Likewise, mean gravid uterine weights were comparable to mean control values. There were no significant treatment-related effects on fetal sex ratios. Mean fetal sex ratios in the lactitol-treated groups ranged from 46.9% to 51.1% and were comparable to the 48.9% in controls.
Necropsy findings Offspring	There were no significant treatment-related fetal external, visceral and skeletal abnormalities (malformation or aberration).

Prenatal and Postnatal Development

Study title/ number: Study of Toxic Effects on Pre- and Postnatal Development, including Maternal Function in Rats (Study No. 2062-025)

Key Study Findings

- For F0 animals, no significant treatment-related effects were observed on survival, clinical findings, gestation/lactation body weights and body weight change, food consumption, and parturition, F1 pup data to weaning (survival, sex ratio, body weights, physical development, and neuropharmacological examinations), and macroscopic findings.
- In the F1 animals, no treatment related effect was observed on body weights (growth or gestation), sexual maturation, clinical findings, behavior (learning and memory), reproductive performance/fertility indices, GD 13 uterine implantation data, and macroscopic findings.
- The NOAEL for toxicity in the F0 females was 2000 mg/kg/day, and for the F1 animals, the NOAEL was 500 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 125, 500, and 2000 mg/kg/day/Once daily
Route of administration: Oral (Gavage)
Formulation/Vehicle: Water
Species/Strain: Sprague Dawley rats
Number/Sex/Group: 25/Group
Satellite groups: None

Study design:	Pregnant female rats were treated from GD 6 through lactation day 20 at a dose volume of 6 mL/kg
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F0 Dams	There were no significant treatment-related effects on survival, clinical signs, body weights, food consumption, and parturition.
F1 Generation	There were no significant treatment-related effects on body weights, sexual maturation, clinical signs, behavior (learning and memory), reproductive performance/fertility indices, GD 13 uterine implantation data, and macroscopic findings. The only treatment-related effect was observed in the F1 pups was an increase in motor activity parameters (basic and fine movements and total distance traveled) at 2000 mg/kg/day in females. However, a similar increase in these motor activity parameters was not observed at 2000 mg/kg/day in F1 males.
F2 Generation	Not evaluated

5.5.5. Other Toxicology Studies

None

Comments on Impurities/Degradants
The impurities for the lactitol active ingredients were identified as heavy metals, related compounds, (b) (4). The Applicant conducted risk assessment for elemental impurities. The elemental data and specifications are summarized in the table (from p 3 of Section 3.2.P.5.5 of the SDN 002 dated 11/21/2018) below (parts per million or ppm [w/w]) based on a 21 grams daily dose.

The following table shows the daily exposure and Permitted Daily Exposure (PDE) vales for these elemental impurities.

Table 2: Daily Exposure and Permitted Daily Exposure Vales for These Elemental Impurities

Element	Class	Oral PDE (µg/day)	Daily Exposure from 21g DP (µg/day)	Acceptable
(b) (4)				Yes
				Yes
				Yes
				Yes
				Yes
				Yes
				Yes

Abbreviations: DP, drug product; PDE, permitted daily exposure

As shown in the above Table 2, the exposures to all elemental impurities from the drug product were within the respective PDE values for the oral daily dose limits per the ICH Q3D guidance and are acceptable.

The Applicant stated on page 2 of Section 3.2.S.3.2 that no Class 1, 2, or 3 residual solvents are likely to be present in the drug substance (b) (4). The Applicant submitted residual solvent declarations from the manufacturers ((b) (4)) of the drug substance, which state that lactitol monohydrate is free from residual organic solvents ((b) (4)) and there is no significant potential for any of the ICH Q3C Class 1, Class 2, or Class 3 solvents or any other organic solvents to be present in lactitol ((b) (4)). The following Table 3 (from page 2 of Section 3.2.S.3.2) shows the impurities specifications for the drug substance for two manufacturers ((b) (4)).

Table 3: Impurities Specifications for the Drug Substance for (b) (4)

Impurity	Specification
(b) (4)	

Table 4: Impurities Specifications for the Drug Substance for (b) (4)

Impurity	Specification
(b) (4)	

Abbreviations: NMT, not more than

(b) (4) Per the ICH Q3D, a PDE for (b) (4). At (b) (4) ppm, the exposure to (b) (4) would be (b) (4) µg/day ((b) (4) ppm x 21 g/day = (b) (4) µg/day) from 21 g daily dose. The ICH Q3D refers to (b) (4) Per the above (b) (4) document, the reference dose (RfD) for chronic oral exposure to (b) (4) is (b) (4) mg/kg/day ((b) (4) mg/day based on 60-kg body weight, which

is much higher than the expected daily exposure ([(b) (4)] µg/day) from 21 g of drug product. Therefore, the proposed specification for [(b) (4)] at not more than (NMT) [(b) (4)] ppm is acceptable.

[(b) (4)] The oral PDE for [(b) (4)] is [(b) (4)] µg/day (ICH Q3D). At NMT [(b) (4)] ppm ([(b) (4)]%), the exposure to [(b) (4)] would be [(b) (4)] µg/day from 21 g daily dose, which is the PDE of [(b) (4)] and is acceptable.

The proposed related substances specification of NMT [(b) (4)]% is higher than the qualification threshold (QT) of 0.15% for daily dose >2 g per the ICH Q3B guidance. However, these are qualified in the 90-day toxicology study in rats. The NOAEL was 2000 mg/kg/day in the 90-day study in rats. Drug substance batch (11462RD) used in the above study contained related compounds at NMT [(b) (4)]%. Therefore, the NOAEL for the related substances was [(b) (4)] mg/kg/day ([(b) (4)]% of 2000 mg/kg/day) in rats. The PDE was calculated as [(b) (4)] mg/day using the NOAEL of 2000 mg/kg/day in rats and appropriate safety factors per the ICH Q3C guidance. The exposure to these related compounds would be about [(b) (4)] mg/day ([(b) (4)]% of 21 g = [(b) (4)] mg/day) based on 21 g daily dose. The above PDE of [(b) (4)] mg/day for related substance is about [(b) (4)] fold higher than the daily exposure of [(b) (4)] mg/day from 21 g daily dose. Therefore, the proposed specification (NMT [(b) (4)]%) for related substances does not appear to raise a safety concern and is acceptable.

6 Clinical Pharmacology

6.1. Executive Summary

Lactitol monohydrate, also known as BLI400, is an osmotic laxative. The proposed indication is for the treatment of chronic idiopathic constipation in adults. The proposed dose is 20 g lactitol (equivalent to 21 g lactitol monohydrate) administered orally once daily. The dosage form of lactitol is a powder for solution. The formulation of lactitol is composed of a single component of lactitol monohydrate.

The Applicant evaluated the efficacy and safety of the 20 g lactitol daily dose in two phase 3 trials (BLI400-301 and BLI400-302). The Applicant additionally conducted a phase 1 PK study (BLI400-101) that evaluated the effect of food on the pharmacokinetics (PK) of lactitol in healthy subjects. The key review findings with specific recommendations and comments are summarized in Table 5.

Table 5 Summary of Clinical Pharmacology Findings and Recommendations

Review issues	Recommendations and comments
Pivotal or supportive evidence of effectiveness	• The efficacy of lactitol for the treatment of CIC in adults is established in a phase 3 trial (BLI400-302) and other supportive trials. • The Applicant did not conduct clinical studies to evaluate exposure-response relationship or other pharmacodynamic response of lactitol as supportive evidence of effectiveness.
General dosing instructions	• The efficacy and safety data from the phase 3 and other trials support the assessment that the proposed 20 g lactitol daily dose is acceptable. • The PK results of the food effect study support the recommendation that lactitol is preferably taken with meals to minimize systemic absorption.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Dose individualization based on intrinsic or extrinsic factors is not necessary.
Drug interactions	• The Applicant has not conducted in vitro or in vivo studies to evaluate the drug interaction potential for lactitol. See the recommended PMR to address this issue. • Lactitol may reduce the absorption of concomitantly administered oral medications. We recommend not taking concomitant oral medications within 2 hours before or after oral lactitol administration.
Bridge between the to-be-marketed and clinical trial formulations	• The to-be-marketed formulation was used in the phase 3 trial; therefore, there is no need to bridge the to-be-marketed formulation to the clinical trial formulation.

Abbreviations: CIC, chronic idiopathic constipation; PK, pharmacokinetic; PMR, postmarketing requirements

6.1.1. Recommendations

From a Clinical Pharmacology standpoint, this NDA is acceptable to support the approval of lactitol for the treatment of chronic idiopathic constipation in adults, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling.

We recommend that the Applicant conduct in vitro studies as Postmarketing Requirements (PMRs) to evaluate the drug interaction potential for lactitol. The results of the in vitro studies will be reviewed for further determination of whether in vivo drug interaction studies are needed. See Section 13 Postmarketing Requirements and Commitments.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Lactitol is an osmotic laxative that causes the influx of water into the small intestine leading to a laxative effect in the colon.

Following a single oral dose of 21 g lactitol monohydrate in healthy adult subjects, the mean±SD peak plasma lactitol concentrations (C_{max}) were 2,780 ± 1,711 ng/mL under fasted condition and 776 ± 253 ng/mL under fed condition with a high-fat meal. Taking lactitol with a meal reduced the total systemic lactitol exposure in plasma (AUC_{inf}) from 14,941 ± 8,966 ng·hr/mL to 6,019 ± 1,771 ng·hr/mL (i.e., >50% reduction of lactitol exposure by a high-fat meal). The mean plasma half-life of lactitol was approximately 2.4 hours under fed condition.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Overall, the efficacy and safety data from the phase 3 and other trials support the assessment that the proposed 20 g lactitol daily dose is acceptable. The phase 3 data also supported a dose reduction to 10 grams once daily for patients who developed persistent diarrhea or loose stools. The PK results of the food effect study support that lactitol is preferably taken with meals to minimize systemic absorption. Note that the phase 3 trial was conducted in CIC patients with lactitol administered under fed conditions.

6.2.2.2. Therapeutic Individualization

Dose individualization based on intrinsic or extrinsic factors is not necessary.

6.2.2.3. Outstanding Issues

There are no outstanding issues that would preclude the approval of this NDA from a clinical pharmacology perspective.

The Applicant has not conducted in vitro or in vivo studies to evaluate the drug interaction potential for lactitol. Although the absolute bioavailability of lactitol is expected to be low following oral administration, considerably high plasma concentrations were observed at the recommended oral dose of 21 g lactitol monohydrate. For example, individual plasma C_{max} concentrations ranging from 922 to 6,300 ng/mL in fasted condition and from 439 to 1,330 ng/mL in fed condition were observed following a single oral dose administration in healthy adult subjects. Currently, there is no information to adequately address the drug interaction potential for lactitol at these observed systemic concentrations. Therefore, we recommend that the Applicant conduct in vitro studies as PMRs to evaluate the drug interaction potential for lactitol. The results of the in vitro studies will be reviewed for further determination of whether in vivo drug interaction studies are needed.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A summary of the general clinical pharmacology and pharmacokinetics characteristics of lactitol is provided in Table 6.

Table 6: Summary of Clinical Pharmacology and Pharmacokinetic Characteristics of Lactitol

Pharmacology	
Mechanism of action	Lactitol is an osmotic laxative. Following oral administration, lactitol causes the influx of water into the small intestine leading to a laxative effect in the colon.
Pharmacodynamics	The pharmacodynamic effect of lactitol for the treatment of CIC has not been characterized.
General Information	
Bioanalysis	Lactitol concentrations in human plasma were quantified using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. The calibration range of the assay was from 25 ng/mL (LLOQ) to 10,000 ng/mL (ULOQ) using 50 µL human plasma.
PK model	Noncompartmental PK parameters were used to describe PK of lactitol following oral administration.
PK in healthy subjects	Table 7 below provides a summary of the PK parameters of lactitol following a single oral dose of 21 g lactitol monohydrate in healthy adult subjects under fed and fasting conditions. The mean plasma lactitol concentration-time profiles are shown in Figure 1.
PK in CIC patients	PK of lactitol in CIC patients has not been well characterized. Sparse PK samples were collected in a subset of CIC patients in phase 3 study BLI400-302; however, majority of PK samples had plasma lactitol concentrations that were lower than the LLOQ of the assay. For patients with measurable plasma lactitol concentrations, the plasma lactitol concentrations ranged from 26 ng/mL to 5,500 ng/mL. The limited PK data do not allow for a meaningful analysis to evaluate the effect of intrinsic factors on PK of lactitol in CIC patients.
Drug concentrations at steady state	The Applicant has not conducted multiple dose PK studies to evaluate the potential for drug accumulation or to characterize the drug concentrations at steady state; however, considering the short half-life of approximately 2-3 hours following a single dose administration in healthy subjects, there should be minimal or no accumulation of plasma lactitol following daily dose administration of 21 g lactitol monohydrate. Note that the limited PK data in Study BLI400-302 did not suggest a potential for drug accumulation at the recommended dose in CIC patients.
Drug interactions	The Applicant has not conducted in vitro or in vivo studies to evaluate the drug interaction potential for lactitol.
Renal or Hepatic impairment	The Applicant has not conducted formal clinical trials to evaluate the effect of hepatic or renal impairment on the PK of lactitol. The limited PK data in phase 3 study BLI400-302 did not suggest evidence of effect of renal or hepatic impairment on PK of lactitol in CIC patients.

QT Prolongation	The Applicant has not conducted a dedicated QT prolongation study. The ECG data from phase 3 studies BLI400-301 and BLI400-302 did not indicate clinically relevant effects of lactitol on the QT interval in CIC patients. The postmarketing data from European Medicines Agency also did not indicate safety concerns related to QT prolongation, other proarrhythmic risk, or cardiac events. Refer to Section 8.2 for more information.
Food effect	The PK results in Study BLI400-101 in healthy subjects showed that C_{max} and AUC values were more than 2-fold greater under fasted conditions compared to fed conditions.
ADME	
Absorption	Lactitol is minimally absorbed systemically; however, the absolute bioavailability of lactitol has not been characterized. Following a single oral dose of 21 g lactitol monohydrate in healthy subjects, the mean±SD peak plasma lactitol concentrations (C_{max}) were 2,780 ± 1,711 ng/mL under fasted condition and 776 ± 253 ng/mL under fed condition with a high-fat meal. The median Tmax was 4 hours. See Table 7 for a summary of PK parameters.
Distribution	The plasma protein binding of lactitol has not been characterized. It is not feasible to derive the PK parameter of distribution volume because lactitol is minimally absorbed systemically and the absolute bioavailability of lactitol is unknown.
Elimination	The median half-lives of lactitol were 2.5 hours and 2.2 hours under fed and fasted conditions, respectively. Unabsorbed lactitol is expected to be degraded in the colon. The amount excreted in feces has not been characterized.
Metabolism	The metabolic pathway of lactitol has not been characterized.
Excretion	The renal excretion of lactitol has not been characterized.

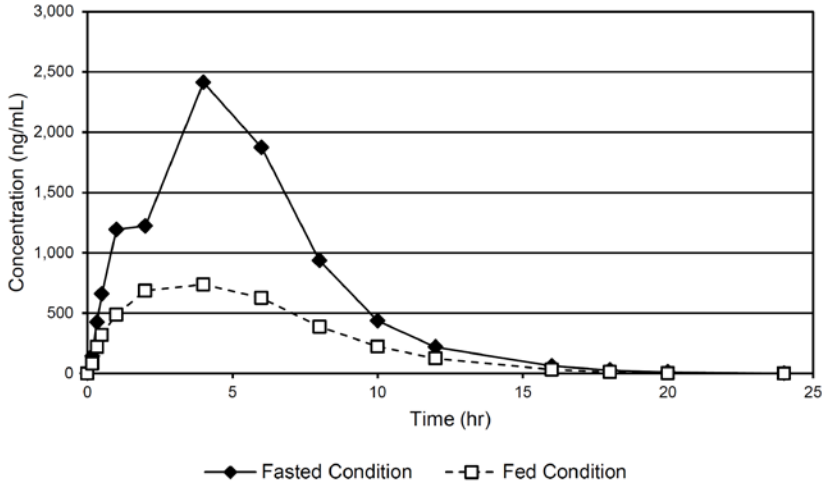
Abbreviations: CIC, chronic idiopathic constipation; LLOQ, lower limit of quantitation; PK, pharmacokinetic; SD, standard deviation; ULOQ, upper limit of quantitation

Table 7 Pharmacokinetic Parameters of Lactitol Under Fed and Fasted Conditions in Healthy Subjects in Study BLI400-101

PK Parameters	Condition	Mean ± SD (n=16)	Median [range]
C_{max} (ng/mL)	Fasted	2,780 ± 1,711	2,140 [922-6,300]
	Fed	776 ± 253	736 [439-1,330]
T_{max} (hr)	Fasted	3.22 ± 1.74	4 [0.5-6]
	Fed	3.56 ± 1.21	4 [1-6]
AUC_{0-t} (ng•hr/mL)	Fasted	14,827 ± 8,964	12,522 [5,023-31,737]
	Fed	5,842 ± 1,825	5,629 [3,605-9,947]
AUC_{inf} (ng•hr/mL)	Fasted	14,941 ± 8,966	12,623 [5,175-31,850]
	Fed	6,019 ± 1,771	5,752 [3,817-10,045]
$T_{1/2}$ (hr)	Fasted	2.16 ± 0.38	2.09 [1.66-3.03]
	Fed	2.43 ± 0.34	2.48 [1.79-2.90]

Abbreviations: C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; AUC_{0-t}, area under the curve from time zero to time t; AUC_{inf}, area under the curve to infinity; $T_{1/2}$, half life
Study BLI400-101 was a randomized, open-label, cross-over, two-period, and sequential PK study.
For each dose, 21 g lactitol monohydrate were mixed with 8 ounces of water for oral administration.
For the fed period, a high-fat, high-calorie meal was given to the subjects after a 10-hour overnight fast. Lactitol was given 30 minutes after the meal.
For fasted period, the subjects had over-night fast, received lactitol and continued to fast for 6 hours after lactitol administration.
Plasma samples were collected at pre-dose, at 10, 20, 30, and 60 min, and at 2, 4, 6, 8, 10, 12, 16, 18, 20, and 24 hours post-dose.
Abbreviations: PK, pharmacokinetic; SD, standard deviation
Source: Pharmacokinetic Report BLI400-101

Figure 1: Mean Plasma Lactitol Concentrations-Time Profiles Under Fasted and Fed Conditions After a Single Oral Dose of 20 Gram Lactitol in Healthy Subjects in Study BLI400-101



See footnotes of Table 7 for study design information.
Source: clinical study report BLI400-101, synopsis Figure 1, pg. 5.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy of lactitol for the treatment of CIC in adults is established in the phase 3 (BLI400-302) and other studies. The Applicant did not conduct clinical studies to evaluate dose-response or exposure-response relationship for efficacy or other pharmacodynamic response of lactitol in CIC patients.

Phase 3 Study BLI400-302 compared 20 g lactitol (N=299) once daily to placebo (N=304) in a 6 month treatment period. Patients who developed persistent diarrhea or loose stools were allowed to reduce their dose to 10 g lactitol once daily. The efficacy was assessed using a responder analysis and change-from-baseline in complete spontaneous bowel movements endpoint. A responder was defined as a patient who had at least 3 CSBMs in a given week and an increase of at least 1 CSBM from baseline in the same week for at least 9 weeks out of the first 12-week treatment period and at least 3 of the last 4 weeks (Weeks 9-12). A statistically significantly higher response rate of 25% was observed in the lactitol group compared to 13% in the placebo group. The lactitol group had a mean increase of 0.8 CSBM/week from baseline to week 12 over the placebo group. Other data sources provided supportive evidence that lactitol improves stool frequency in adult patients with CIC. See Section 8.1 for more details of the efficacy studies.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed oral dose of 20 g lactitol once daily is appropriate for the general adult CIC patients. The phase 3 data also support a dose reduction to 10 grams once daily for patients who develop persistent diarrhea or loose stools. The PK results of the food effect study (Study BLI400-101) in healthy subjects support that lactitol is preferably taken with meals to minimize systemic absorption. Note that the phase 3 trials in CIC patients were also conducted with lactitol administration under fed conditions.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No, a dose adjustment or management strategy for subpopulations based on intrinsic factors is not necessary.

Lactitol is administered orally and causes the influx of water into the small intestine leading to a laxative effect in the colon. The effectiveness of lactitol for the treatment of CIC is not dependent on the systemic exposure of lactitol; therefore, a systemic exposure-response (E-R) analysis for efficacy is not needed for further analysis of optimal dosing regimens in subpopulations. While systemic exposure of lactitol may be pertinent to its safety, it is not feasible to evaluate the E-R for safety in clinical trials because majority of patients in phase 3 trials had PK concentrations that are lower than the lower limit of quantitation of the assay. Additionally, the currently available PK information did not suggest any intrinsic factor that would significantly affect PK of lactitol.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food effect

The PK results of the food effect study (Study BLI400-101) in healthy subjects support the recommendation that lactitol is preferably taken with meals to minimize systemic absorption. The PK results in Study BLI400-101 showed that C_{max} and AUC values increased greater than 2-fold under fasted conditions compared to fed conditions. See Table 7 and Figure 1 in Section 6.3.1 for the PK results and OCP Appendix 15.4 for the individual study summary of Study BLI400-101.

Metabolism- or transporter-mediated drug-drug interactions

The Applicant has not conducted in vitro or in vivo studies to evaluate the potential for metabolism- or transporter-mediated drug interactions for lactitol. Although lactitol is expected to be minimally absorbed, individual plasma C_{max} concentrations ranging from 922 to 6,300 ng/mL in fasted condition and from 439 to 1,330 ng/mL in fed condition were observed following a single oral dose of 21 g lactitol monohydrate. The drug interaction potential for lactitol at these observed systemic concentrations is unknown.

The Applicant conducted an analysis for treatment-emergent adverse events in subjects taking narrow therapeutic index drugs in the phase 3 Study BLI400-302 and did not identify adverse events that were attributable to drug-drug interactions. See OCP Appendix 15.4 for the individual study summary of Study BLI400-302.

Mechanism of action- or PD-mediated drug-drug interactions

Lactitol is poorly absorbed and its osmotic laxative effect in the GI lumen may reduce the absorption of concomitantly administered oral medications, especially for those with poor intestinal permeability. The review team noted that adverse events (AEs) of hypertension were observed in some patients who were taking co-administration of anti-hypertension drugs in the phase 3 Study BLI400-302. The possibility could not be excluded that lactitol may have reduced absorption of anti-hypertension drugs and contributed to observed hypertension AEs. See OCP appendix for the individual study summary of Study BLI400-302. To mitigate the potential risk, the review team recommends including appropriate labeling language to inform that lactitol may reduce the absorption of concomitantly administered oral medications and patients should not take concomitant oral medications within 2 hours before or after lactitol administration.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 8: Table of Clinical Trials

Study #	Objective	Study design	Dosage regimen	N Patients	Key inclusion criteria	Treatment duration	Status
Trials for efficacy and safety evaluation, phase 3							
BLI400-301	To compare the safety and efficacy of BLI400 to Amitiza (lubiprostone) in adults with CIC.	Double-blind, randomized, parallel, active control	Mix two packets of BLI400 (lactitol) (21 g)* with 4-8 oz of juice or other beverage and take once daily. Amitiza (lubiprostone) 24 mcg capsules, 1 capsule twice daily.	459	Age ≥18 yrs Chronic constipation (defined by adapted ROME II criteria) Average <3 CSBM/week during 14 day screening period	12 weeks	Complete
BLI400-302	To compare the safety and efficacy of BLI400 to placebo in adults with CIC.	Double-blind, randomized, parallel, placebo-controlled	Mix 2 capfuls of BLI400 (lactitol) (21 g)* in 4-8 oz. of juice or other beverage and take once daily.	623	Age ≥18 yrs Chronic constipation (defined by adapted ROME II criteria) Average <3 CSBM/week during 14 day screening period	6 months; primary endpoint assessment at 12 weeks	Complete
BLI400-303	To evaluate the safety of chronic use of BLI400 in adults with CIC.	Open-label, uncontrolled	Mix 2 capfuls of BLI400 (lactitol) (21 g)* in 4-8 oz. of juice or other beverage and take once daily.	330	Age ≥18 yrs Chronic constipation (defined by adapted ROME II criteria)	12 months	Complete

Abbreviations: CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movement
*lactitol monohydrate 21 g is equivalent to lactitol 20 g
Source: Reviewer's table adapted from applicant's submission, NDA 211281, Tabular listing of all clinical studies, module 5.2, pages 1-2.

7.2. Efficacy Review Strategy

The Applicant's primary efficacy results were verified for both randomized, double-blind, controlled trials (studies 301 and 302). Additional exploratory analyses were performed to assess the robustness of the efficacy results for both studies. The review team decided that Study 301, a non-inferiority study with Amitiza as an active comparator, could not be relied on as one of the adequate, well-controlled trials after determining that the Applicant chose the non-inferiority (NI) margin based on results from a different drug (linaclotide) and an appropriate non-inferiority margin could not be established for the primary endpoint due to the lack of placebo-controlled data with the active comparator on that endpoint; furthermore, the study results were borderline with respect to the proposed non-inferiority margin. However, as lactitol has been marketed in other countries for decades, there are several publications on placebo-controlled and active-controlled efficacy trials with lactitol in CIC. The team determined that those publications, along with a comparison of the responder rate in the lactitol arm from Study 301 to placebo responder rates from other trials in CIC could provide supportive information on the efficacy of lactitol.

During the filing review of the initial NDA submission dated June 29, 2018, the team noted that there were duplicate patients who enrolled in both Study 301 and Study 302. The NDA was not filed at that time due to lack of an Agreed iPSP. The Refuse to File letter, dated August 28, 2018, contained additional concerns and recommendations that, although not refuse to file issues, should be addressed in a future resubmission. Because of the duplicate patients, the review team recommended that patients who enrolled in more than one phase 3 study (i.e., Study 301 and Study 302) should be included in the intent to treat (ITT) efficacy and safety populations only once, corresponding to the first study in which they enrolled. There were 11 patients who participated in both studies. Additional analyses were included in the NDA submission, dated November 21, 2018, excluding the patients who participated in Study 301 from the efficacy and safety analyses for Study 302. Therefore, any analysis conducted using a population noted as "FDA" population (e.g., FDA-mITT population or FDA-safety population) excludes these duplicate patients. An overview of the sample size used in each analysis population and the reasons why differences exist, if applicable, is provided in the Patient Disposition Section in this document.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used To Support Efficacy

8.1.1. BLI400-302 (Study 302)

Trial Design

Title: A Safety and Efficacy Evaluation of BLI400 Laxative in Constipated Adults

Primary Objective: To determine the effect of lactitol or placebo on patient constipation status over a twelve-week treatment period.

Secondary Objective: To evaluate responses by sex and age, weeks 13-24, rescue medication use, and BM frequency and symptoms.

Study design: BLI400-302 was a phase 3, randomized, double-blind, parallel group, placebo-controlled, multi-center study in adult patients with CIC. Patients were treated with 20 grams of lactitol or placebo daily for 6 months. The primary efficacy endpoint was assessed at 12 weeks of treatment and is defined below under Study Endpoints.

Study population: 623 patients were randomized in this study.

Key inclusion criteria:

1. Male or female subjects at least 18 years of age
2. Constipated, defined by the following adapted ROME II definition: Fewer than 3 spontaneous defecations per week and at least one of the following symptoms for at least 12 weeks (which need not be consecutive) in the preceding 12 months:
    a. Straining during >25% of defecations
    b. Lumpy or hard stools in >25% of defecations
    c. Sensation of incomplete evacuation for >25% of defecations
3. If female, and of child-bearing potential, is using an acceptable form of birth control (hormonal birth control, IUD, double-barrier method, depot contraceptive, sterilized, abstinent, or vasectomized spouse).
4. Negative serum pregnancy test at screening, if applicable
5. In the Investigator's judgment, subject is mentally competent to provide informed consent to participate in the study.

In addition, patients had to meet the following criteria during the 14 day screening period to be eligible for randomization:

6. Average of fewer than 3 complete spontaneous bowel movements per week during the 14 day Screening Period
7. Average of fewer than 6 spontaneous bowel movements (SBMs) per week
8. No more than 1 SBM with a Bristol Stool rating of 6
9. No SBMs with a Bristol Stool rating of 7
10. Completed an average of 5 or more days of bowel movement diary entries per week

Key exclusion criteria:

1. Reported loose (mushy) or water stools in the absence of laxative use for more than 25% of BMs during the 12 weeks before Visit 1
2. Met the Rome II criteria for Irritable Bowel Syndrome: reported abdominal discomfort or pain that had two or more of the following three features for at least 12 weeks, which need not have been consecutive, in the 12 months before Visit 1:
    a. Relieved with defecation
    b. Onset associated with a change in frequency of stool
    c. Onset associated with a change in form (appearance of stool)
3. Subjects with known or suspected ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, toxic megacolon
4. Subjects who had major surgery 30 days before Visit 1; appendectomy or cholecystectomy 60 days before Visit 1; abdominal, pelvic, or retroperitoneal surgery 6 months before Visit 1; bariatric surgery or surgery to remove a segment of the GI tract at any time before Visit 1

5. Subjects taking laxatives, enemas or prokinetic agents that refused to discontinue these treatments from Visit 1 until after completion of the study
6. Subjects who were pregnant or lactating, or intended to become pregnant during the study
7. Subjects taking narcotic analgesics or other medications known to cause constipation
8. Subjects with clinically significant cardiac abnormalities identified at the Visit 1 ECG

Study Endpoints

The primary endpoint was the proportion of patients who were weekly responders for at least 9 weeks out of the first 12-week treatment period, with at least 3 of those weeks occurring in the last 4 weeks of the first 12-week treatment period. A weekly responder was defined as having ≥3 CSBMs and an increase from baseline of >1 CSBM for that given week.

No secondary endpoints were adjusted for multiplicity.

The following exploratory endpoints were specified in the SAP.

- Overall response by sex and age group (<65, >65 years, >75 years)
- Overall response using Weeks 13 to 24
- Number of study medication doses taken per week
- Number of rescue doses taken per week (includes bisacodyl and other non-study laxative)
- % of subjects not meeting ROME criteria at the end of each treatment week and by month
- Time to first BM
- BM Frequency per week (SBM and CSBM)
- BM Frequency per month (SBM and CSBM)
- BM Symptom Ratings per week
    - Straining
    - Consistency (lumpy/hard)
    - Urgency
    - Bristol Stool Form
- BM Symptom Ratings per month
- Number of diarrhea episodes per week (diarrhea is defined as >3 watery stools per day) and by month
- Number of subjects who reduced their dose

Statistical Analysis Plan

Sample Size Calculation

Approximately 600 subjects were to be randomized to lactitol or placebo in a 1:1 ratio. It was anticipated that the proposed sample size would have approximately 90% power to detect a difference of 10% between the treatment groups at a two-sided significance level of 0.05, assuming 20% of lactitol subjects and 10% of placebo subjects would be classified as responders for the primary endpoint.

Study Populations Definitions

Intention-to-Treat (ITT) Population: This population was defined as all patients randomized to treatment; however, there were 20 randomized patients not included in the Applicant's ITT population due to study site misconduct at Site 32, a fire at Site 6, patients enrolling in multiple

investigational studies, and a patient randomized in error. Refer to the Appendix, Section 15.5 Additional Information on the Analysis Populations for details on the randomized patients excluded from the ITT population. The 20 randomized patients excluded from the ITT population were also excluded from the Modified Intention-to-Treat and Per-Protocol populations. The actual ITT population, i.e., all randomized patients, was used as a sensitivity analysis of the primary endpoint.

Modified Intention-to-Treat (mITT) Population: Page 11 of the SAP defined the mITT population as "all randomized subjects that took at least one dose of study medication." This definition was consistent with the information provided in both versions of the protocol. However, page 31 of the clinical study report (CSR) states, "the mITT population included subjects that were randomized to treatment and were confirmed to have taken at least one dose of study medication and provided at least one BM diary entry during the Treatment Period." The Applicant specified in the SAP that the mITT population would be used as the primary analysis population for all safety and efficacy analyses.

Per-Protocol (PP) Population: Page 11 of the SAP defined the PP population as all subjects in the mITT population who completed Visit 8 (Study Day 180) without a major protocol violation. Both the original protocol and its amendment defined the PP population as all subjects in the mITT population who met the study eligibility criteria and have no significant protocol deviations during the study. Page 31 of the CSR indicates that the PP population included both mITT subjects that completed the study through Week 12 (Study Day 84) without a major protocol violation, and non-completers through Week 12 that discontinued due to reasons related to safety or lack of efficacy.

FDA Primary Analysis Population

Research misconduct led to a violation of data integrity at site 32. A fire resulted in a loss of efficacy or safety data for patients at site 6. Two patients had enrolled at multiple sites in the study and several patients did not have post-baseline BM diary entries despite participating in the study for several months. Refer to the section on disposition for additional details. FDA was able to perform a thorough review despite these data issues.

The FDA primary analysis population includes all randomized subjects except subjects enrolled in both Study 301 and Study 302, subjects enrolled at site 32 (research site misconduct) and site 6 (fire). The FDA primary analysis population was defined by the review team and is used as the primary analysis population for all efficacy analyses. Refer to Appendix 15.6 for additional details on the analysis populations.

Missing Data

The number of CSBMs for a week are considered missing if a subject was missing daily diary assessments for 4 or more days during that week. The number of CSBMs in a week are computed as 7 × (number of CSBMs/number of days with non-missing diary entries) for subjects with daily diary entries in at least 4 days of a given week. All patients with a missing number of CSBMs for a week were imputed as non-responders for that week.

Efficacy Analyses

The SAP stated, "overall response rates will be analyzed by constructing a two-sided 95% confidence interval for the difference in response rates between lactitol and placebo." Based on the Applicant's results, the Wald method was used to construct 95% confidence intervals.

The SAP also indicated that a CMH chi-square test adjusting for the effect of investigator site will be performed as a secondary analysis of the primary endpoint. The presence of a treatment-by-center interaction was investigated by the Breslow-Day test of homogeneity of the odds ratio.

Secondary endpoints were analyzed using the CMH chi-square test adjusting for any site effects for counts (percentage responses) and two-way ANOVA with terms for treatment, site, and their interaction for mean responses.

Protocol Amendments

There was one amendment to the original protocol, dated September 19, 2016. Protocol Amendment 1 added pharmacokinetic laboratory testing for blood lactitol levels at Visit 1, 3-7, and at Visit 8 (or early Termination Visit). In addition, the Diary Compliance Criterion for qualification in the study was clarified to require a subject to have completed an average of at least one bowel movement diary entry per day for 5 or more days per week during the 14 day screening period.

In addition to the protocol amendment, the following study analyses were altered in the final standalone SAP (August 23, 2017) and/or CSR (November 6, 2018) compared to the final amended protocol (September 19, 2016):

- The per-protocol population was amended in the SAP to require subjects to complete Visit 8 without a major protocol violation
- The per-protocol population was again amended in the CSR to require subjects to complete Week 12 without a major protocol violation

The definition of the mITT population was amended from the protocol and SAP in the CSR to require subjects to have provided at least one BM diary entry during the Treatment Period, in addition to being randomized to treatment and confirmed to have taken study medication.

Patient Disposition

Table 9 displays the disposition of patients in the FDA primary analysis population. A similar proportion of patients completed the treatment period in both groups. The reasons for discontinuation are similar between the two groups, except for withdrawal by subject where 9% of patients withdrew in the lactitol group compared to 4% in the placebo group.

Table 9: Patient Disposition in FDA Primary Analysis Population

	Lactitol (N = 291) n (%)	Placebo (N = 303) n (%)	Total (N = 594) n (%)
Completion Status			
Completed	231 (79%)	251 (83%)	482 (81%)
Discontinued	60 (21%)	52 (17%)	112 (19%)
Discontinuation due to			
Lack of Efficacy	5 (2%)	8 (3%)	13 (2%)
Lost to Follow-up	12 (4%)	14 (5%)	26 (4%)
Physician Decision	4 (1%)	5 (2%)	9 (2%)
Protocol Violation	0 (0%)	1 (<1%)	1 (<1%)
Withdrawal by Subject	25 (9%)	12 (4%)	37 (6%)
Other	3 (1%)	2 (1%)	5 (1%)
Averse Event	11 (4%)	10 (3%)	21 (4%)

Source: Reviewer's analysis created from ADSL.xpt

For discussion on the adverse events that led to dropouts and/or discontinuations, refer to section 8.2.4 Safety Results, Dropouts and/or Discontinuations Due to Adverse Effects.

Protocol Violations/Deviations

Table 10 shows major protocol deviations for all randomized patients in Study BLI400-302. The number and type of major protocol deviations are generally balanced between the lactitol and placebo arms. The most common major protocol deviations included missing assessment, prohibited concomitant medication, and study procedure error. The percentages of patients with these protocol violations are relatively small. Since the primary efficacy endpoint accounted for rescue medication use and missing diary data, these protocol deviations are unlikely to have influenced the results of the trial. The major protocol deviations with the FDA primary analysis population were consistent with the major protocol deviations with all randomized patients.

Table 10: Major Protocol Deviations for All Randomized Patients

	Lactitol (N=307) n (%)	Placebo (N=313) n (%)	No treatment dispensed (N=3) n (%)
Total major protocol deviations	63 (20.5)	64 (20.4)	1 (33.3)
Deviation category, n (%)			
Duplicate subject	2 (0.7)	1 (0.3)	0
Eligibility criteria	1 (0.3)	1 (0.3)	0
Prohibited concomitant medication	13 (4.2)	15 (4.8)	0
Study drug compliance	4 (1.3)	2 (0.6)	0
Rescue medication compliance	6 (2.0)	4 (1.3)	0
Missing assessment	19 (6.2)	21 (6.7)	0
Missing visit	4 (1.3)	2 (0.6)	0
Study Procedure Error	14 (4.6)	18 (5.8)	1 (33.3)

Source: Applicant's IR response, Table 2: BLI400-302: Major Protocol Deviations, dated November 5, 2019

Demographic and Baseline Characteristics

Table 11 displays the demographic characteristics of the FDA primary analysis population. The two treatment groups are similar in terms of sex, age, race, and ethnicity. It appears that the demographics of this study reasonably well represents the overall population of patients with

CIC in the US with respect to sex and age. CIC disproportionately affects women and the elderly,[11] as reflected in this study population.

Table 11: Demographic Characteristics of the FDA Primary Analysis Population

	Treatment Group(s)		
Demographic Parameters	**Lactitol (N=291) n (%)**	**Placebo (N=303) n (%)**	**Total (N=594) n (%)**
Sex			
Male	75 (26%)	65 (22%)	140 (24%)
Female	216 (74%)	238 (78%)	454 (76%)
Age			
Mean years (SD)	52.5 (15.3)	51.0 (15.9)	51.7 (15.6)
Median (years)	53	51	52
Min, Max (years)	18, 88	19, 85	18, 88
Age Group			
<65 years	214 (73%)	221 (73%)	435 (73%)
≥65 years	77 (27%)	82 (27%)	159 (27%)
Race			
White	182 (62%)	177 (58%)	359 (60%)
Black or African American	85 (29%)	101 (33%)	186 (31%)
Asian	19 (7%)	21 (7%)	40 (7%)
American Indian or Alaska Native	0	1 (0.3%)	1 (0.2%)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	5 (2%)	3 (1%)	8 (1%
Ethnicity			
Hispanic or Latino	113 (39%)	113 (37%)	226 (38%)
Not Hispanic or Latino	178 (61%)	190 (63%)	368 (62%)
Region			
United States	291 (100%)	303 (100%)	594 (100%)
Rest of the World	0	0	0
Canada	0	0	0
South America	0	0	0
Europe	0	0	0
Asia	0	0	0
Africa	0	0	0

Abbreviations: SD, standard deviation
Source: Reviewer's table adapted from response to information request May 21, 2019 fda-ir-bli400-302---items-1-3.xls

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

As shown in Table 12 below, baseline characteristics and constipation history were comparable between the lactitol and placebo arms. The patients in both arms have a relatively long-standing history of constipation. Bisacodyl use during the screening period was also similar between the lactitol and placebo arms.

[11] Lacy, BE. Update on the Management of Chronic Idiopathic Constipation. Am J Manag Care. 2019 Mar;25(4 Suppl):S55-S62.

Table 12: Baseline Characteristics and Constipation History of the FDA Primary Analysis Population

	Lactitol (N=291)	Placebo (N=303)
History of constipation (years)		
Mean (SD)	16.6 (17.1)	14.5 (14.9)
Median (Min; Max)	9.2 (0.3; 74.7)	9.6 (0.3; 72.6)
Baseline weekly CSBM		
Screening Week 1 Mean (SD)	0.32 (0.65)	0.31 (0.63)
Screening Week 2 Mean (SD)	0.46 (0.93)	0.43 (0.80)
Bisacodyl use during the screening period		
Mean dose (SD)	7.0 (2.5)	7.2 (2.5)
Mean number of rescue bisacodyl doses taken per week (SD)	1.7 (1.1)	1.7 (1.3)

Abbreviations: CSBM, complete spontaneous bowel movement; SD, standard deviation
Source: Applicant's IR response, Table 3: 3: BLI400-302: Constipation History, dated November 5, 2019

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Patients reported taking assigned study drug on about 77% of eligible treatment days. Compliance rates were similar between the treatment groups. Returned study drug materials were reviewed by site personnel at each visit to confirm treatment compliance.

Concomitant Medications

As shown in Table 13 below, the percentages of patients using each of the classes of baseline concomitant medications were generally similar between the lactitol and placebo arms. Medications included in Table 13 (including laxatives) all had start dates that preceded study participation. Laxatives were required to be discontinued immediately following the screening visit. The most frequently reported drug classes of concomitant medications included anti-hypertensive agents (29.2% in the lactitol group and 29.7% in the placebo group) and lipid-modifying agents (21.6% in the lactitol group and 19.5% in the placebo group), reflecting the frequent use of these medications in the general population. There were relatively low numbers of patients taking medications that could have a side effect of constipation (e.g., thyroid therapy, iron preparations).

Table 13: Baseline Concomitant Medications of the FDA Primary Analysis Population

	Lactitol (N=291) n (%)	Placebo (N=303) n (%)
Laxatives	50 (17.2)	42 (13.9)
Bulk-Forming Laxatives	4 (1.4)	1 (0.3)
Contact Laxatives	24 (8.2)	24 (7.9)
Enemas	2 (0.7)	1 (0.3)
Osmotically Acting Laxatives	13 (4.5)	12 (4.0)
Other Drugs For Constipation	7 (2.4)	3 (1.0)
Softeners, Emollients	7 (2.4)	7 (2.3)
Analgesics	44 (15.1)	30 (9.9)
Anti-inflammatory and antirheumatic products	48 (16.5)	41 (13.5)
Lipid-modifying agents	63 (21.6)	59 (19.5)
Anti-hypertensive agents	85 (29.2)	90 (29.7)
Agents Acting On The Renin-Angiotensin System	69 (23.7)	78 (25.7)
Antihypertensives	7 (2.4)	10 (3.3)
Beta Blocking Agents	30 (10.3)	33 (10.9)
Thyroid therapy	22 (7.6)	25 (8.3)
Iron preparations	4 (1.4)	0
Drugs for acid-related disorders	38 (13.1)	35 (11.6)

Source: Applicant's IR response, Table 3: BLI400-302: Baseline Concomitant Medications, dated November 5, 2019.

Rescue Medication

Rescue medication use was permitted during the trial and was accounted for in the primary endpoint analysis; a CSBM was defined as a BM that occurred with no rescue laxative use in the previous 24 hours and that was accompanied by a sense of complete evacuation.

Patients were given bisacodyl tablets (5 mg) at each study visit and were instructed to take 5 to 10 mg (1 to 2 tablets) of bisacodyl if they experienced severe discomfort due to their constipation, or had not had a BM in 4 days.

Patients in the lactitol group and patients in the placebo group took an estimated average of 1.7 and 1.8 bisacodyl doses per week, respectively, during the first 12 week treatment period. The use of rescue medication was generally similar between the groups and since the primary endpoint accounted for rescue medication use, any small differences are unlikely to impact the overall conclusions.

Efficacy Results

Primary Endpoint

The SAP specified using the 95% confidence intervals for the difference in proportions to test the primary endpoint for overall CSBM responder. A secondary analysis tested the primary endpoint using a CMH test stratified by study site. The efficacy results for the FDA primary analysis population are presented in Table 14 below. Due to the Applicant's analysis populations including a patient that had re-enrolled and excluding patients that should have been included according to the population definition in the CSR, the FDA primary analysis population is being used for the efficacy analysis. Lactitol demonstrated efficacy in the FDA primary analysis population (the confidence interval for the treatment difference excludes zero and $p < 0.001$ from the CMH test). Efficacy results from the Applicant's CSR for the FDA-ITT, FDA-mITT, and FDA-per-protocol populations were similar.

Table 14: Efficacy Results for the FDA Primary Analysis Population

	Lactitol	Placebo
N	291	303
Responders (%)	73 (25.1)	39 (12.9)
Treatment Difference (95% CI)	12.2 (6.0, 18.5)	
P-value*	<0.001	

Abbreviations: CI, confidence interval
*P-value calculated from CMH test stratifying by study site.
Source: Reviewer's analysis created from ADEFF.xpt

Additional analyses were performed by FDA to determine the robustness of the efficacy results with respect to missing data. The primary analysis computes the average number of CSBMs in a week as 7 × (number of CSBMs/number of days with non-missing diary entries) for subjects with 4 or more days with non-missing diary entries. Under this method, patients with 2 CSBMs and 4 days of diary data would be considered responders for that week, though they might not have been if they did not have missing data. Similarly, patients with 3 CSBMs in a week could be non-responders for that week if they had less than 4 days of diary data. Using the observed number of CSBMs instead would only have changed 2 patients from responder to non-responder in the lactitol group and 1 patient from non-responder to responder in the placebo group. Because it would have required 19 fewer responders in the lactitol group or 17 additional responders in the placebo group in order for the efficacy results to no longer be statistically significant, this method for calculating the weekly number of CSBMs in the presence of missing diary data was unlikely to affect efficacy results.

The primary analysis also assumes that all patients with a missing number of CSBMs for a week were non-responders during that week; however, some of those patients could have met the criteria to be a weekly responder had the data been observed. For the FDA primary analysis population, the number of CSBMs is missing in 17% of available weeks during the first 12 weeks of treatment due to both dropout and missing diary entries. The missing data rate was very similar for both treatment groups. Among study weeks with a non-missing number of CSBMs, placebo patients were responders for 30% of weeks and lactitol patients were responders in 45% of weeks. The primary analysis uses non-responder imputation for all missing study weeks. As sensitivity analyses, approximately 40% , 50% , and 60% of weeks with a missing number of CSBMs were imputed as responder weeks in the placebo arm. The sensitivity analyses were performed in the FDA primary analysis population. Imputations were repeated a total of 20 times. The 40% imputation yielded an average of 5.4 (range 3-8) additional placebo responders. The chance imputation yielded an average of 8.5 (range 4-13) additional placebo responders. The 60% imputation yielded an average of 12.2 (range 5-18) additional placebo responders. Under the assumption that all patients in the lactitol treatment group with a missing number of CSBMs for a study week were non-responders during that week, these analyses indicate that placebo patients would have to have been responders in a high percentage of weeks with missing data in order to obtain 17 additional placebo responders and alter our efficacy conclusions. Thus, the efficacy results are fairly robust to missing data.

Secondary and other relevant endpoints

None of the secondary endpoints were adjusted for multiplicity.

In this section the following exploratory secondary endpoints that were considered clinically important for FDA review are discussed:

Response during Weeks 13 to 24

Although the primary endpoint only looks at responders over the first 12 weeks of treatment, the double-blind treatment period lasted for 180 days (approximately 26 weeks) and efficacy data were collected during the entire treatment period. The Applicant specified using responders for weeks 13 to 24 as an exploratory analysis to examine the longer term efficacy of lactitol.

The table below displays the responder analysis using the later study weeks for the FDA primary analysis ITT population. The first analysis uses study weeks 13 to 24. The weekly responder definition is the same as for the primary endpoint (responder in 9 of 12 weeks and 3 of the last 4). The overall response rate was slightly lower in the lactitol group and slightly higher in the placebo group compared to the first 12 weeks of the study. The estimated treatment difference favors lactitol, but the estimated treatment effect is slightly smaller compared to the estimated effect during the first 12 weeks.

Response during Weeks 1-24

An additional exploratory analysis was performed by the FDA review team using study weeks 1 to 24. A patient is considered an overall responder if they were a responder in at least 18 of 24 weeks (i.e. at least 75% of the weeks) and a responder in at least 3 of the last 4 study weeks. The estimated treatment effect again favors lactitol.

Table 15: Responder Analysis Using the Later Study Weeks for the FDA Primary Analysis Population

		Lactitol (n = 291)	Placebo (n =303)
Responder Weeks 13 – 24 (9/12 and last 3/4)	Responders (%)	71 (24.4)	49 (16.2)
	Treatment Difference (95% CI)	8.2 (1.8, 14.7)	
Responder Weeks 1 – 24 (18/24 and last 3/4)	Responders (%)	59 (20.3)	37 (12.2)
	Treatment Difference (95% CI)	8.1 (2.2, 14.0)	

Abbreviations: CI, confidence interval
Source: Reviewer's analysis created from ADEFF.xpt

Change in the number of CSBM per week

One limitation of the responder analysis used for the primary endpoint is it dichotomizes patients as either a responder or not. Using a different definition for overall responder, such as 8/12 weeks instead of 9/12, could potentially change efficacy conclusions; however, 9/12 weeks is what has been typically used and accepted for products intended to treat CIC in adults. To further examine the treatment difference, the FDA review team conducted an exploratory analysis of the secondary endpoint of change in the number of CSBMs from baseline for each week using mixed model repeated measures (MMRM). Site ID, treatment, visit, a treatment-by-visit interaction, and the stratification factor, age (≥65 or <65), were included as factors and baseline number of CSBMs was included as a covariate in the MMRM. Data are assumed to be missing at random when using MMRM. The Applicant analyzed this endpoint using ANCOVA models, which only used the observed change from baseline at the analyzed visit. The estimated treatment difference was similar when comparing results from ANCOVA to MMRM. The number of CSBMs for a week is calculated using the same method for computing number of CSBMs for a week in the primary endpoint derivation.

The estimated mean change in the number of CSBMs for each treatment group, the estimated treatment difference, and 95% confidence intervals from the MMRM model are displayed in Table 16 below. Although the table only shows results for weeks 1-12, Week 16, Week 20, and Week 24, Weeks 1 to 25 were used in the model and the results are consistent across all study weeks. Week 25 is the last scheduled complete week of study treatment. The estimated mean

change in number of CSBMs was significantly greater for lactitol at every week and the estimated treatment difference was generally between 0.7 CSBMs to 0.9 CSBMs. Analyses were not adjusted for multiplicity.

Table 16: Estimated Mean Change in Number of CSBMs for Each Treatment Group, Estimated Treatment Difference, and 95% Confidence Intervals From the MMRM Model

Week	Lactitol	Placebo	Difference
1	2.1 (1.7, 2.4)	1.0 (0.7, 1.4)	1.0 (0.6, 1.4)
2	2.2 (1.8, 2.6)	1.5 (1.1, 1.9)	0.7 (0.3, 1.2)
3	2.4 (2.0, 2.8)	1.6 (1.3, 2.0)	0.8 (0.3, 1.2)
4	2.4 (2.1, 2.8)	1.7 (1.3, 2.0)	0.8 (0.3, 1.2)
5	2.8 (2.5, 3.2)	1.6 (1.3, 2.0)	1.2 (0.7, 1.7)
6	2.5 (2.2, 2.9)	1.7 (1.3, 2.0)	0.9 (0.4, 1.3)
7	2.6 (2.2, 2.9)	1.9 (1.5, 2.2)	0.7 (0.3, 1.2)
8	2.6 (2.3, 3.0)	1.9 (1.5, 2.2)	0.8 (0.3, 1.2)
9	2.6 (2.3, 3.0)	1.8 (1.4, 2.2)	0.8 (0.4, 1.3)
10	2.6 (2.3, 3.0)	1.9 (1.5, 2.2)	0.8 (0.3, 1.2)
11	2.8 (2.5, 3.2)	1.9 (1.5, 2.3)	0.9 (0.4, 1.4)
12	2.8 (2.4, 3.1)	1.9 (1.5, 2.3)	0.8 (0.4, 1.3)
16	2.8 (2.4, 3.2)	2.0 (1.6, 2.4)	0.8 (0.3, 1.3)
20	2.9 (2.5, 3.3)	2.1 (1.7, 2.5)	0.8 (0.3, 1.3)
24	3.0 (2.6, 3.4)	2.1 (1.7, 2.5)	0.9 (0.4, 1.4)

Abbreviations: CSBM, complete spontaneous bowel movements; MMRM, mixed model repeated measures
Source: Reviewer's analysis created from ADEFF.xpt

Straining, Stool Consistency, and Urgency

Analyses indicated that the number of BMs with straining per week and the number of hard or lumpy stools per week while on treatment (or placebo) were similar between the lactitol group and placebo. However, the lactitol group had a higher number of BMs per week and analyses for the proportion of BMs with straining and the proportion of BMs with hard or lumpy stools showed a favorable trend for lactitol. Furthermore, the average Bristol Stool Form Scale score was higher in the lactitol group, indicating softer stool consistency. BM Urgency ratings were similar between the two treatment groups.

Dose/Dose Response

Not applicable as this study evaluated the efficacy of 20 g of lactitol compared to placebo. Although the protocol allowed patients with persistent diarrhea or loose stools to reduce their dose to 10 g of lactitol per day, the study was not designed to compare the efficacy of the 20 g and 10 g lactitol dose groups. The majority of patients did not have any dose reductions during the study. Of the patients who reduced their dose from 20 g to 10 g, the number of doses at the lower 10 g dose was small and unlikely to influence the results of the trial given that lactitol was administered once daily for 12 weeks during the trial. There were 24/291 (8.2%) patients in the lactitol group and 17/303 (5.6%) on placebo who dose reduced for 1 dose, 8/291 (2.7%) patients on lactitol and 3/303 (1%) on placebo for 2 doses, and 4/291 (1.4%) patients on lactitol and 5/303 (1.7%) on placebo for 3 doses; the proportion of patients who dose reduced for 4 or more doses was <1% in either treatment arm (information provided by the Applicant in a response, dated February 5, 2019, to an information request). Dose reduction is discussed in further detail below in the subsection on Additional Analyses Conducted on the Individual Trial.

Durability of Response

Although the magnitude of the treatment difference between the lactitol and placebo groups fluctuated at each week, overall the improvements in the frequency of CSBMs/week were greater in the lactitol-treated patients compared to placebo through week 24. Refer to the above section Efficacy Results – Secondary and other relevant endpoints for further discussion.

Persistence of Effect

Available data did not permit a robust analysis of persistence of effect (i.e., treatment benefit after the drug was stopped).

Additional Analyses Conducted on the Individual Trial

Study BLI400-302 allowed subjects that developed persistent diarrhea or loose stools to adjust their dose down to 10 g per day. Subjects were categorized into three groups based on the frequency of dose reduction: no dose reduction, dose reduction for <25% of doses, and dose reduction for ≥25% of doses. The number of subjects and number of overall responders per dose reduction group for the FDA primary analysis population are displayed by each treatment arm in Table 17 below. Because dose reduction occurred after randomization and was related to efficacy, results from these subgroups cannot be used to evaluate efficacy across doses or estimate the treatment effect within a dose. The majority of patients did not have any dose reductions during the study. More subjects in the lactitol group had a dose reduction during the study compared to placebo and a much larger number of subjects had a dose reduction in over 25% of doses in the lactitol group.

Table 17: Number of Subjects and Overall Responders per Dose Reduction Group (FDA Primary Analysis Population)

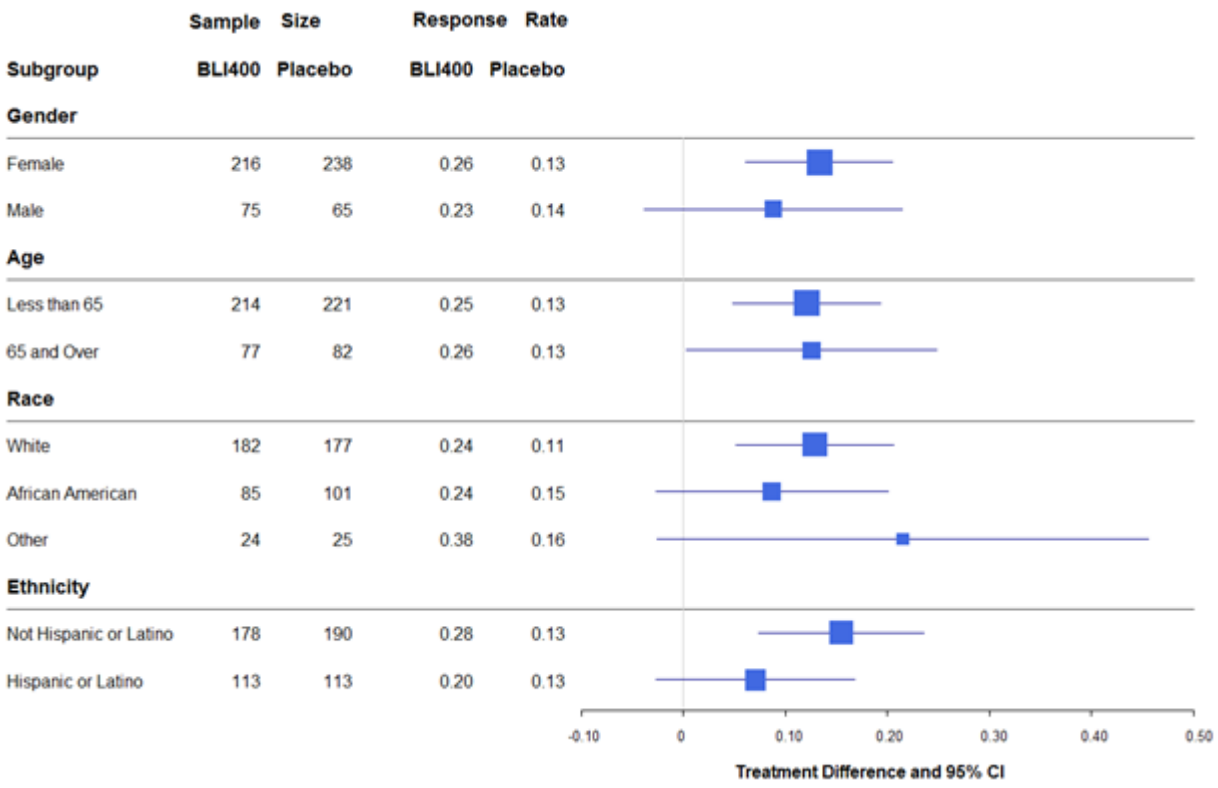
		Lactitol (n = 291)	Placebo (n = 303)
No Dose Reduction	N	217	261
	Responders (%)	51 (23.5)	31 (11.9)
Dose Reduction <25% of Doses	N	46	34
	Responders (%)	13 (28.3)	5 (14.7)
Dose Reduction ≥25% of Doses	N	28	8
	Responders (%)	9 (32.1)	3 (37.5)

Source: Reviewer's analysis created from ADEFF.xpt and ADSL.xpt

Demographic Subgroups: Primary Efficacy Endpoint

To assess efficacy across sex, age, race, and ethnicity, exploratory subgroup analyses were performed for Study 302. Figure 2 displays the response rate for the primary endpoint of CSBM responder by subgroup, along with the estimate and 95% Wald CI of the treatment difference. The estimated treatment difference is consistent across subgroups.

Figure 2: Forest Plot of Subgroup Analyses for CSBM Responders (Study 302)



Abbreviations: CSBM, complete spontaneous bowel movements
Source: Reviewer's analysis created from ADEFF.xpt and ADSL.xpt

8.1.2. BLI400-301 (Study 301)

Trial Design

Title: A Safety and Efficacy Evaluation of BLI400 Laxative vs Amitiza in Constipated Adults

Objectives:

Primary: To determine the effect of lactitol or Amitiza on patient constipation status over a 12-week treatment period.

Secondary: To evaluate responses by sex and age, rescue medication use, BM frequency and symptoms.

Study design: BLI400-301 was a phase 3, randomized, double-blind, active-controlled, parallel group, multi-center study in adult patients with CIC. Patients were treated with 21 grams BLI400 or 48 µg Amitiza daily for 12 weeks. The primary efficacy endpoint was assessed at 12 weeks and is defined below under Study Endpoints.

Study population: 459 patients were randomized in this study.

Key inclusion and exclusion criteria:
The inclusion and exclusion criteria were generally similar between studies BLI400-301 and BLI400-302. Refer to Section 8.1.1 BLI400-302, Key inclusion criteria and key exclusion criteria above.

Study Endpoints

The primary endpoint was the proportion of subjects who were weekly responders for at least 9 out of 12 weeks, with at least 3 of those weeks occurring in the last 4 weeks of treatment. A weekly responder was defined as having ≥3 CSBMs and an increase from baseline of >1 CSBM for that given week.

Statistical Analysis Plan

Study Population Definitions

The definitions for ITT, mITT, and per-protocol populations were similar to Study 302. The mITT population included all randomized subjects who took at least one dose of study drug. The per-protocol population required patients to complete Visit 5 (Week 12) without any major protocol deviations.

The Applicant changed the primary analysis population from the ITT population in the final amended protocol (May 4, 2015) to the per-protocol population in the SAP. The Applicant cited consistency with the FDA Draft Guidance on Non-Inferiority Clinical Trials from March 2010. The guidance does not state to use the PP population for the primary analysis, but, on page 33, it notes that, "In non-inferiority trials, many kinds of problems fatal to a superiority trial, such as non-adherence, misclassification of the primary endpoint, or measurement problems more generally (i.e., "noise"), or many dropouts who must be assessed as part of the treated group, can bias toward no treatment difference (success) and undermine the validity of the trial, creating apparent non-inferiority where it did not really exist. Although an "as-treated" analysis is therefore often suggested as the primary analysis for non-inferiority (NI) studies, there are also significant concerns with the possibility of informative censoring in an as-treated analysis. It is therefore important to conduct both ITT and as-treated analyses in NI studies. Differences in results using the two analyses will need close examination." The reasons for exclusion from the PP population were documented prior to unblinding of treatment assignments. Due to misconduct at study site 30, 14 patients (7 lactitol and 7 Amitiza) from the PP population are excluded from efficacy analyses. During the NDA review Site 33 was identified as being associated with Zain Research, which is under investigation for falsifying data. Analyses were conducted prior to identifying this site and the 8 patients enrolled at Site 33 (4 lactitol patients and 4 Amitiza patients) are included in the analyses; however, the exclusion of these patients does not alter efficacy results and conclusions.

Missing Data

The number of CSBMs for a week are considered missing if a subject was missing daily diary assessments for 4 or more days during that week. The number of CSBMs in a week are computed as 7 X (number of CSBMs/number of days with non-missing diary entries) for subjects with daily diary entries in at least 4 days of a given week. All subjects with missing number of CSBMs for a week were imputed as non-responders for that week.

Efficacy Analyses

The Applicant's prespecified efficacy analyses are described in this section. Due to issues with deriving an appropriate NI margin for the active comparator in this trial (described below), we concluded the Applicant's prespecified analysis of the primary endpoint cannot be relied on to establish efficacy.

The null hypothesis tested by the Applicant is whether the response rate (for the primary endpoint) of Amitiza minus the response rate of lactitol is greater than or equal to some specified NI margin. The alternative hypothesis is the response rate of Amitiza minus the response rate of lactitol is less than the NI margin. The Applicant specified a 12.6% NI margin in the SAP. The original protocol and amendment on 5/4/2015 specified a 15% NI margin.

The hypothesis is tested using the two-sided 95% confidence interval for the difference in response rates between the two treatment groups. The null hypothesis is rejected if the upper bound of the 95% CI for the response rate of Amitiza minus the response rate of lactitol is less than 12.6%. This is equivalent to if the lower bound of the 95% CI for the response rate of lactitol minus the response rate of Amitiza is greater than -12.6%. The Wald method was used to construct asymptotic 95% confidence intervals.

The Applicant chose the 12.6% margin based on preserving 30% of an estimated 18% treatment difference between Linzess (linaclotide) and placebo. The proposed margin does not account for the statistical uncertainty in the historical estimate of 18%. Furthermore, the active comparator for this trial was Amitiza (lubiprostone), which is not in the same drug class as linaclotide. Amitiza was approved based on results from 4-week studies using the frequency of spontaneous bowel movements (SBMs), not CSBMs, as a primary endpoint. The Applicant provided justification for the use of results from linaclotide studies to determine a NI margin in Response to Information Request (01/15/2019). They showed a similar number of SBMs per week in the first 4 weeks of treatment for Amitiza compared to Week 12 of treatment for the linaclotide studies; however, there was no comparison of treatment results for CSBMs. Neither the results from the linaclotide studies nor the results from the Amitiza studies can be used to directly estimate the treatment difference between Amitiza and placebo for the primary endpoint in this study. As a result, it is uncertain whether a 12.6% non-inferiority margin provides assurance that the effect of Amitiza over placebo was preserved and hypothesis testing for the primary endpoint could not reliably establish efficacy.

A CMH chi-square test for superiority, adjusting for the effect of investigator site, was performed as a secondary analysis of the primary endpoint. The presence of a treatment-by-center interaction was investigated by the Breslow-Day test of homogeneity of the odds ratio.

Secondary endpoints were analyzed using the CMH chi-square test for superiority, adjusting for any site effects, for counts (percentage responses) and two-way ANOVA with terms for treatment, site, and their interaction for mean responses.

Sample Size Calculation

The Applicant's stated plan in the protocol and SAP was to randomize approximately 400 subjects to lactitol or Amitiza in 1:1 ratio. According to the SAP, the Applicant anticipated that a sample size of 198 subjects/arm would provide 86% power to demonstrate noninferiority at a two-sided α of 0.05 for a 12.6% noninferiority margin, assuming true response rates of 20% for the primary endpoint in each arm. It was also anticipated that there would be 160 patients per arm in the per-protocol analysis, yielding a power of 76%.

Note that the sample size calculation for randomizing 400 patients in the study protocol was based on a 10% noninferiority margin, but the primary endpoint was to be tested at a 15% margin. It was still assumed that the true response rate was 20% in both arms. The protocol did not provide a power estimate.

Protocol Amendments

There was one amendment, dated May 4, 2015, to the original protocol. Amendment 1 added an exclusion for subjects with known or suspected moderate to severe hepatic insufficiency (Child Pugh Classes B and C). This exclusion was added because the labeling for lubiprostone requires lower doses for this patient group. The amendment also added an allowance for re-dispensing of study drug at certain times as well as a definition of diarrhea as more than three large watery stools per day.

In addition to protocol amendments, the following study analyses were altered in the standalone SAP (January 7, 2016) compared to the final amended protocol (May 4, 2015):

- The primary analysis population was changed from the ITT population to the PP population
- The NI margin was changed from 15% to 12.6%
- The safety analyses are based on the mITT population instead of the ITT population

Analysis Populations

The analysis populations for Study 301 are shown in Table 18 below. Of note, research misconduct was confirmed at site 30 (the same site as site 32 in Study 302) and the data for the 14 patients randomized at site 30 were not included in any efficacy analyses by the applicant and in this review, which was consistent with the recommendation of the Contract Research Organization. Although the data from these 14 patients were excluded, the Applicant's analyses relied on a total sample size (i.e., denominator for calculations) that included the patients at site 30. After review of the audit report which discussed violations of data integrity, the review team decided that these 14 patients from site 30 should be excluded entirely and not included in the total sample size for both the efficacy and safety analyses. The safety findings from these patients were reviewed independently to ensure that relevant adverse events were not overlooked.

Table 18: Study 301 Analysis Populations

	Lactitol N	Amitiza N	All N
Patients randomized			459
ITT patients	230	229	459
ITT patients (excluding patients from site 30)	223	222	445
mITT patients	225	229	454
mITT patients (excluding patients from site 30)	218	222	440
PP patients	194	206	400
PP patients (excluding patients from site 30)	187	199	386
Total safety population	225	229	454
Total safety population (excluding patients from site 30)	218	222	440

Abbreviations: ITT, intent to treat; mITT, modified intent to treat; PP, per protocol
Source: Reviewer's table adapted from applicant's submission, NDA 211281, Study BLI400-301 CSR, Table 301- 2 Patient Disposition, page 35/77.

All randomized patients were included in the ITT population (including patients at site 30). There were 5 patients in the ITT population who did not take study medication and were excluded from the mITT population. These patients were all in the lactitol group and the following reasons for discontinuation were noted in one patient each: lost to follow-up, family matters out of town; noncompliant; personal schedule; and diarrhea.

Of note, the total safety population included all mITT patients.

Patient Disposition

The patient disposition for all randomized patients who took study drug (mITT population) is displayed in Table 19 below. The overall discontinuation rates were similar between the two groups (though slightly higher in the lactitol group). There was more discontinuation due to loss to follow-up and subject withdrawal in the lactitol group.

Table 19: Patient Disposition for All Randomized Patients (Including Site 30)

	Lactitol (N = 230) n (%)	Amitiza (N = 229) n (%)	Total (N = 459) n (%)
Completion Status			
Completed	184 (80.0)	193 (84.3)	377 (82.1)
Discontinued	46 (20.0)	36 (15.7)	82 (17.9)
Discontinuation due to			
Lost to Follow-up	11 (4.8)	5 (2.2)	16 (3.5)
Physician Decision	4 (1.7)	5 (2.2)	9 (2.0)
Withdrawal by Subject	22 (9.6)	8 (3.5)	30 (6.5)
Other	3 (1.3)	7 (3.1)	10 (2.2)
Averse Event	6 (2.6)*	11 (4.8)	17 (3.7)

*Includes one patient randomized to BLI400 who discontinued due to AE of diarrhea but did not take study drug and is not included in the safety population
Source: Reviewer's analysis created from ADSL.xpt

For discussion on the adverse events that led to dropouts and/or discontinuations among patients who took study drug, refer to section 8.2.4 Safety Results, Dropouts and/or Discontinuations Due to Adverse Effects.

Protocol Violations/Deviations

Table 20 shows major protocol deviations for all randomized patients in Study BLI400-301. The number and type of major protocol deviations are generally balanced between the lactitol and lubiprostone arms. The most common major protocol deviations included study drug compliance and missing assessment. These violations do not appear to affect the overall efficacy of the study.

Table 20: Major Protocol Deviations for All Randomized Patients

	Lactitol (N=230) n (%)	Lubiprostone (N=229) n (%)
Total major protocol deviations	59 (25.7)	49 (21.4)
Deviation category		
Eligibility criteria	0 (0)	3 (1.3)
Prohibited concomitant medication	3 (1.3)	3 (1.3)
Study drug compliance	19 (8.3)	21 (9.2)
Rescue medication compliance	3 (1.3)	1 (0.4)
Missing assessment	18 (7.8)	9 (3.9)
Missing visit	2 (0.9)	0 (0)
Study drug return deviation	2 (0.9)	0 (0)
Duplicate subject	0 (0)	0 (0)

Source: Applicant's IR response, Table 1: BLI400-301: Major Protocol Deviations, dated November 5, 2019.

Demographic and Baseline Characteristics

Table 21 displays the demographic characteristics of the mITT population, excluding patients from site 30. The two treatment groups are generally similar in terms of sex, age, race, and ethnicity.

Table 21: Demographic Characteristics for All Randomized Patients

	Treatment Group(s)		
Demographic Parameters	Lactitol (N=230) n (%)	Amitiza (N=229) n (%)	Total (N=459) n (%)
Sex			
Male	43 (19%)	50 (22%)	93 (20)
Female	187 (81%)	179 (78%)	366 (80)
Age			
Mean years (SD)	45.3 (13.6)	45.6 (14.6)	45.5(14.1)
Median (years)	45	46	46
Min, Max (years)	18, 79	19, 87	18, 87
Age Group			
<65 years	214 (93%)	206 (90%)	420 (92%)
≥65 years	16 (7%)	23 (10%)	39 (8%)
Race			
White	156 (68%)	146 (64%)	302(66%)
Black or African American	63 (27%)	68 (30%)	131 (29%)
Asian	8 (3%)	7 (3%)	15 (3%)

Demographic Parameters	Treatment Group(s) Lactitol (N=230) n (%)	Amitiza (N=229) n (%)	Total (N=459) n (%)
American Indian or Alaska Native	1 (0.4%)	0	1 (0.2%)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	2 (0.9%)	8 (3%)	10 (2%)
Ethnicity			
Hispanic or Latino	95 (41%)	98 (43%)	193 (42%)
Not Hispanic or Latino	135 (59%)	131 (57%)	266 (58%)
Region			
United States	230 (100%)	229 (100%)	459 (100%)
Rest of the World	0	0	0
Canada	0	0	0
South America	0	0	0
Europe	0	0	0
Asia	0	0	0
Africa	0	0	0

Abbreviations: SD, standard deviation
Source: Reviewer's analysis created from ADSL.xpt

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

As shown in Table 22 below, baseline characteristics and constipation history were comparable between the lactitol and lubiprostone arms. The patients in both arms have a relatively long-standing history of constipation. Bisacodyl use during the screening period was also similar between the lactitol and lubiprostone arms.

Table 22: Baseline Characteristics and Constipation History for All Randomized Patients

	Lactitol (N=230)	Lubiprostone (N=229)
History of constipation, (years)		
Mean (SD)	14.8 (14.3)	14.5 (14.5)
Median (Min; Max)	10.4 (0.5; 63.4)	8.4 (0.4; 77.5)
Baseline weekly CSBM		
Screening Week 1 Mean (SD)	0.33 (0.69)	0.39 (0.96)
Screening Week 2 Mean (SD)	0.40 (0.71)	0.40 (1.04)
Bisacodyl use during the screening period		
Mean dose (SD)	6.6 (2.4)	6.9 (2.4)
Mean number of rescue bisacodyl doses taken per week (SD)	1.6 (1.2)	1.5 (1.2)

Abbreviations: SD, standard deviation
Source: Applicant's IR response, Table 1: BLI400-301: Constipation History, dated November 5, 2019

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Patients reported taking a dose of the study drug on 83% of eligible study days. Compliance rates were similar between the treatment groups.

Concomitant Medications

As shown in Table 23 below, the percentages of patients using each of the classes of baseline concomitant medications were similar between the lactitol and lubiprostone arms. Medications included in Table 23 (including laxatives) all had start dates that preceded study participation. Laxatives were required to be discontinued immediately following the screening visit. The most frequently reported drug classes of baseline concomitant medications were laxatives (18.3% in the lactitol group and 17.9% in the lubiprostone group) and anti-hypertensive agents (18.7% in the lactitol group and 17.5% in the lubiprostone group), which is expected given the long-standing history of constipation and frequency of hypertension in the population.

Table 23: Baseline Concomitant Medications, All Randomized Patients

	Lactitol (N=230) n (%)	Lubiprostone (N=229) n (%)
Laxatives	42 (18.3)	41 (17.9)
Bulk-Forming Laxatives	3 (1.3)	2 (0.9)
Contact Laxatives	24 (10.4)	26 (11.4)
Osmotically Acting Laxatives	12 (5.2)	11 (4.8)
Other Drugs For Constipation	1 (0.4)	1 (0.4)
Softeners, Emollients	5 (2.2)	3 (1.3)
Analgesics	20 (8.7)	19 (8.3)
Anti-inflammatory and antirheumatic products	34 (14.8)	36 (15.7)
Lipid-modifying agents	26 (11.3)	28 (12.2)
Anti-hypertensive agents	43 (18.7)	40 (17.5)
Agents Acting On The Renin-Angiotensin System	36 (15.7)	29 (12.7)
Beta Blocking Agents	11 (4.8)	14 (6.1)
Thyroid therapy	19 (8.3)	17 (7.4)
Iron preparations	0	1 (0.4)
Drugs for acid-related disorders	21 (9.1)	22 (9.6)

Source: Applicant's IR response, Table 1: BLI400-301: Baseline Concomitant Medications, dated December 2, 2019.

Rescue Medication

Similar to Study 302, rescue medication use was permitted during the trial and was accounted for in the primary endpoint analysis, with a CSBM defined as a BM that occurred with no rescue laxative use in the previous 24 hours and that was accompanied by a sense of complete evacuation. Patients were given bisacodyl tablets (5 mg) at each study visit and were instructed to take 5 to 10 mg (1 to 2 tablets) of bisacodyl if they experienced severe discomfort due to their constipation, or had not had a BM in 4 days.

Patients in the lactitol group and patients in the Amitiza group took an estimated average of 1.3 bisacodyl doses per week during the treatment period.

Efficacy Results

Primary Endpoint

The Applicant's primary analysis was performed on the per-protocol population. The ITT and mITT were used as sensitivity analyses. The primary analysis is based on an asymptotic Wald 95% CI for the difference in response rates for the two treatment groups. A non-inferiority margin of -12.6% was specified in the SAP, thus non-inferiority is demonstrated if the lower bound of the 95% CI for the treatment difference is greater than -12.6%. As discussed in section 8.1.2 BLI400-301 under Statistical Analysis Plan, the 12.6% margin was not based on studies comparing the active control to placebo using the primary endpoint and no such studies

exist. It is unclear how much of the active comparator's treatment effect would be preserved by a 12.6% margin or if this margin provides assurance that lactitol would demonstrate superiority to placebo. If the 12.6% margin were to be accepted, all three analysis populations should demonstrate non-inferiority; however, the ITT analysis barely beats the margin. The estimated response probability on lactitol was slightly lower than that on Amitiza in all analyses. The per-protocol analysis produces more favorable results for lactitol than the other two analyses; however, the per-protocol analysis does not account for the slightly higher rate of dropout and major protocol deviations for the lactitol group compared to the Amitiza group. The subsets of randomized patients being compared between the two arms in the per-protocol analysis may not be similar, making results difficult to interpret. Because of this, the ITT and mITT analyses may be more relevant for comparing the two arms. The responder definition was based on calculating the number of CSBMs per week as 7 × (number of CSBMs/number of days with non-missing diary entries) for subjects with 4 or more days with non-missing diary entries. Using the observed number of CSBMs for a week produced similar results.

Table 24: Efficacy Results for the ITT, mITT, and Per-Protocol Populations (Excluding Patients From Site 30)

		Lactitol	Amitiza
ITT	N	223	222
	Responders (%)	47 (21.1)	57 (25.7)
	Treatment Difference (95% CI)	-4.6 (-12.5, 3.3)	
mITT	N	218	222
	Responders (%)	47 (21.6)	57 (25.7)
	Treatment Difference (95% CI)	-4.1 (-12.0, 3.8)	
Per-Protocol	N	187	199
	Responders (%)	47 (25.1)	56 (28.1)
	Treatment Difference (95% CI)	-3.0 (-11.8, 5.8)	

Abbreviations: CI, confidence interval; ITT, intent to treat; mITT, modified intent to treat
Source: Reviewer's analysis created from ADEFF.xpt

The review team performed additional analyses to determine the robustness of the efficacy results with respect to missing data. Using only the observed number of CSBMs for a given week or changing the assumption that patients are non-responders for weeks with less than 4 days of diary data could alter the number of responders. The primary statistical analysis was repeated after altering the number of responders in the Amitiza arm to determine how many additional responders in the Amitiza arm it would take in order for the study to not demonstrate non-inferiority at a margin of 12.6%. This was done for both the per-protocol and ITT populations. Results are displayed in Table 25 below. The analysis for the per-protocol population would not have beaten the NI margin had there been two additional patients meeting the responder definition in the Amitiza group. Results are also concerning for the ITT analysis, where one additional responder in the Amitiza group would have changed the efficacy conclusions. For patients in the ITT population, there were 45 patients in the Amitiza group who could have potentially met the responder definition if they did not have missing data. A sensitivity analysis for the ITT population where approximately 20% of weeks with a missing number of CSBMs were imputed as a responder week in both study arms resulted in at least 2 additional responders in the Amitiza group in 90% of imputations (18 out of 20 imputations). This imputation method also resulted in no additional responders in the lactitol group for 65% of imputations (13 out of 20 imputations). This sensitivity analysis is assuming a lower response rate for missing study weeks than what was observed in the placebo arm of Study 302. These observations support the assessment that, in Study 301, the efficacy results of the primary endpoint are not robust to missing data, as changes to the non-responder imputation assumption or the absence of missing data could plausibly alter efficacy conclusions.

Table 25: Exploratory Analyses to Determine Robustness of Efficacy Results

			Lactitol (N = 187)	Amitiza (N = 199)
Per-Protocol Population Sensitivity Analyses	Two more Responders for Amitiza	Responders (%)	47 (25.1)	58 (29.1)
		Treatment Difference (95% CI)	-4.0 (-12.9, 4.8)	
			Lactitol (N = 223)	**Amitiza (N = 222)**
ITT Population Sensitivity Analyses	One more Responder for Amitiza	Responders (%)	47 (21.1)	58 (26.1)
		Treatment Difference (95% CI)	-5.0 (-12.9, 2.8)	

Abbreviations: CI, confidence interval; ITT, intent to treat
Source: Reviewer's analysis created from ADEFF.xpt

The estimated change in number of CSBMs for each treatment group, the estimated treatment difference, and 95% confidence intervals from an MMRM model with site ID, treatment, visit, and a treatment-by-visit interaction included as factors and baseline number of CSBMs included as a covariate are displayed in Table 26 below. The estimated change in number of CSBMs are lower for the lactitol group at every week, i.e., there was less improvement observed on lactitol than Amitiza. The difference is statistically significant in 3 of the last 6 weeks (weeks 7, 8, and 12). Analyses are not adjusted for multiplicity. The numbers in the table are rounded to the nearest tenth. A value of -0.0 indicates a negative value between -0.05 and 0.

Table 26: Estimated Change in the Number of CSBMs From Baseline

Week	Lactitol	Amitiza	Difference
1	1.9 (1.4, 2.4)	2.3 (1.8, 2.7)	-0.3 (-1.0, 0.3)
2	2.5 (2.0, 3.0)	2.8 (2.3, 3.3)	-0.3 (-1.0, 0.4)
3	2.4 (1.9, 3.1)	3.0 (2.5, 3.5)	-0.6 (-1.3, 0.1)
4	2.5 (2.0, 3.1)	3.1 (2.6, 3.7)	-0.6 (-1.4, 0.2)
5	2.5 (1.9, 3.0)	3.2 (2.7, 3.7)	-0.7 (-1.4, 0.1)
6	2.6 (2.0, 3.1)	3.2 (2.7, 3.8)	-0.6 (-1.4, 0.1)
7	2.6 (2.0, 3.2)	3.4 (2.8, 4.0)	-0.8 (-1.6, -0.0)
8	2.6 (2.1, 3.2)	3.4 (2.9, 3.9)	-0.8 (-1.5, -0.0)
9	2.9 (2.4, 3.4)	3.3 (2.8, 3.8)	-0.4 (-1.1, 0.2)
10	2.9 (2.4, 3.4)	3.4 (2.9, 3.9)	-0.5 (-1.3, 0.2)
11	2.9 (2.4, 3.4)	3.3 (2.8, 3.8)	-0.4 (-1.1, 0.3)
12	2.8 (2.3, 3.3)	3.6 (3.1, 4.1)	-0.9 (-1.6, -0.2)

Abbreviations: CSBM, complete spontaneous bowel movements
Source: Reviewer's analysis created from ADEFF.xpt

The estimated change from baseline in CSBMs per week in the lactitol group in this study is similar to the estimated change from baseline in CSBMs from Study 302. A comparison of the estimated change from baseline in CSBMs per week for the lactitol groups in Study 301 and Study 302 is presented in Section 8.1.7.

Dose/Dose Response

Not applicable as this study evaluated the efficacy of 20 g of lactitol compared to Amitiza. Although the protocol allowed patients with persistent diarrhea or loose stools to reduce their dose to 10 g of lactitol per day, the study was not designed to compare the efficacy of the 20 g and 10 g lactitol dose groups.

Durability of Response

The magnitude of the treatment difference between the lactitol and Amitiza groups fluctuated at each week and the estimated change in number of CSBMs from baseline is lower for the lactitol group compared to the Amitiza group at every week during the 12-week treatment period. The treatment effect continued through week 12 as shown in the above Table 26: Estimated change in the number of CSBMs from baseline in the section Efficacy Results – Primary Endpoint.

Persistence of Effect

Available data did not permit a robust analysis of persistence of effect (i.e., treatment benefit after the drug was stopped).

Additional Analyses Conducted on the Individual Trial

An additional non-inferiority analysis was performed by the FDA to compare Amitiza and lactitol with respect to SBM responder over a 4 week period. A subject was defined as a responder if they had at least 3 SBMs per week over the first 4 weeks of the study with no rescue medication taken during those 4 weeks or the 24 hours preceding the first week. Although the primary endpoint was the frequency of SBMs at Week 1 in the trials used for the approval of Amitiza, the SBM responder endpoint was considered more clinically meaningful in the 2005 FDA statistical review to support approval Amitiza (NDA 021908 REV-BIOMETRICS-01 12/16/2005). The Division's thinking has evolved since Amitiza was approved and this endpoint definition is not currently recommended for CIC trials. A treatment difference of 19.5% and 16.2% between Amitiza and placebo was seen for this endpoint in studies SC0131 and SC0232, respectively. The estimated treatment effect from the two studies combined, taking an average weighted by study sample size, is 17.9% with a 95% confidence interval of (9.6%, 26.1%). Results for this endpoint for the mITT population (excluding site 30) in Study 301 are displayed in Table 27 below. The lower bound of -14.3% for the 95% CI is close to the estimated 17.9% treatment difference between Amitiza and placebo and exceeds both half of the estimated treatment difference and the 9.6% lower bound for the 95% CI of the treatment difference between Amitiza and placebo. Therefore, the review team could not conclude that lactitol demonstrated non-inferiority to Amitiza for the endpoint of SBM responder over 4 weeks.

Table 27: SBM Responder Over First 4 Weeks of Treatment

	Lactitol	Amitiza
N	218	222
Responders (%)	75 (34.4)	88 (39.6)
Treatment Difference (95% CI)	-5.2 (-14.3, 3.8)	

Abbreviations: CI, confidence interval

8.1.3. Review of Supportive Literature

Given the concerns with the choice of the non-inferiority margin and the robustness of Study BLI400-301, and the understanding that lactitol has been widely marketed in other countries for many years, the review team requested that the Applicant provide additional efficacy information to supplement the data submitted in the NDA. We recommended that the Applicant submit a comprehensive summary of published efficacy trials in adults with CIC, including placebo- and active-controlled trials. The tables below summarize the reviewed studies and their main design elements, followed by a discussion of the similarities and limitations of these studies to Study

BLI400-302. Notable differences in the design of the published literature and Study BLI400-302 are noted in ***bold/italicized*** font in the tables below.

Table 28: Randomized, Placebo-Controlled Trial

Study	Study Design	N	Patients	Constipation definition/ Duration	Dosing Schedule	Mean Dosage (g/day)	Treatment duration
Vanderdonckt et al (1990)[1]	Randomized DB, PC crossover	46	Mean age (years): 84 Females: 65% Mean BMI: 23 kg/m2 ***Elderly, Institutionalized, but not bedridden***	Chronic functional constipation; ≤3 BMs per week when abstaining from laxatives, with stools that are generally hard to pass; duration ≥6 Months	20 g in week 1; ***Dose adjustment permitted at the end of week 1 or week 2 based on response***	***35 g***	4 weeks, then a 4 week washout period, 4 weeks with alternate medication.

Abbreviations: BMI, body mass index; DB, double-blind; PC, placebo-controlled
[1] Vanderdonckt J, Coulon J, Denys W, Ravelli GP, 1990. Study of the laxative effect of lactitol (Importal®) in an elderly institutionalized, but not bedridden, population suffering from chronic constipation. J Clin Exp Gerontol;12:171–89.
Source: Adapted from sponsor's response to filing communication, dated 2/28/2019, Summary of Supporting Literature, pages 4- 6 and the cited article.

Efficacy was assessed on the average number of bowel movements per week and average scores for stool consistency for weeks 3 and 4 of the treatment period. The reported results show that during weeks 3 and 4 of lactitol treatment, patients experienced an increase of approximately 2 bowel movements per week, a reduction in stool consistency from hard to soft, and reduced use of rescue laxative (enemas or suppositories) compared to placebo.

There are some key differences between the design of the Vanderdonckt et al study and Study BLI400-302. In the Vanderdonckt et al study, the patient population is older with an age range of 63-101 years and a mean age of 84 years. In the BLI400-302 study, the age range of the patients is 18 to 88 years, with a mean age of 52 years. Vanderdonckt et al discuss that the relatively high average dosage of lactitol of 35 grams used in this study reflects the severity of chronic constipation in the elderly patients studied. Despite patients increasing the dose from a starting dose of 20 grams/day to 35 grams/day on average, lactitol was generally well tolerated and all reported adverse reactions were limited to the gastrointestinal class. For the lactitol-placebo sequence cohort, reports of flatulence, bloating, abdominal cramps, and diarrhea were higher in the lactitol than placebo groups, but in the placebo-lactitol sequence cohort, reports of flatulence, bloating, and abdominal cramps were higher in the placebo than lactitol groups. Although the average dosage of lactitol is higher in the Vanderdonckt et al study compared to Study BLI400-302, the reported results show that lactitol demonstrated favorable efficacy and safety. As shown in Table 29 below, four active controlled trials were reviewed, and major design elements were compared to Study BLI400-302 with differences noted in bold/italicized.

Table 29: Randomized, Active Comparator (Lactulose) Controlled Trials

Study	Study Design	N	Patients	Constipation Definition/Duration	Dosing Schedule	Mean Dosage (g/day)	Treatment Duration (days)
Heitland and Mauresberger (1988)[1]	RCT Parallel Lactulose comparator	60	Mean age (years): 55 Females: 37% Mean BMI: 25 kg/m2	Chronic constipation, requiring the use of laxatives; duration 5.6 years (mean)	20 g starting dose; 10, 20, or 30 g thereafter based on response; ***Dose adjustments***	20g	14
Doffoel et al (1990)[2]	RCT Crossover Lactulose comparator	60	Mean age (years): 79; ***Elderly patients*** Females: 87%	Chronic functional constipation requiring laxative therapy, ≤3 BMs per week; duration not reported	15 g starting dose; 15–30 g thereafter based on response; ***Dose adjustments***	20g	Two 12 day treatment periods with a 2 day drug-free interval between treatments
Hammer and Ravelli (1992)[3]	RCT Parallel Lactulose comparator	61	Mean age (years): 54 Females: 81% Mean BMI: 23 kg/m2	***Chronic functional constipation, "irritable colon", or psychological conditions attributable to constipation***, ≤3 BMs per week without taking laxatives; duration not Reported	20 g for first 3 days; ***10 g thereafter***	20g	28
Xu et al (2012)[4]	RCT Parallel Lactulose comparator	129	Mean age (years): 42 Females: 71%	Constipation <3 BMs per week; duration >3 days	***20 g on day 1, 5–10 g thereafter based on response Dose adjustments***	NR	***7***

Abbreviations: BMI, body mass index; RCT, randomized controlled trial; NR, not reported
[1] Heitland W, Mauersberger H. Study of the laxative effect of lactitol as opposed to lactulose in an open, randomized comparative study. Schweizerische Rundschau für Medizin Praxis.1988; 77: 493-495.
[2] Doffoel M, Berthel M, Bockel R. Comparative study of lactitol and lactulose in the treatment of functional constipation in elderly subjects. Med Chir Dig 1990; 19:257–259.
[3] Hammer B and Ravelli GP. Chronic functional constipation lactitol Maintenance dose, a multicentre comparative study with lactulose. Ther Schweiz 1992; 8: 328–335.
[4] Xu Z, Dai J, Shi R, et al. A multicenter, randomized, single-blinded, parallel-controlled trial on lactitol in treatment of constipation. Chinese Journal of Gastroenterology. 2012;17(3):168–172.
Source: Adapted from Applicant's response to filing communication, dated 2/28/2019, Summary of Supporting Literature, pages 4- 6 and the cited articles.

The results of the Heitland and Mauresberger study suggested that both lactitol and lactulose may be efficacious in increasing stool frequency; patients receiving lactitol experienced at least one bowel movement per day on 75% of the days of the study and patients receiving lactulose on 70% of the days. Both the lactitol and lactulose group showed similar improvements in stool consistency. Both laxatives were well tolerated with no significant differences in reported AEs. A limitation of this study is the short treatment duration of 14 days.

The results of the Doffoel et al study were similar for both the lactitol and lactulose arms. The average number of BMs during the 12 day treatment period was 9.4 ± 0.5 in the lactitol group and 8.4 ± 0.4 in the lactulose group. Similarly, 85% percent of patients receiving lactitol reported normal stool consistency as compared to 83% of those receiving lactulose. The frequency of GI AEs was similar between the treatment groups. Of note, the Doffoel et al study has an elderly patient population with a mean age of 79 years. Although the starting dose of 15 grams is less than the starting dose of 20 grams in Study BLI400-302, patients in the Doffoel et al study were permitted to dose adjust based on response and the mean dosage was 20 grams/day.

The hypothesis of the Hammer and Ravelli study was that when given purely for its laxative effect, lactitol can be administered at a maintenance dose of 10 g/day (vs. 20 g/day initial dose) without loss of efficacy but with improved tolerability. The results showed that the frequency of bowel movements per week in the lactitol group was 6.7 ±4.39 and in the lactulose group it was 7.4 ± 4.48. However, the investigators reported that a total of 10 of 32 patients (31%) in the lactitol group complained of side effects; in the lactulose group, the corresponding numbers were 16/26 (62%). Similar to Study BLI400-302, this study supports that patients who reduce the lactitol dose to 10 g/day may maintain efficacy while reducing adverse events. One limitation of this study is the broader patient population including patients with chronic functional constipation, irritable bowel syndrome, or psychological conditions attributable to constipation.

The results of the Xu et al study show that within 3 days of treatment, the frequency of bowel movements was normalized in approximately 78% of the patients of both the lactitol and lactulose groups, reaching approximately 95% by day 7. Rates of AEs in these two groups were similar. Of note, the treatment duration was only 7 days. The mean dosage per day was not reported.

The sponsor submitted and we reviewed the following single arm or open label studies. It is difficult to use these data as supportive evidence for the efficacy and safety of lactitol in the absence of comparative controlled data.

Single arm studies:

- Walder M, Buclin T, Biollaz J, Kitler ME, Schelling JL. [Dose-response curve and preliminary clinical study of a laxative, lactitol]. Schweiz Med Wochenschr. 1988;118:1925–1927. French.
- Delas N, Gislon J, Glikmanas M, Henri-Biabaud E, Lemerez M, Licht H, Slama JL, Gillaume PN. [Lactitol in the treatment of constipation in the adult. Open, non-comparative study of its efficacy and its clinical and biological tolerance]. Ann Gastroenterol Hepatol (Paris). 1991 Oct;27(5):231-3.
- Goovaerts L, Ravelli GP. Lactitol monohydrate for the treatment of chronic constipation: a multicentre study on the efficacy and tolerability of an individually adjusted daily dose. Acta Therapeutica. 1993;19:61–69.

- Ravelli GP, Whyte A, Spencer R, Hotten P, Harbron C, Keenan R. The effect of lactitol intake upon stool parameters and the faecal bacteria flora in chronically constipated women. Acta Therapeutica. 1995;21: 243–254.

Open label study:

- Kumar S, Jagadeesh K, Revankar S. Clinical Efficacy And Safety Of Lactitol Versus Lactulose In The Treatment Of Constipation International Journal of Institutional Pharmacy and Life Sciences 5(2):265-271 2015

Supportive Literature Conclusions

The above placebo-controlled and active comparator-controlled trials show that patients treated with lactitol showed improvements in BM frequency and consistency from baseline, and that efficacy measures in patients treated with lactitol were generally slightly improved or similar to patients treated with lactulose. Both products were well tolerated with the most common AEs in the gastrointestinal class, which were expected given the mechanism of action of both laxatives. Lactitol showed improvement in the Vanderdonckt et al study compared to placebo. While these investigator trials do not have the same statistical rigor as Studies BLI400-301 and BLI400-302, these published trials provide supplemental evidence that lactitol is efficacious and improves BM frequency.

8.1.4. Comparison of Lactitol to Historical Controls

As a supportive analysis to help address the limitations with relying on Study 301, we requested that the Applicant submit a meta-analysis comparing the data from the lactitol treatment group in Study 301 to historical placebo data from other recent CIC studies. The Applicant identified 12 placebo-controlled trials across three approved drugs that were included in the meta-analysis. Placebo response rates range from 2.9% to 13.0%. Results are presented for both fixed effects and random effects meta-analysis. The random effects meta-analysis accounts for heterogeneity in the placebo response rate across studies. Only one of the included trials (Study SP304203-03) has a higher placebo response rate than Study 302. Two other trials (Study SPD-555-302 and Study SPD-555-401) had similar placebo response rates to Study 302. The team performed a third meta-analysis analysis using those three studies. The lower bound of the 95% CI for the lactitol response rate is greater than the upper bound of the 95% CI for the placebo response rates from all three meta-analyses, providing additional support for the effectiveness of lactitol. Table 30 below lists the trials, drugs, number of placebo patients, and response rates.

Table 30: Meta-analysis of Historical Clinical Trials to Estimate Placebo Response

Product	Study	Number of Placebo Subjects	Placebo Response Rate (%)
Linaclotide	MCP-103-303	209	2.9
	LIN-MD-01	215	5.6
	Lacy et al, 2015	171	7.6
	Schoenfeld et al, 2017	401	4.7
Plecanatide	SP304203-00	452	10.2
	SP304203-03	440	13.0
Prucalopride	PRU-CRC-3001	252	8.3
	SPD-555-302	181	12.2
	PRU-INT-6	240	5.0
	PRU-USA-11	193	6.7
	PRU-USA-13	212	5.2
	SPD-555-401	169	12.4
		Response Rate (%)	**95% CI**
Fixed Effects Meta-analysis (All Trials)		**8.1**	**(7.2, 9.1)**
Random Effects Meta-analysis (All Trials)		**7.5**	**(5.8, 9.6)**
Random Effects Meta-analysis (SP304203-03, SPD-555-302, SPD-555-401)		**12.7**	**(10.5, 15.2)**
Lactitol Arm in Study 301		**21.1**	**(15.7, 26.4)**

Abbreviations: CI, confidence interval
Source: Reviewer's table. Placebo response rates from studies adapted from Table 4 of Meta-analysis of BLI400 (Study BLI400-301) versus Placebo (May 21, 2019 Response to IR). Meta-analysis results obtained from reviewer's analysis.

8.1.5. BLI400-303 (Study 303)

Trial Design

Title: An Open Label Study of Chronic Use of BLI400 Laxative in Constipated Adults

Objective: To evaluate the safety of chronic use of BLI400 laxative in constipated adults.

Study design: BLI400-303 is a phase 3, open-label, multi-center study in adult patients with CIC who received lactitol for 12 months. Of the 298 patients exposed to lactitol in Study 303, 243 were not previously enrolled in Study 301 or 302, 53 were previously enrolled in Study 301, and 2 were previously enrolled in Study 302.

Study population: 330 patients were enrolled in this study.

Select inclusion and exclusion criteria:
The inclusion and exclusion criteria were generally similar between Studies BLI400-303 and BLI400-302. Refer to Section 8.1.1 BLI400-302, Key inclusion and exclusion criteria above.

Study Endpoints

Efficacy: Patient constipation symptoms and quality of life indicators were analyzed using data from the Patient Assessment of Constipation Symptom (PAC-SYM) and Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaires.

Safety: Safety variables for the study population included physical examination measures, adverse events, blood chemistry and hematology, urinalysis and ECG data.

Statistical Analysis Plan

Analysis Populations Definitions

Intention-to-Treat (ITT) Population – includes all subjects dispensed treatment. This population is used for sensitivity analyses of the primary and secondary endpoints.

Modified Intention-to-Treat (mITT) Population – consists of all subjects in the ITT population who took at least one dose of study medication. This population is used in all safety analyses and for the primary and secondary efficacy endpoints. Seven patients from Site 25 were excluded from the efficacy and safety analyses due to confirmed research misconduct by the site coordinator.

Per-Protocol (PP) Population – consists of all subjects in the mITT population who completed Visit 6 without a major protocol violation. This population is used for sensitivity analyses of the primary and secondary endpoints.

Safety Population – consists of all subjects in the mITT population excluding 7 subjects from site 25 (data integrity concerns).

Analyses for Efficacy Endpoints

Descriptive statistics are produced for efficacy endpoints. For continuous variables, descriptive statistics consist of the mean, median, standard deviation, minimum, and maximum values. For categorical variables, the number and percent of each category are displayed.

Missing Data

Descriptive statistics consist of only observed data and the number of patients with completed PAC-SYM and PAC-QOL questionnaires at each study visit is shown in Table 31 below.

Table 31: Number of Patients[1] With a Completed PAC-SYM and PAC-QOL Average/Overall Score and Change From Baseline at Each Study Visit

Visit	Number of Patients with Overall PAC-SYM score	Number of Patients with Change from Baseline PAC-SYM score	Number of Patients with Overall PAC-QOL score	Number of Patients with Change from Baseline PAC-QOL score
Visit 1 (Day 0)	294		294	
Visit 2 (Month 2)	280	278	280	278
Visit 3 (Month 4)	247	245	248	246
Visit 4 (Month 6)	234	232	234	232
Visit 5 (Month 9)	224	222	224	222
Visit 6 (Month 12)	218	217	218	217

Abbreviations: PAC-SYM, patient assessment of constipation symptom; PAC-QOL, patient assessment of constipation quality of life
[1] Number of patients who took study drug, excluding site 25 with research misconduct.
Source: Reviewer's analysis

Protocol Amendments

There were no amendments to the protocol.

Patient Disposition

For the 298 patients exposed to lactitol in Study 303, 243 were not previously enrolled in Study 301 or 302. Of the 55 patients that were previously enrolled in Study 301 or 302, 28 had previously been exposed to lactitol, 21 were randomized to Amitiza, and 6 were screen failures. Fifty-three of the 55 previously enrolled patients had been enrolled in Study 301.

Table 32 below shows the patient disposition for Study BLI400-303. Twenty-five enrolled patients were not included in the mITT safety analysis population for the following reasons:

- 16 patients' study records (site 5) were lost in a fire
- 5 patients were lost to follow-up after Visit 1
- 4 patients had enrolled themselves in multiple investigational studies and were, therefore, excluded.

Thirty-two patients were not included in the efficacy analysis. Of the 32 excluded patients, 25 patients were not included in the mITT safety analysis described above and 7 patients (from site 25) were excluded due to confirmed research misconduct by the site coordinator.

Table 32: Patient Disposition, All Dosed Patients

	Lactitol n
ITT Patients	330
mITT Patients	305
Efficacy Patients	298
Safety Population (excluding site 25)	298

Abbreviations: ITT, intent to treat; mITT, modified intent to treat
Source: 303 CSR, submitted June 29, 2018, Table 303- 2 Patient Disposition, page 27/56.

Discontinuation

The reasons for patient discontinuation are displayed in Table 33 below. The most common reasons for patient discontinuation are patient withdrew consent, lost to follow up, and adverse event. For discussion on the adverse events that led to dropouts and/or discontinuations, refer to Section 8.2.4 Safety Results, Dropouts and/or Discontinuations Due to Adverse Effects.

Table 33: Patient Discontinuation

	Lactitol (N=305) n (%)
Completion Status	
Completed	221 (72.5)
Discontinued	84 (27.5)
Discontinuation due to	
Adverse event	13 (4.3)
Lost to follow up	16 (5.2)
Physician decision	7 (2.3)
Patient withdrew consent	37 (12.1)
Lack of Efficacy	5 (1.6)
Prohibited medication	5 (1.6)
Other	1 (0.3)

Source: 303 CSR, submitted June 29, 2018, Table 303- 2 Patient Disposition, page 27/56.

Protocol Violations/Deviations

Table 34 shows major protocol deviations for the safety population (all dosed patients) in Study 303. The most common major protocol deviations included prohibited concomitant medication and missing assessment. The percentages of patients with these protocol violations are relatively small and these violations do not appear to affect the overall efficacy and safety results of the study.

Table 34: Major Protocol Deviations, All Dosed Patients

	Lactitol (N=305) n (%)
Total major protocol deviations	49 (16.1)
Deviation category	
Eligibility criteria	1 (0.3)
Prohibited concomitant medication	15 (4.9)
Study drug compliance	6 (2.0)
Missing assessment	14 (4.6)
Missing visit	2 (0.7)
Study Procedure Error	11 (3.6)

Source: Applicant's IR response, Table 4: BLI400-303: Major Protocol Deviations, dated November 5, 2019

Demographic and Baseline Characteristics

Table 35 below shows the demographic characteristics for the safety population (all dosed patients) in Study 303.

Table 35: Demographic Characteristics for All Dosed Patients

Demographic Parameters	Lactitol (N=305) n (%)
Sex	
Male	82 (27)
Female	223 (73)
Age	
Mean years (SD)	54.5 (16.0)
Median (years)	55
Min, Max (years)	18, 88
Age Group	
<65 years	197 (65)
≥65 years	108 (35)
Race	
White	205 (67)
Black or African American	91 (30)
Asian	3 (1)
American Indian or Alaska Native	1 (0.3)
Native Hawaiian or Other Pacific Islander	2 (0.7)
Other	3 (1)
Ethnicity	
Hispanic or Latino	133 (44)
Not Hispanic or Latino	172 (56)
Region	
United States	305 (100)

Abbreviations: SD, standard deviation
Source: Reviewer's analysis created from ADSL.xpt

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The patients have a long-standing history of constipation, with a mean (SD) of 17.1 (16.8) years and a median (min; max) of 11.3 (0.2; 81.6) years.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Bottle weights were measured at each return visit to assess treatment compliance. Based on these measurements and the duration of each patient's participation in the study, treatment compliance was about 92% of expected product usage.

Concomitant Medications

Table 36 below shows the baseline concomitant medications for all dosed patients. Medications included in Table 36 (including laxatives) all had start dates that preceded study participation. Laxatives were required to be discontinued immediately following the screening visit. The most frequently reported drug classes of baseline concomitant medications were anti-hypertensive agents (33.1%), lipid-modifying agents (24.6%), anti-inflammatory and antirheumatic products (13.4), and drugs for acid-related disorders (13.1%). These drug classes are commonly used in the general population. There were relatively low numbers of patients taking medications that could have a side effect of constipation (e.g., thyroid therapy, iron preparations).

Table 36: Baseline Concomitant Medications, All Dosed Patients

	Lactitol (N= 305) n (%)
Laxatives	33 (10.8)
Bulk-Forming Laxatives	1 (0.3)
Contact Laxatives	21 (6.9)
Osmotically Acting Laxatives	10 (3.3)
Other Drugs For Constipation	4 (1.3)
Softeners, Emollients	4 (1.3)
Analgesics	33 (10.8)
Anti-inflammatory and antirheumatic products	41 (13.4)
Lipid-modifying agents	75 (24.6)
Anti-hypertensive agents	101 (33.1)
Agents Acting On The Renin-Angiotensin System	93 (30.5)
Antihypertensives	1 (0.3)
Beta Blocking Agents	22 (7.2)
Thyroid therapy	31 (10.2)
Iron preparations	1 (0.3)
Drugs for acid-related disorders	40 (13.1)

Source: Applicant's IR response, Table 4: BLI400-303: Baseline Concomitant Medications Safety Population (All Dosed), dated November 5, 2019

Rescue Medication Use

Patients were given bisacodyl tablets (5mg) at each study visit and were instructed to take 5 to 10mg (1 to 2 tablets) of bisacodyl if they experienced severe discomfort due to their constipation, or had not had a BM in 4 days. Patients used bisacodyl an average of 2.7 times during screening to Month 2, 2.4 times during Month 2 to Month 4, 2.9 times during Month 4 to Month 6, 2.3 times during Month 6 to Month 9, and 1.2 times during Month 9 to Month 12.

Rescue medication use appears stable during the trial with a decline of use during Month 9 to Month 12.

Efficacy Results

Table 37 below shows improvements in symptoms and quality of life scores from baseline by Visit 2 (2 months of treatment) and progressive improvement throughout the course of the study to Visit 6 (12 months). These quality of life questionnaires are not recommended as primary efficacy endpoints but could be considered as part of the collective evidence to support clinical benefit to patients. In the absence of a comparator arm in this open-label study, it is difficult to determine whether any observed benefit is due to the study drug.

Table 37: Change in PAC-SYM and PAC-QOL Scores From Baseline by Visit

Mean Change in PAC-SYM Score[1] by Domain (SD)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Abdominal Symptoms	2.06	-0.85 (1.0)	-1.09 (1.1)	-1.20 (1.2)	-1.33 (1.1)	-1.48 (1.1)
Rectal Symptoms	1.61	-0.95 (1.0)	-1.13 (1.1)	-1.18 (1.1)	-1.24 (1.2)	-1.34 (1.1)
Stool Symptoms	2.66	-1.49 (1.2)	-1.66 (1.2)	-1.73 (1.2)	-1.88 (1.2)	-2.02 (1.1)
Overall	2.20	-1.14 (0.9)	-1.34 (1.0)	-1.42 (1.0)	-1.54 (1.0)	-1.67 (1.0)
Mean Change in PAC-QOL Score[2] by Domain (SD)	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Extent/Intensity of Constipation	2.59	-1.36 (1.2)	-1.54 (1.2)	-1.54 (1.3)	-1.75 (1.3)	-1.95 (1.2)
Effect Constipation on Daily Life	1.92	-0.87 (0.9)	-1.06 (1.0)	-1.14 (1.1)	-1.22 (1.1)	-1.37 (1.1)
Feelings Related to Constipation	2.13	-0.95 (1.0)	-1.14 (1.0)	-1.17 (1.1)	-1.28 (1.1)	-1.41 (1.1)
Life with Constipation	2.71	-1.36 (1.1)	-1.58 (1.3)	-1.59 (1.2)	-1.69 (1.2)	-1.79 (1.2)
Degree of Satisfaction	0.41	1.55 (1.2)	1.74 (1.2)	1.79 (1.3)	1.91 (1.3)	1.92 (1.4)
Overall	65.8	-29.9(23.0)	-35.3 (25.4)	-36.6 (26.6)	-39.6 (27.2)	-43.0 (26.8)

Abbreviations: PAC-SYM, patient assessment of constipation symptom; PAC-QOL, patient assessment of constipation quality of life; SD, standard deviation
[1] PAC-SYM symptoms scored on a 0 to 4 scale: 0=Absent 1=Mild 2=Moderate 3=Severe 4=Very Severe.
Negative values indicate improvement, except for Degree of Satisfaction (+ values = improvement)
[2] PAC-QOL questions scored on a 0 to 4 scale: 0=None (of time) 1=A Little 2=Some 3=Most 4=All; Overall = the sum of all 28 question scores
Source: 303 CSR, submitted June 29, 2018, Table 303- 4 Change in PAC-SYM and PAC-QOL Scores from Baseline by Visit, page 30/56.

Durability of Response

Patient scores on the PAC-SYM and PAC-QOL instruments showed improvement throughout the course of the study to Visit 6 (12 months). Refer to the above Table 37: Change in PAC-SYM and PAC-QOL Scores From Baseline by Visit.

Persistence of Effect

The study was not designed to analyze persistence of effect (i.e., treatment benefit after the drug was stopped).

8.1.6. Assessment of Efficacy Across Trials

Primary Endpoint

The table below shows the number of responders and percent of responders from the lactitol treatment groups using the ITT population (excluding site 30) for study 301 and the FDA primary analysis population for study 302. The overall response rates appear to be similar in the two studies.

Table 38: Number of and Percent of CSBM Responders From the Lactitol Treatment Groups using the Primary Analysis Population From Each Trial

	Study 301 (n = 223)	Study 302 (n = 291)
Number of Responders	47	73
% of Responders (95% CI)	21.1 (15.7, 26.4)	25.1 (20.1, 30.1)

Abbreviations: CI, confidence interval; CSBM, complete spontaneous bowel movements
Source: Reviewer's analysis created from ADEFF.xpt

Secondary and Other Endpoints

The table below displays the estimated mean change from baseline in CSBMs per week for the lactitol groups in Study 301 and 302. The estimated changes and 95% confidence intervals were obtained from separate MMRM models in each individual trial. The models were described in sections 8.1.1 and 8.1.2. The mean change from baseline per week was very similar between the studies.

Table 39: Estimated Change From Baseline in CSBMs per Week for the Lactitol Groups in Study 301 and 302

Week	Study 301	Study 302
1	1.9 (1.4, 2.4)	2.1 (1.7, 2.4)
2	2.5 (2.0, 3.0)	2.2 (1.8, 2.6)
3	2.4 (1.9, 3.1)	2.4 (2.0, 2.8)
4	2.5 (2.0, 3.1)	2.4 (2.1, 2.8)
5	2.5 (1.9, 3.0)	2.8 (2.5, 3.2)
6	2.6 (2.0, 3.1)	2.5 (2.2, 2.9)
7	2.6 (2.0, 3.2)	2.6 (2.2, 2.9)
8	2.6 (2.1, 3.2)	2.6 (2.3, 3.0)
9	2.9 (2.4, 3.4)	2.6 (2.3, 3.0)
10	2.9 (2.4, 3.4)	2.6 (2.3, 3.0)
11	2.9 (2.4, 3.4)	2.8 (2.5, 3.2)
12	2.8 (2.3, 3.3)	2.8 (2.4, 3.1)

Abbreviations: CSBM, complete spontaneous bowel movements
Source: Reviewer's analysis created from ADEFF.xpt

8.1.7. Integrated Assessment of Effectiveness

Integrated Review of Effectiveness

The Applicant submitted two double-blind phase 3 trials. Study 302, the placebo-controlled trial, demonstrated favorable efficacy results for lactitol. Efficacy results for the primary endpoint were robust to the primary method for handling missing data. Additional exploratory analyses for the long-term treatment effect and change in number of CSBMs supported results for the primary endpoint. Study 301, the non-inferiority active comparator trial, is not recommended as one of two adequate, well-controlled trials to support approval due to concerns with the non-inferiority margin. The 12.6% margin specified by the Applicant was not based on comparisons between the active comparator and placebo, there are no historical 12-week trials comparing Amitiza to placebo for the primary endpoint that can be used to derive an appropriate margin, and a post-hoc analysis of Study 301 using a relevant endpoint from historical placebo-controlled Amitiza trials failed to reliably establish efficacy for lactitol. Furthermore, the 95% CI for the treatment difference barely excluded the non-inferiority margin and the efficacy results were not robust to missing data.

The Applicant submitted a comprehensive summary of published literature for lactitol trials and a meta-analysis of placebo response rates for recent CIC trials to provide additional support for efficacy. The published literature provide supplemental evidence that lactitol improves BM frequency and consistency. Comparisons of the response rate for the lactitol arm in Study 301 versus placebo response rates in other CIC trials were favorable to lactitol. The totality of evidence, based on results from the placebo-controlled Study 302 in conjunction with supportive results from published literature and Study 301, supports the assessment that lactitol is effective in increasing stool frequency for patients with CIC.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review for lactitol was based on the data obtained from three phase 3 trials: one active-controlled trial (Study 301), one placebo-controlled trial (Study 302), and one long-term open-label safety study (Study 303). Because of the varying study designs, the safety data were analyzed for each trial independently and trends in adverse events (AEs) were evaluated across each trial.

Safety evaluations included analyses of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), and severe TEAEs, as well as measurements of laboratory values, vital signs and ECGs. Because a thorough QT (TQT) study was not conducted, our review of the safety data from the clinical trials focused on cardiac safety, including ECG data and postmarketing safety experience from countries in which lactitol is currently marketed, to determine whether lactitol has effects on the QT interval at the intended dose. The ECG data from Studies 301 and 302 support the assessment that a dedicated TQT study is not warranted at this time.

In addition, the team focused on hypertension as an AE of special interest because an imbalance was observed between patients receiving lactitol compared to placebo. To determine if hypertension could be related to lactitol, the team further evaluated patients with AEs of hypertension for baseline cardiovascular risk factors, concomitant medications, comorbid conditions and blood pressures at each visit. To evaluate patients with increases in blood

pressure (BP) but who may not have had reported hypertension events, we also analyzed patients who experienced increases of various degrees in systolic and diastolic blood pressure after treatment initiation.

Of note, patients from site 30 in Study 301, site 32 in Study 302, and site 25 in Study 303 were excluded from the safety analyses due to data integrity concerns; these modifications to the analysis population are noted in footnotes under the tables in the following safety sections of this multi-disciplinary review. These sites had confirmed research misconduct and upon review of the reports, we determined that these data could not be relied on to support the efficacy or safety of lactitol. In addition, the safety data from the sites that were excluded due to data integrity concerns were reviewed separately to determine if excluding these data changed the overall conclusions on the safety profile of lactitol.

8.2.2. Review of the Safety Database

Overall Exposure

The safety database included 807 patients treated with lactitol from three phase 3 trials. Based on the available exposure data, we determined that reasonable exposure ranges for study completion would be defined as follows: Patients exposed for 3 months if they were on treatment for 75 or more days, for 6 months if they were on treatment for 165 or more days, and for 12 months if they were on treatment for 350 or more days. Of note, there was no comparative data for patients exposed to lactitol for 12 months because Study 303 was a single arm trial. Therefore, of the 807 patients, 698 (86%) patients were exposed to lactitol for 3 months, 473 (59%) patients were exposed to lactitol for 6 months, and 220 (27%) patients were exposed to lactitol for 12 months. Overall, the duration of exposure appears adequate to assess the safety in the intended patient population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events

We compared verbatim terms with the Applicant's coded/preferred term to help ensure consistency in coding and we made revisions as needed. Overall, the results of ours analyses were similar to that of the Applicant; however, we had to recode several terms prior to our analyses of the safety data. Refer to the Appendix, Supplementary Tables, for information on the recoded terms for Studies 301 and 302.

Routine Clinical Tests

In Studies 301, 302, and 303, patients were evaluated with physical examination, vital signs, laboratory testing (blood samples for chemistry and hematology, urinalysis) and ECGs before and during the trial as outlined in Section 15.7 Appendix Supplementary Tables, and Table 54 (Study 301), Table 55 (Study 302) and Table 56 (Study 303) show the Schedule of Events.. The routine clinical testing and safety monitoring appear to be adequate to ensure the safety of the patients enrolled in these studies.

8.2.4. Safety Results

Deaths

Study 301

There was 1 death during Study 301. Patient (b) (6) was a 39-year-old female with a history of schizophrenia and ongoing depression. The patient completed 83 days of study treatment with lactitol. The study site received a phone call from a police officer stating that the patient was found dead in her apartment on the morning of (b) (6), that is, two weeks after completing the study treatment and the day she was scheduled for her 98 day follow-up phone call. There is limited information about the cause of death; however, the cause of death was not described as a suicide. As stated in the Coroner's Report, this patient has a long history of mental illness, with multiple psychiatric diagnoses including schizophrenia, paranoid type, major depressive disorder, and schizoid personality. Although the postmortem toxicology was negative for psychiatric medications, the patient's concomitant psychiatric medications were recorded as including Trileptal for bipolar disorder, Risperdal for schizophrenia, and Cymbalta for depression. There was no evidence of injury or intoxication. The Coroner ascribed the cause of death as " "Sudden unexplained death in schizophrenia" and the manner of death as "Natural." The principal investigator reported this death as unrelated to lactitol. In general, the patient's psychiatric history makes ascertainment of any concurrent non-psychiatric illness that may have contributed to her death difficult. The patient's death occurred two weeks after completing lactitol treatment and is unlikely to be related to lactitol.

Study 302

There were no deaths during Study 302.

Study 303

There were no deaths during Study 303.

Serious Adverse Events

Study 301

There were 2/218 (0.9%) patients with 1 SAE each (cellulitis and death) in the lactitol group and 1/222 (0.5%) patient with an SAE (gastric ulcer) in the Amitiza group. In addition, there were 3 SAEs (non-cardiac chest pain, atrial fibrillation, and pancreatitis) that occurred prior to study medication dispensation and are not described further in this review.

The 2 SAEs (death and cellulitis) that occurred in the lactitol group were reported as unrelated to lactitol and an overview is included below:

- Death: The SAE occurred in patient (b) (6) and is discussed previously.
- Cellulitis: The SAE occurred in patient (b) (6), a 57-year-old female with a history of diabetes. She presented to the ER with high blood sugars and lower extremity edema. The patient was hospitalized for cellulitis, which was also reported as severe. The AE stop date was about 1 month after presenting to the ER. Although the cause of the cellulitis is unclear, uncontrolled blood glucose increases the risk of infections in diabetic patients. There does not appear to be a plausible mechanism for lactitol to cause cellulitis. Furthermore, based on the postmarketing experience of lactitol in countries outside the US and published literature reports that lactitol has a

low glycemic index, with little or no effect on glucose, insulin, and C-peptide levels,[12] [13] it is unlikely that lactitol would impair glucose or insulin secretion in diabetic patients to increase their risk for cellulitis. In a discussion with the Division of Metabolism and Endocrinology Products, lactitol does not appear to be unsafe to administer in diabetic patients. Refer to the consult by Suchitra Balakrishnan, MD, PhD, dated July 18, 2019, for further information.

Gastric ulcer was the only SAE that occurred in the Amitiza group, and was reported as possibly related to treatment.

- Gastric Ulcer: Patient (b) (6) was a 59-year-old female who informed the study coordinator approximately two weeks after study completion that she had been admitted to the emergency room for severe abdominal pain. The onset date for the AE was noted as 3 days prior to the phone call to the study coordinator and after study completion. Ulcers are not reported in the Amitiza label, and given this drug's mechanism of action as a chloride channel activator which increases intestinal fluid secretion and motility, the gastric ulcer is unlikely to be related to Amitiza. Other causes of gastric ulcers, such as infection with Helicobacter pylori or long-term use of nonsteroidal anti-inflammatory drugs, were not discussed in the narrative.

Study 302

There were 2/291 (0.7%) patients with one SAE each in the lactitol group: blood pressure increased and cerebrovascular accident. The narratives for these patients are discussed below.

- Cerebrovascular Accident: Patient (b) (6) was a 68-year-old female with ongoing osteoarthritis in both knees, who was randomized to the lactitol treatment group. The patient discontinued the study medication on (b) (6) due to elevated blood pressure (around Visit 7, 5 months). At Visit 1 the patient's standing blood pressure was 145/82 mmHg, compared to 136/90 at randomization. At Visit 6 (4 months) her standing BP was 161/98 and increased to 182/102 by Visit 7 (5 months). Two weeks after the patient stopped taking the study medication, she was hospitalized with a "mini stroke." The patient reported that she was given Atorvastatin and aspirin. The patient's blood pressure at Visit 1 was consistent with hypertension stage 2 (defined as ≥140 systolic blood pressure or ≥90 mm Hg diastolic blood pressure based on the clinical practice guidelines by the American College of Cardiology/American Heart Association Task Force[14]), and in conjunction with her age ≥55 years, places her at higher risk for a cerebrovascular event such as a stroke. Given the need for discontinuation of lactitol due to the upward trend in

[12] Natah SS, Hussien KR, Tuominen JA, Koivisto VA. Metabolic response to lactitol and xylitol in healthy men. Am J Clin Nutr. 1997 Apr;65(4):947-50.
[13] Shimomura Y, Maeda K, Nagasaki M, Matsuo Y, Murakami T, Bajotto G, Sato J, Seino T, Kamiwaki T, Suzuki M. Attenuated response of the serum triglyceride concentration to ingestion of a chocolate containing polydextrose and lactitol in place of sugar. Biosci Biotechnol Biochem. 2005 Oct;69(10):1819-23.
[14] Whelton, PK, Carey, RM, Aronow, WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018 May 15;71(19).

blood pressure during the study, it is possible that there was concern that lactitol may have contributed to this SAE. However, the lack of information on the patient's BPs after discontinuing lactitol and a complete cardiovascular history limit our ability to fully evaluate the role of lactitol in the patient's SAE.

- Blood pressure increased: The SAE occurred in a 71-year-old male (patient (b) (6)) with a history of hypertension who was hospitalized for elevated blood pressure secondary to poor compliance with his blood pressure medication. This SAE was reported by the investigator as not related to study medication. The confounding effect of the patient's past medical history of hypertension and noncompliance to antihypertensive medication make it difficult to attribute causality to lactitol.

In the placebo group, there were 9 SAEs reported in 8/302 (2.6%) patients: cerebrovascular accident, acute myocardial infarction, anxiety, arthralgia, coronary artery disease, enterocolitis, forearm fracture, non-cardiac chest pain, and uterine leiomyoma. The SAEs of cerebrovascular accident and acute myocardial infarction were reported in the same patient; as this patient received placebo, there is no relation of these SAEs to lactitol.

As previously described in this review, there were several duplicate patients across Studies 301 and 302. Because patients were analyzed only for one trial each, SAEs reported for those patients were evaluated separately to ensure that relevant AEs were not being overlooked. We identified one other SAE of a bile duct stone reported in a patient in the lactitol group during Study 302; however, since this patient (subject ID for Study 302: (b) (6)) participated in both studies, the patient was only included in our safety analysis for study 301 (unique subject ID BLI400301(b) (6)). Therefore, the event was not captured in the analysis of safety data from Study 301 because the event occurred during participation in Study 302. This patient was a 55-year-old female with onset of abdominal pain on (b) (6) and had cholecystectomy on (b) (6). This SAE was reported as unrelated to lactitol. The narrative did not describe whether the patient had risk factors for bile duct stones; therefore, we are unable to attribute or exclude causality to lactitol.

Study 303

There were 2/298 (0.7%) patients with one SAE each, severe alcoholic cirrhosis and moderate spondylolisthesis. Although there was no comparator arm in this open-label study, the two SAEs are unlikely to be related to lactitol given the mechanism of action of lactitol and considering that alcoholic cirrhosis and spondylolisthesis tend to be chronic conditions with other predisposing factors.

Dropouts and/or Discontinuations Due to Adverse Events

Study 301

In Study 301, there were 5/218 (2.3%) patients in the lactitol group and 11/222 (5.0%) patients in the Amitiza group who discontinued from the study due to an AE. The AEs specified as reasons for discontinuation in the lactitol treatment group included cellulitis, abnormal EKG result (anterolateral ischemic changes asymptomatic), nausea, "extremely low" hemoglobin and hematocrit, and irregular heartbeat. The patient with the AE of irregular heart beat was a 70-year-old male with limited details on medical history, although there was no reported cardiac history per the case report form. The AE was reported by the investigator as unrelated to lactitol and the outcome was recovered/resolved. Overall, the percentage of patients in the lactitol

treatment group who discontinued from the study due to an AE was small (2.3%) and lower than in the Amitiza group.

The AEs specified as reasons for discontinuation in the Amitiza group were increased alanine transaminase, patient's physician suggestion due to elevated CPK, abnormal EKG, abdominal pain, unplanned surgery on right foot, nausea x 3, abdominal cramping x 2 (1 with dizziness), and swelling in throat. Some of these events are described in the approved labeling for Amitiza, including abdominal pain, nausea, and swelling.

Study 302

In Study 302, there were 11/291 (3.8%) patients in the lactitol group and 10/302 (3.3%) patients in the placebo group who discontinued from the study due to an AE. The AEs specified as reasons for discontinuation in the lactitol treatment group were elevated creatine kinase x 3 (1 with elevated ALT levels), flatulence x 2, common cold and diarrhea, newly diagnosed hypertension and hypothyroidism, stomach cramps and diarrhea, blood pressure increased, bowel incontinence, and stomach pain. AEs that resulted in discontinuation and occurred in at least 1% of patients and greater than in placebo are recommended for inclusion in the label (elevated creatinine kinase, flatulence, diarrhea, and blood pressure increased); the terms blood pressure increased and hypertension will be combined under the term, blood pressure increased, for the label. The types of AEs that resulted in discontinuation are generally similar to the common TEAEs reported, and those in the gastroenterology category are expected due to the mechanism of action of lactitol. The patients who discontinued due to hypertension are discussed in the Hypertension subsection below in this document.

The AEs specified as reasons for discontinuation in the placebo group were abdominal bloating, new diagnosis of hypothyroidism, knee replacement, bloody diarrhea, abdominal cramping, increased blood in urine, vomiting and dizziness, stroke, elevated GGT, and intermittent heartburn.

Overall, the percentage of patients who discontinued was small and generally similar between the lactitol and placebo treatment groups.

Study 303

In Study 303, there were 13/298 (4.4%) patients who discontinued from the study due to an AE. The most common AEs leading to discontinuation were flatulence x 6 and diarrhea x 4 with 1 patient reporting flatulence, diarrhea, nausea and abdominal pain. Some patients reported several AEs leading to discontinuation. Although there was no direct comparator arm in this single-arm, open-label trial, the AEs that led to patient discontinuation were generally similar to the types of AEs that were reported during Studies 301 and 302.

Significant/Severe Adverse Events[15]

Study 301

In the lactitol group, there were 3/218 (1.4%) patients with one severe event each: death, abdominal distension, and cellulitis. In the Amitiza group, 8 severe events were reported in

[15] Severe was described as severe discomfort, treatment needed, severe and undesirable, causing inability to carry out usual activities. Source: Protocol BLI400-302, Section 5.1 Adverse Event Definition and Reporting, page 23/68.

5/222 (2.3%) patients: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, gastric ulcer, headache, limb injury, and victim of abuse. There were a small number of severe TEAEs in both the lactitol and Amitiza groups and each event was only reported once. The event of abdominal distension in the lactitol treatment group occurred in patient (b) (6), who incorrectly took 3 packets of powder daily during the first week in the study. This corresponds to the timing of this AE and the outcome of the AE was recovered/resolved. The death and cellulitis events are discussed above in the deaths and SAE sections.

There were 4 severe TEAEs that occurred in the same patient (patient (b) (6)) in the Amitiza group. These include alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, and gamma-glutamyl transferase increased. The AE start date was study day 28 and the AE end date was not recorded for the 4 AEs. The AE outcome was reported as unknown for all 4 AEs. Of note, the baseline values for alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase were all normal. This patient discontinued/early terminated the trial on study day 28 due to travel to Russia for 3 months. Increased alanine aminotransferase and aspartate aminotransferase are described in the Amitiza labeling as less common adverse reactions in adults with irritable bowel syndrome with constipation. With this patient's normal liver tests at baseline, the abnormal liver tests could be drug induced; however, the elevated transaminases cannot be definitively attributed to Amitiza because a complete medical history and list of concomitant medications were not provided. .

Study 302

There were 10 severe events reported in 8/291 (2.7%) patients in the lactitol group. In the placebo group, there were 12 severe events reported in 11/302 (3.6%) patients. In the lactitol treatment group, abdominal distension and flatulence were reported in the same patient (patient (b) (6)), and abdominal pain and diarrhea were reported in the same patient (patient (b) (6)). In the placebo group, acute myocardial infarction and cerebrovascular accident were reported in the same patient (patient (b) (6)). Table 40 below summarizes the severe TEAEs that were reported during Study 302.

Table 40: Severe Treatment-Emergent Adverse Events: Study 302

Event	Lactitol (N=291)[1] n (%)	Placebo (N=302)[1] n (%)
Abdominal pain	2 (0.7)	0 (0)
Diarrhea	2 (0.7)	0 (0)
Abdominal distension	1 (0.3)	0 (0)
Cerebrovascular accident	1 (0.3)	1 (0.3)
Flank pain	1 (0.3)	0 (0)
Flatulence	1 (0.3)	0 (0)
Gastroenteritis	1 (0.3)	0 (0)
Medical device complication	1 (0.3)	0 (0)
Acute myocardial infarction	0 (0)	1 (0.3)
Anxiety	0 (0)	1 (0.3)
Arthralgia	0 (0)	1 (0.3)
Blood pressure increased	0 (0)	1 (0.3)
Coronary artery disease	0 (0)	1 (0.3)
Enterocolitis	0 (0)	1 (0.3)
Forearm fracture	0 (0)	1 (0.3)

Event	Lactitol (N=291)[1] n (%)	Placebo (N=302)[1] n (%)
Head injury	0 (0)	1 (0.3)
Hypercalcemia	0 (0)	1 (0.3)
Nerve compression	0 (0)	1 (0.3)
Non-cardiac chest pain	0 (0)	1 (0.3)

[1] Total N is FDA safety population excluding site 32.
Source: Reviewer's analysis using applicant's data, NDA 211281, study 302, ADAE dataset, module 5.3.5.1.

Overall, severe AEs occurred in a small number of patients in both the lactitol and placebo arms.

The 2 severe events of diarrhea occurred in two patients (patients (b) (6)). Patient (b) (6) was a 60-year-old male who experienced diarrhea starting on study day 20 and ending on day 23. This patient also had an AE of stomach cramps and discontinued from the study due to stomach cramps and diarrhea. Patient (b) (6) was a 50-year-old female who experienced diarrhea starting on study day 1 and ending on the same day. Due to this AE, the patient's dose was reduced and the outcome was reported as recovered/resolved. This patient also had other GI AEs of bloating, abdominal pain, and flatulence. Neither of these patients had electrolyte abnormalities secondary to severe diarrhea.

In addition, there was 1 severe event of a cerebrovascular accident in patient (b) (6), which was previously discussed under the SAEs. Of note, one cerebrovascular accident also occurred in the placebo group. There were 2 severe events in the placebo group. These included non-cardiac chest pain in patient (b) (6) discussed above in the SAE section and blood calcium increased in patient (b) (6). As these patients received placebo, the findings are unrelated to lactitol. There was 1 event of coronary artery disease in the placebo group reported as life threatening, but unrelated to treatment.

Study 303

There were 19 severe events reported in 16/298 (5.4%) patients during Study 303. The most common severe TEAEs were flatulence in 4 patients and diarrhea in 3 patients. The other severe TEAEs occurred in 1 patient each. The severe AEs reported during Study 303 were generally similar to the types of AEs reported in Studies 301 and 302.

Treatment-Emergent Adverse Events (Common Adverse Events)

Study 301

Overall, 63/218 (28.9%) patients in the lactitol group and 71/222 (32%) patients in the Amitiza group reported at least 1 TEAE. Table 41 below describes the types and frequency of TEAEs.

Table 41: Treatment Emergent Adverse Events Reported in ≥2 Patients in Either the Lactitol or Amitiza Groups: Study 301

TEAE	Lactitol (N=218)[1] n (%)	Amitiza (N=222)[1] n (%)
Flatulence	17 (7.8)	3 (1.4)
Diarrhea	11 (5.0)	12 (5.4)
Headache	5 (2.3)	9 (4.1)
Blood creatine phosphokinase increased	5 (2.3)	6 (2.7)
Abdominal distension	5 (2.3)	0 (0)
Abdominal pain	4 (1.8)	6 (2.7)
Bronchitis	4 (1.8)	0 (0)
Sinusitis	3 (1.4)	0 (0)
Nausea	2 (0.9)	9 (4.1)
Hypertension	2 (0.9)	1 (0.5)
Diabetes mellitus	2 (0.9)	0 (0)
Ear infection	2 (0.9)	0 (0)
Hematuria	2 (0.9)	0 (0)
Pruritus	2 (0.9)	0 (0)
Rash	2 (0.9)	0 (0)
Alanine aminotransferase increased	1 (0.5)	2 (0.9)
Back pain	1 (0.5)	2 (0.9)
Gastroenteritis viral	1 (0.5)	2 (0.9)
Urinary tract infection	1 (0.5)	2 (0.9)
Upper respiratory tract infection	0 (0)	5 (2.3)
Anemia	0 (0)	3 (1.4)
Dizziness	0 (0)	3 (1.4)
Cough	0 (0)	2 (0.9)

Abbreviations: TEAE, treatment emergent adverse event
[1] Total N is safety population (mITT population) excluding data from site 30.
Source: Reviewer's analysis using Applicant's data, NDA 211281, Study 301, ADAE dataset, module 5.3.5.1.
Refer to the Appendix, Table 52 for a complete list of recoded terms.

Flatulence was reported in a higher percentage of patients in the lactitol group (17/218 [7.8%]) compared to the Amitiza group (3/222 [1.4%]). As suggested by the Applicant, this could be due to the mechanism of action of lactitol, which is a fermentable carbohydrate. Of the 17 patients reporting flatulence in the lactitol treatment group, 6 patients reported flatulence as moderate and 11 patients reported flatulence as mild. There were no events reported as severe. In addition, abdominal distension was reported in a higher percentage of patients in the lactitol group (5 [2.3%]) compared to the Amitiza group (0 [0%]). Of the 5 patients reporting abdominal distension in the lactitol group, 1 reported severe distension and is discussed above in the Significant/Severe Adverse Events section (patient (b) (6)). The other patients reported abdominal distension as mild. Similar to flatulence, the abdominal distension could be due to the mechanism of action of lactitol.

The incidence of diarrhea was similar between the lactitol (11/218 [5.0%]) and Amitiza (12/222 [5.4%]) groups. The incidence of abdominal pain was also similar between the lactitol and Amitiza groups, 4/218 (1.8%) and 6/222 (2.7%) patients, respectively. These numbers of events for diarrhea and abdominal pain are small and expected based on the mechanism of action for lactitol and its anticipated effects on the gastrointestinal system.
TEAEs that occurred in a higher percentage of patients in the Amitiza group compared to the lactitol group include headache, nausea, and upper respiratory tract infection. Overall, the remaining TEAEs in Table 41 that were not discussed above occurred in a similar percentage of patients in both treatment groups.

As discussed above in Section 7.2 Review Strategy, patients from site 30 were excluded from the safety analyses. There were 6 TEAEs in patients from site 30 (site with confirmed research misconduct). One patient (patient (b) (6)) in the Amitiza group had 3 TEAEs, which included alanine aminotransferase increased, gamma-glutamyl transferase increased, and insomnia. Three patients in the lactitol group at site 30 had 1 TEAE each: 2 events of insomnia and 1 event of oral herpes. The events reported in the patients treated with lactitol do not impact the overall conclusions on the safety profile of lactitol.

Study 302

Overall, 143/291 (49.1%) patients in the lactitol group and 136/302 (45.0%) patients in the placebo group reported at least 1 TEAE. Table 42 below describes the types and frequency of TEAEs.

Table 42: Treatment Emergent Adverse Events Reported in ≥2 Patients in the Lactitol Treatment Group With a Higher Incidence Than Placebo: Study 302

TEAE	Lactitol (N=291)[1] n (%)	Placebo (N=302)[1] n (%)
Upper respiratory tract infection**	25 (8.6)	19 (6.3)
Flatulence	23 (7.9)	8 (2.6)
Diarrhoea	13 (4.5)	9 (3.0)
Blood creatine phosphokinase increased	12 (4.1)	9 (3.0)
Abdominal distension	10 (3.4)	2 (0.7)
Back pain	7 (2.4)	3 (1.0)
Gastroenteritis	7 (2.4)	2 (0.7)
Hypertension*	5 (1.7)	1 (0.3)
White blood cells urine positive	5 (1.7)	2 (0.7)
Bacterial test positive	4 (1.4)	2 (0.7)
Blood pressure increased*	4 (1.4)	1 (0.3)
Hematuria	4 (1.4)	1 (0.3)
Headache	4 (1.4)	2 (0.7)
Hyperkalemia	4 (1.4)	1 (0.3)
Urinary sediment present	4 (1.4)	2 (0.7)
Urine leukocyte esterase positive	4 (1.4)	2 (0.7)
Vertigo	4 (1.4)	0 (0)
Cough	3 (1.0)	2 (0.7)
Gastrointestinal sounds abnormal	3 (1.0)	0 (0)
Acute sinusitis	2 (0.7)	1 (0.3)
Alanine aminotransferase increased	2 (0.7)	1 (0.3)
Blood creatinine increased	2 (0.7)	0 (0)
Glomerular filtration rate decreased	2 (0.7)	0 (0)
Gout	2 (0.7)	1 (0.3)
Musculoskeletal pain	2 (0.7)	1 (0.3)
Pharyngitis streptococcal	2 (0.7)	0 (0)
Rash	2 (0.7)	1 (0.3)
Respiratory tract infection	2 (0.7)	0 (0)

Abbreviations: TEAE, treatment emergent adverse event
[1] Total N is FDA safety population excluding data from site 32.
Note: Patient (b) (6) reported the same start date for blood creatinine increased and glomerular filtration rate decreased.
*The terms hypertension and blood pressure increased were combined under blood pressure increased in the label.
** The term upper respiratory tract infection includes the terms viral upper respiratory tract infection and nasopharyngitis. Refer to the Appendix, Table 53 for a complete list of recoded terms.
Source: Reviewer's analysis using applicant's data, NDA 211281, Study 302, ADAE dataset, module 5.3.5.1.

The percentage of patients reporting TEAEs were generally similar between lactitol and placebo groups, with the exception of flatulence and abdominal distension. Diarrhea was slightly more frequent in the lactitol group than in placebo (13 [4.5%] and 9 [3.0%], respectively). For an osmotically acting laxative, we expected a greater difference between diarrhea events in the lactitol treatment group and placebo group. That said, the difference between the incidence of diarrhea in the lactitol and placebo group was likely mitigated by patients who developed persistent diarrhea or loose stools in the lactitol group allowed to reduce the dose.

Abdominal pain occurred in a similar percentage of patients between the lactitol and placebo groups (lactitol 9 [3.1%] and placebo 9 [3.0%]). The other TEAEs which occurred with an equal or higher incidence in the placebo group do not appear to be clinically relevant.

There were 2 patients from site 32 (confirmed research misconduct and excluded from the safety analyses) who each reported one TEAE: one patient had influenza and the other patient had nasopharyngitis. Both patients were treated with placebo.

Study 303

Overall, there were 215 TEAEs reported in 108/298 (36.2%) patients. In the 298 patients who were treated with lactitol, the most common AEs included diarrhea in 23 (7.7%), flatulence in 16 (5.4%), urinary tract infection in 16 (5.4%), abdominal pain in 8 (2.7%), abdominal distension in 7 (2.3%), and upper respiratory tract infection in 7 (2.3%). It is expected that the most frequent events were within the Gastrointestinal and the Infections and Infestations system organ classes (SOCs). The incidence of the gastrointestinal TEAEs is likely due to the mechanism of action of lactitol and incidence of the infections is likely due to the duration of the trial.

During months one to six, 82/298 (27.5%) patients reported adverse events compared to 39/234 (16.7%) patients during months 7-12. There were 21/298 (7.0%) patients who reported diarrhea during months 1-6 and only 2/234 (0.9%) patients reported diarrhea during months 7-12. There were 15/298 (5.0%) patients who reported flatulence during months 1-6 and only 1/234 (0.4%) patient who reported flatulence during months 7-12. The higher percentage of patients reporting diarrhea and flatulence during months 1-6 compared to months 7-12 could be explained by having fewer patients in the months 7-12 period (234/298 [78.5%] patients) and the patients who remained in the study may have been better able to tolerate the drug. There were no AEs of interest which increased in frequency over the course of the 12 month treatment period.

Patients from site 25 were excluded from the safety population due to confirmed research misconduct (patients and data could not be confirmed). There were no patients at site 25 who reported TEAEs.

Laboratory Findings

Studies 301 and 302

There were no meaningful differences between treatment groups when changes in laboratory measures (chemistry and hematology) were assessed during the treatment period. There were small within group changes, which do not appear to be clinically relevant but more likely measurement variability over time. There were no meaningful differences in the subgroup of patients ≥65 years of age when laboratory measures were assessed during the treatment period.

Refer to Section 8.2.4 Safety Results, subheading Electrocardiograms, subheading QT, for a discussion of possible electrolyte abnormalities related to QT prolongation.

Vital Signs

Studies 301 and 302

With the exception of blood pressure, there were no clinically meaningful differences between treatment groups when changes in vital signs were assessed. For study 302, there were small within group trends detected for both the lactitol and placebo groups for body temperature, but these changes did not appear to be clinically significant.

There was an imbalance of reported AEs of hypertension and increased blood pressure between the lactitol and control groups. Refer to the Hypertension subsection below for further discussion.

Electrocardiograms (ECGs)

Study 301

ECGs were performed at baseline and Visits 2, 3, 4, and 5 or study withdrawal. There were no meaningful differences in measurement trends between the lactitol and Amitiza treatment groups for the following ECG measures and intervals: HR, PR, QT, QTc, and QRS. Refer to the QT section below for further discussion.

Study 302

ECGs were performed at baseline and Visit 8 or study withdrawal. There were no meaningful differences between the lactitol and placebo treatment groups for change from baseline (Visit 1) to Visit 8 for the following ECG measures and intervals: HR, PR, QT, QTc, QTcF, QRS, and RR. There were small within group changes from baseline (Visit 1) to Visit 8 in the lactitol treatment group for HR, QT, QTcF, and RR, and similarly in the placebo group for HR, QT, and RR. These small changes do not appear to be clinically relevant, as discussed further in the QT section below.

QT Interval

To determine whether lactitol has an effect on QT prolongation, the team analyzed patients with a QTc interval change from normal (≤450 msec) at baseline to >450 msec, >500 msec, or >60 msec increase from baseline at different visits during the trial. This cut-off values are based on the FDA Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs[16] which states that for safety monitoring and discontinuation criteria for clinical trials designed to evaluate drug effects on QT/QTc interval, increases in QT/QTc to >500 msec or of >60 msec over baseline are commonly used as thresholds for potential discontinuation. These changes in the QTc interval are considered to be meaningful and should trigger further evaluation for possible causes of QT prolongation, such as electrolyte abnormalities, diarrhea, chest pain or heart failure.

[16]https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf

Study 301

In Study 301, ECGs were performed at baseline and Visits 2, 3, 4, and 5 or study withdrawal. The QTc interval changes were evaluated from normal (≤450 msec) at baseline to >450 msec at Visits 3, 4, 5, and the early termination visit for Study 301. Although the proportion of patients in each arm who experienced these changes varied slightly, the overall proportion at each visit was small with ≤1.8% of patients in the lactitol arm and ≤2.7% of patients in the Amitiza arm. There was only 1 patient ((b) (6)) in the lactitol group who had a normal QTc at baseline and Visits 3 and 4; however, at Visit 5, the QTc increased to 511 msec. This patient is a 34-year-old female with a BMI of 31 who has no known cardiovascular history. The patient was asymptomatic, including at a follow up call approximately 2 weeks after Visit 5. No further information was available.. Refer to Appendix 15.7 for further details. In the lactitol group, the patients with changes in the QTc from normal at baseline to >450 msec were mostly female and ranged from 19 to 79 years old. The abnormal QTc intervals ranged from 451 msec to 511 msec at various study visits. Change from baseline ranged from 9 to 83 msec, with most patients having small (<40 msec) increases in the QTc interval from baseline. Patient (b) (6) who had a QTc interval of 511 msec at Visit 5 was the only patient who had a QTc change from baseline > 60 msec. The patients in the Amitiza group had similar changes in the QTc compared to patients in the lactitol group.

There was only one patient in the lactitol group who had a QTc interval >450 msec at more than 1 visit. Patient (b) (6) had a QTc interval >450 msec at both Visits 3 and 4, with a slight increase from 456 to 474 msec, respectively. For patients who had increases in the QTc interval >450 msec during any visits, the prolongation of the QTc interval appeared transient and normalized on subsequent ECGs.

The recommendations from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology/the American College of Cardiology Foundation/ the Heart Rhythm Society state that the adjusted QT of 460 msec or longer in women and 450 msec or longer in men be considered a prolonged QT interval.[17] In study 301, 21 female patients were identified as having a normal QTc interval at baseline which increased to > 450 msec at any visit. Using this criteria adjusting for female sex, 18 of the 21 female patients would not have a QTc considered to be abnormal.

Adverse events reported for the patients in the lactitol group were reviewed for possible causes of QT prolongation, such as electrolyte abnormalities, diarrhea, chest pain or heart failure. There was only 1 patient who had an AE of diarrhea and QT prolongation that occurred around the same time during the trial:

- Patient (b) (6) was a 41-year-old female in the lactitol treatment group who had an AE of diarrhea starting on study day 58 and ending on study day 59. The QTc interval was 464 msec on the ECG at Visit 4 (day 60). The diarrhea was reported as moderate severity, but the patient's electrolytes at Visit 4 were normal with the exception of a slightly low potassium of 3.4 mEq/L. The AE outcome was reported as recovered/resolved. The mild QT prolongation appears unrelated to the AE of diarrhea.

[17] Rautaharju, PM, Surawicz, B, and Gettes, LS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram. Part IV: The ST Segment, T and U Waves, and the QT Interval. Journal of the American College of Cardiology. Vol. 53, No. 11, 2009, March 17, 2009:982–91.

Study 302

In Study 302, ECGs were performed at baseline and Visit 8 or study withdrawal. Five out of 291(1.7%) patients in the lactitol arm and 7/302 (2.3%) patients in the placebo arm had changes in the QTcF interval from normal (≤450 msec) to >450 msec at Visit 8, and no patients in either the lactitol or placebo arms experienced an increase in the QTcF interval >500 msec at Visit 8. The patients with changes in the QTcF from normal at baseline to >450 msec were mostly female and ranged from 26 to 81 years old; there was one male patient. The QTcF intervals at Visit 8 ranged from 451 msec to 475 msec, with a change from baseline ranging from 12 to 49 msec. Therefore, all patients had small increases in the QTcF interval from baseline. It is difficult to interpret whether changes in the QTcF interval were transient or sustained, given that ECGs were only performed at two time points during Study 302. See Appendix, Table 61 Patients with QTcF Interval Change From Normal (≤450 msec) at Baseline to >450 msec at Visit 8 (FDA Safety Population) for Study 302.

In study 302, 11 female patients were identified as having a normal QTcF interval at baseline which increased to > 450 msec at Visit 8. However, the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology/the American College of Cardiology Foundation/Heart Rhythm Society recommends that the adjusted QT interval of ≥460 msec in women be considered a prolonged QT interval. Using this adjusted criteria in this trial, only 4 of the 11 female patients would have a QTcF interval considered to be abnormal.

Adverse events reported for patients with increases in the QTc interval were reviewed for possible causes of QT prolongation, such as electrolyte abnormalities associated with diarrhea, chest pain or heart failure. See Appendix 15.7 for details.

- Patient (b) (6) was a 62-year-old female in the lactitol treatment group who had an AE of mild hyperkalemia documented as a potassium of 5.2 mEq/L on study day 140 and ending on study day 187 The outcome was recovered/resolved. Elevated potassium causes ECG changes in a dose-dependent manner, with a potassium of 5.5 to 6.5 mEq/L showing tall, peaked t-waves.[18] This patient's potassium is mildly elevated, so no ECG changes would be expected. In addition, hyperkalemia may cause a shortened QT interval, and this electrolyte abnormality is unlikely to cause the prolonged QT interval in this patient's ECG at Visit 8 since the opposite effect is expected.

- Patient (b) (6) is an 81-year-old female in the lactitol treatment group who had an AE of diarrhea starting at study day 68 and ending on study day 69. This AE was reported as mild severity and the outcome was recovered/resolved. Given that diarrhea was mild and lasted one day, it was less likely to cause electrolyte abnormalities and QT prolongation on an ECG performed at Visit 8.

- Patient (b) (6) is a 69-year-old female in the placebo group who had an AE of blood phosphorus increased starting at study day 29 with no ending study day recorded. The phosphate level was high on Visits 3, 4, 5, and 7 ranging from 5.0 to 5.3 mg/dL, but was normal at Visit 8. Although hyperphosphatemia is a risk factor for cardiovascular events and vascular calcification, the phosphate level was only mildly elevated and normalized

[18] https://www.ncbi.nlm.nih.gov/books/NBK470284/

by the end of the study. These findings are not related to lactitol as this patient was in the placebo group.

In summary, the assessment of the available data did not identify AEs that raised concerns for potential contributing factors to the observed QT prolongation in the patients in Studies 301 and 302. There were similar numbers of patients in the lactitol and control arms with a QTc measurement >450 msec at different visits. More importantly, most patients had small increases in the QTc interval from baseline; only 1 patient had a normal QTc at baseline (≤450 msec) that increased to >500 msec at Visit 5 in Study 301. The ECG data from Studies 301 and 302 support that a dedicated TQT study does not appear to be warranted at this time.

Hypertension

A small imbalance was noted between the lactitol and placebo groups for patients with TEAEs of hypertension or "blood pressure increased" in Study 302. Although it would be unusual for a drug for chronic idiopathic constipation that functions as an osmotic laxative to cause hypertension, this imbalance prompted an assessment of events related to blood pressure (hypertension, blood pressure increased, blood pressure systolic increased) for the three phase 3 trials to determine if lactitol was causally associated with these events. The review focused on patients with normal baseline blood pressure who had an increase of various degrees in systolic and diastolic BP.

In Study 301, there were 2/218 (0.9%) patients in the lactitol group and 1/222 (0.5%) patient in the Amitiza group with an AE of hypertension.

In Study 302, there were 5/291 (1.7%) patients in the lactitol group and 1/302 (0.3%) patient in the placebo group with an AE of treatment emergent hypertension. There were 4/291 (1.4%) patients in the lactitol group and 1/302 (0.3%) patient in the placebo group with an AE of "blood pressure increased."

In Study 303, hypertension and related terms were reported as AEs. Given that hypertension is a common event in the general population and the absence of a comparator arm in this long-term trial (up to 1 year duration), it is difficult to determine whether the hypertension reported is related to the study drug. In Study 303, there were 6/305 (2.0%) patients with hypertension, 2/305 (0.7%) patients with "blood pressure increased," and 1/305 (0.3%) patient with "blood pressure systolic increased."

Of the 20 patients treated with lactitol and who had an AE of hypertension or increased blood pressure, 17 patients were identified to have baseline cardiovascular risk factors, including one or more of the following: history of hypertension, diabetes, and/or hypercholesterolemia, age ≥55 years, obesity (BMI >30), and tobacco use/active smoking. Although there were 3 patients who did not have the aforementioned baseline cardiovascular risk factors, other confounding factors were identified (e.g., elevated blood creatine kinase, glucose tolerance impairment) or the available information was incomplete. Therefore, due to various confounding factors and in some cases, limited information, it was difficult to determine whether a relationship existed between the onset of hypertension and lactitol use.

Because of the confounding factors and given that the trial was not prospectively designed to evaluate changes in blood pressure, the team's assessment focused on patients who had normal baseline BP to further investigate the relationship between hypertension and lactitol. Patients were selected with "normal" BP (defined as systolic BP <120 mm Hg and diastolic BP

<80 mm Hg based on the clinical practice guidelines from the American College of Cardiology/American Heart Association Task Force[19]) or "elevated" BP (defined as systolic BP 120-129 mm Hg and diastolic BP <80 mm Hg based on the clinical practice guidelines from the American College of Cardiology/American Heart Association Task Force[20]) at baseline. Of those, patients who had a documented increase systolic or diastolic BP by 10 or 20 mmHg at any visit during Study 302 were evaluated. Of note, approximately half of the patients in the lactitol and placebo arms had abnormal baseline BPs, defined by BP >130/80 mm Hg. The number of patients with increases in systolic or diastolic blood pressure by 10 or 20 mm Hg at any visit are generally balanced between the lactitol and placebo arms. Refer to the Appendix 15.7 for details on patients with increases in systolic or diastolic blood pressure by 10 or 20 mm Hg at any visit during study 302 by treatment arm. Furthermore, review of the Applicant's analyses (Table 302-26 on page 81/96 of the BLI400-302 Clinical Study Report) of blood pressure measurements at Visits 1, 3, 5, and 8 for the 147 patients who had sitting systolic blood pressure greater than 130 at baseline (the uppermost quartile) did not reveal meaningful trends between the lactitol and placebo groups during Study 302. Therefore, the small numeric imbalances that were observed in the initial TEAE analyses of the overall trial populations do not appear to represent a safety concern given that the additional analyses on patients with normal baseline BP and patients with baseline hypertension did not reveal meaningful differences between the drug and placebo arms.

8.2.5. Safety Analyses by Demographic Subgroups

Age

The subgroup analyses by age were based on the age categories of <65 and ≥65 years.

Study 301

In Study 301, there were 16/218 (7.3%) patients ≥65 years of age in the lactitol arm and 22/222 (9.9%) in the Amitiza arm.

For the patients ≥65 years of age, there were a total of 12 TEAEs in 7/16 (43.8%) patients in the lactitol treatment group and 8 TEAEs in 6/22 (27.3%) patients in the Amitiza treatment group. The most common TEAEs that occurred in more than 1 patient included flatulence (5/16 [31.3%] patients) and diarrhea (2/16 [12.5%] patients) in the lactitol group, and diarrhea (2/22 [9.1%] patients) in the Amitiza group. All other TEAEs occurred in 1 patient each. Diarrhea was the only TEAE that occurred in more than 1 patient in both the lactitol and Amitiza arms. Although the proportion of patients ≥65 years of age who experienced at least one TEAE was larger in the lactitol treatment group compared to the Amitiza treatment group (43.8% vs 27.3%), the number of patients with TEAEs is small and the total number of patients ≥65 years is small; the

[19] Whelton, PK, Carey, RM, Aronow, WS et al.
2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High BloodPressure in Adults: A Report of the American College of Cardiology/AmericanHeart Association
Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018 May 15;71(19):e127-e248.

[20] Whelton, PK, Carey, RM, Aronow, WS et al.
2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High BloodPressure in Adults: A Report of the American College of Cardiology/AmericanHeart Association
Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018 May 15;71(19):e127-e248.

differences in the proportion of patients ≥65 years with TEAE between lactitol and Amitiza may be an artifact of the differences in exposures. Overall, the types of TEAEs reported in patients ≥65 years of age generally align with those seen in the broader patient population.

In patients < 65 years of age, there were 56/202 (27.7%) patients who reported at least 1 TEAE in the lactitol arm and 65/200 (32.5%) patients in the Amitiza arm. As the majority of patients in the safety population were <65 years of age, the proportion of patients <65 years of age who reported at least one TEAE and the types of TEAEs are similar to the TEAEs observed in the lactitol and placebo groups for the entire safety population.

The proportion of patients < 65 years of age with TEAEs was 4.8% lower in the lactitol group vs Amitiza and was 16.5% higher in the lactitol group versus Amitiza for patients ≥ 65 years of age. Inferences regarding the rate of TEAEs in the subgroup of patients ≥ 65 years of age are limited by the small number of patients. Overall, there did not appear to be meaningful differences between the lactitol and Amitiza treatment groups in the types of TEAEs by age.

Study 302

In Study 302, there were 79/291 (27.1%) patients were ≥65 years of age in the lactitol arm and 82/302 (27.2%) in the placebo arm.

For the ≥ 65 years of age, there were a total of 70 TEAEs in 36/79 (45.6%) patients in the lactitol treatment group and 79 TEAEs in 35/82 (42.7%) patients in the placebo group. The most common TEAEs occurring in >2 patients ≥ 65 years of age in the lactitol treatment group included upper respiratory tract infection (8/79 [10.1%] patients), urinary tract infection (6/79 [7.6%]patients), flatulence (4/79 [5.1%] patients), blood creatine phosphokinase increased (3/79 [3.8%] patients), and diarrhea (3/79 [3.8%] patients). The most common TEAEs occurring in >2 patients ≥ 65 years of age in the placebo group included urinary tract infection (9/82 [10.9%] patients) and diarrhea (4/82 [4.9%] patients). All other TEAEs occurred in ≤2 patients. Urinary tract infection and diarrhea were the only TEAEs that occurred in both lactitol and placebo groups in patients ≥ 65 years of age. Of note, in the subgroup of patients ≥65 years of age, the incidence of diarrhea in the lactitol treatment group was (3.8%) slightly lower than in the placebo group (4.9%).

In patients < 65 years of age, there were 107/212 (50.5%) patients < 65 years of age who reported at least 1 TEAE in the lactitol arm and 101/220 (45.9%) patients in the placebo arm. As the majority of patients in the safety population were <65 years of age, the proportion of patients <65 years of age who reported at least one TEAE and the types of TEAEs are similar to the TEAEs observed in the lactitol and placebo groups for the entire safety population.

The proportion of patients < 65 years of age with TEAEs was greater than for patients ≥ 65 years of age for both lactitol and placebo. The proportion of patients < 65 years of age with TEAEs was 4.6% higher in the lactitol group vs placebo and 2.9% higher in the lactitol group vs placebo for patients ≥ 65 years of age. The proportion of patients < 65 years of age with diarrhea was 1.4% higher in the lactitol group vs placebo and patients 1.1% lower in lactitol vs placebo ≥ 65 years of age. Overall, there did not appear to be meaningful differences between the lactitol and placebo groups in the types of TEAEs by age.

Sex

Study 301

In Study 301, 177/218 (81.2%) patients in the lactitol arm were female and 41/218 (18.8%) patients were male. In the Amitiza arm, 175/222 (78.8%) patients were female and 47/222 (21.2%) patients were male.

In the female subgroup, there were 92 TEAEs in 53/177 (29.9%) female patients in the lactitol treatment group and 95 TEAEs in 57/175 (32.6%) female patients in the Amitiza treatment group. The most common TEAEs occurring in >3 female patients in the lactitol treatment group included flatulence (14 patients), diarrhea (10 patients), headache (5 patients), abdominal distension (4 patients), abdominal pain (4 patients), and bronchitis (4 patients). The most common TEAEs in >3 female patients in the Amitiza treatment group included diarrhea (10 patients), headache (8 patients), nausea (8 patients), abdominal pain (6 patients), and blood creatine phosphokinase increased (4 patients). The other TEAEs occurred in ≤3 patients.

In the male subgroup, there were 15 TEAEs in 10/41 (24.4%) male patients in the lactitol treatment group and 20 TEAEs in 14/47 (29.8%) male patients in the Amitiza treatment group. The most common TEAEs occurring in >1 patient in the lactitol treatment group included flatulence (3 patients) and blood creatine phosphokinase increased (2 patients). The most common TEAEs in >1 male patient in the Amitiza treatment group included upper respiratory tract infection (3 patients), blood creatine phosphokinase increased (2 patients), and diarrhea (2 patients). The other TEAEs occurred in 1 patient.

The proportion of female patients with TEAEs was slightly higher than in males for both lactitol and Amitiza. The difference in the proportion of female patients with TEAEs was 2.7% lower in the lactitol group vs Amitiza and was 5.4% lower in the lactitol group vs Amitiza for males. Overall, there did not appear to be meaningful differences in the proportion of patients with TEAEs or the types of TEAEs between the lactitol and Amitiza treatment groups for either the female or male subgroups.

Study 302

In Study 302, 215/291 (73.9%) patients in the lactitol arm were female and 76/291 (26.1%) patients were male. In the placebo arm, 237/302 (78.5%) patients were female and 65/302 (21.5%) patients were male.

In the female subgroup, there were 258 TEAEs in 114/215 (53.0%) in the lactitol treatment group and 220 TEAEs in 111/237 (46.8%) in the placebo group. The most common TEAEs occurring in >7 patients in the lactitol treatment group included flatulence (21 patients), upper respiratory tract infection (20 patients), urinary tract infection (16 patients), abdominal distension (10 patients), and blood creatine phosphokinase increased (8 patients). The most common TEAEs in >7 patients in the placebo group included urinary tract infection (24 patients), upper respiratory tract infection (14 patients), abdominal pain (8 patients), and diarrhea (8 patients). The other TEAEs occurred in ≤7 patients.

In the male subgroup, there were 51 TEAEs in 29/76 (38.2%) in the lactitol treatment group and 56 TEAEs in 25/65 (38.5%) in the placebo group. The most common TEAEs occurring in >2 patients in the lactitol treatment group included diarrhea (6 patients), upper respiratory tract infection (5 patients), blood creatine phosphokinase increased (4 patients), and abdominal pain (3 patients). The most common TEAEs in >2 male patients in the placebo group included upper

respiratory tract infection (5 patients) and blood creatine phosphokinase increased (3 patients). The other TEAEs occurred in ≤2 patients.

The proportion of patients with TEAEs was higher in female patients than in male patients for both the lactitol and placebo treatment groups. The difference in the proportion of female patients with TEAEs was 6.2% higher in the lactitol group vs placebo and was generally similar between lactitol and placebo for male patients (0.3% lower in the lactitol group vs placebo). There did not appear to be meaningful differences on the types of TEAEs between the lactitol and placebo treatment groups for either the female or male subgroups.

Race

Study 301

In Study 301, 148/218 (67.9%) patients in the lactitol arm were Caucasian, 59/218 (27.1%) patients were African American, 8/218 (3.7%) patients were Asian, 2/218 (0.9%) patients were other, and 1/218 (0.5%) patient was American Indian or Alaska native. In the Amitiza arm, 140/222 (63.1%) patients were Caucasian, 67/222 (30.2%) patients were African American, 7/222 (3.2%) patients were Asian, and 8/222 (3.6%) patients were other.

In the Caucasian subgroup, there were 74 TEAEs in 42/148 (28.4%) patients in the lactitol treatment group and 72 TEAEs in 40/140 (28.6%) patients in the Amitiza treatment group. The most common TEAEs occurring in >3 Caucasian patients in the lactitol treatment group included flatulence (15 patients), diarrhea (7 patients), and blood creatine phosphokinase increased (4 patients). The most common TEAEs in >3 Caucasian patients in the Amitiza treatment group included nausea (7 patients), headache (5 patients), and blood creatine phosphokinase increased (4 patients). The other TEAEs occurred in ≤3 patients.

In the African American subgroup, there were 29 TEAEs in 18/59 (30.5%) patients in the lactitol treatment group and 38 TEAEs in 26/67 (38.8%) in the Amitiza treatment group. The most common TEAEs occurring in >1 African American patient in the lactitol treatment group included diarrhea (4 patients), abdominal distension (2 patients), flatulence (2 patients), and hypertension (2 patients). The most common TEAEs occurring in >1 African American patient in the Amitiza treatment group included diarrhea (9 patients), abdominal pain (3 patients), dizziness (3 patients), blood creatine phosphokinase increased (2 patients), cough (2 patients), headache (2 patients), and nausea (2 patients). The other TEAEs occurred in 1 patient.

The proportion of Caucasian patients with TEAEs was slightly lower for both the lactitol and Amitiza groups as compared to African American patients. The difference in the proportion of Caucasian patients with TEAEs was similar between lactitol and Amitiza (0.2% lower in the lactitol group vs Amitiza), and 8.3% lower in the lactitol group vs Amitiza for African American patients. Overall, there were no meaningful differences in the types of TEAEs in Caucasian and African American patients in the lactitol treatment group and those in the Amitiza treatment group. When summarized by race, the types of AEs in the Caucasian and African American subgroups generally align with those seen in the broader patient population. The numbers of patients identified as Asian, or other races were too small to allow for a meaningful analysis of the safety data.

Study 302

In Study 302, 184/291 (63.2%) patients in the lactitol arm were Caucasian, 83/291 (28.5%) patients were African American, 19/291 (6.5%) patients were Asian, and 5/291 (1.7%) patients

were other. In the placebo arm, 177/302 (58.6%) patients were Caucasian, 100/302 (33.1%) patients were African American, 21/302 (7.0%) patients were Asian, 3/302 (1.0%) patients were other, and 1/302 (0.3%) patient was American Indian or Alaska native.

In the Caucasian subgroup, there were 180 TEAEs in 85/184 (46.2%) patients in the lactitol treatment group and 167 TEAEs in 80/177 (45.2%) patients in the placebo group. The most common TEAEs occurring in >4 Caucasian patients in the lactitol treatment group included flatulence (16 patients), urinary tract infection (11 patients), upper respiratory tract infection (9 patients), abdominal distension (8 patients), diarrhea (8 patients), blood creatine phosphokinase increased (6 patients), abdominal pain (5 patients), and gastroenteritis (5 patients). The most common TEAEs occurring in >4 Caucasian patients in the placebo group included urinary tract infection (11 patients), upper respiratory tract infection (9 patients), flatulence (6 patients), abdominal pain (5 patients), and diarrhea (5 patients). The other TEAEs occurred in ≤4 patients.

In the African American subgroup, there were 101 TEAEs in 42/83 (50.6%) patients in the lactitol treatment group and 90 TEAEs in 40/100 (40%) patients in the placebo group. The most common TEAEs occurring in >2 African American patients in the lactitol treatment group included upper respiratory tract infection (12 patients), flatulence (6 patients), back pain (3 patients), blood creatine phosphokinase increased (3 patients), hypertension (3 patients), and urinary tract infection (3 patients). The most common TEAEs occurring in >2 African American patients in the placebo group included urinary tract infection (9 patients), upper respiratory tract infection (7 patients), blood creatine phosphokinase increased (5 patients), abdominal pain (4 patients), and hypokalemia (3 patients). The other TEAEs occurred in ≤2 patients.

The difference in the proportion of Caucasian patients with TEAEs was similar between lactitol and placebo (1% higher in the lactitol group vs placebo), and was 10.6% greater in the lactitol group versus placebo for African American patients. Overall, there were no meaningful differences in the types of TEAEs in Caucasian and African American patients in the lactitol treatment group and those in the placebo group. When summarized by race, the types of AEs in the Caucasian and African American subgroups generally align with those seen in the broader patient population. The numbers of patients identified as Asian or other races were too small to allow for a meaningful analysis of the safety data.

Ethnicity

The ADAE Adam datasets did not include an ethnicity flag. An Information Request was sent on May 7, 2019 for the efficacy and safety data by demographic subgroups and the Applicant responded on May 21, 2019. The TEAE subgroup analysis by ethnicity is limited to “Hispanic or Latino” and “not Hispanic or Latino.”

Study 301

In Study 301, 89/218 (40.8%) patients in the lactitol treatment group were Hispanic or Latino and 129/218 (59.2%) patients were not Hispanic or Latino. In the Amitiza treatment group, 92/222 (41.4%) patients were Hispanic or Latino and 130/222 (58.6%) patients were not Hispanic or Latino.

In the Hispanic or Latino subgroup, 23/89 (25.8%) patients in the lactitol treatment group and 19/92 (20.7%) patients in the Amitiza treatment group reported at least 1 TEAE. The most common TEAEs occurring in >1 Hispanic or Latino patient in the lactitol treatment group

included flatulence (7 patients), blood creatine phosphokinase increased (3 patients), diarrhea (3 patients), abdominal distension (2 patients), and headache (2 patients). The most common TEAEs occurring in >1 Hispanic or Latino patient in the Amitiza group included headache (4 patients), anemia (3 patients), blood creatine phosphokinase increased (3 patients), and nausea (3 patients). The other TEAEs occurred in <1 patient.

In the non-Hispanic or non-Latino subgroup, 40/129 (31.0%) patients in the lactitol treatment group and 52/130 (40.0%) patients in the Amitiza treatment group reported at least 1 TEAE. The most common TEAEs occurring in >2 non-Hispanic or non-Latino patients in the lactitol treatment group included flatulence (10 patients), diarrhea (8 patients), abdominal distension (3 patients), bronchitis (3 patients), and headache (3 patients). The most common TEAEs occurring in >2 non-Hispanic or non-Latino patients in the Amitiza treatment group included diarrhea (11 patients), nausea (6 patients), abdominal pain (5 patients), headache (4 patients), blood creatine phosphokinase (3 patients), dizziness (3 patients), and upper respiratory tract infection (3 patients). The other TEAEs occurred in ≤2 patients.

The proportion of Hispanic or Latino patients with TEAEs was lower than in non-Hispanic or non-Latino patients for both the lactitol and Amitiza groups. The proportion of Hispanic or Latino patients with TEAEs was 5.1% higher in the lactitol group vs Amitiza, and was 9% lower in the lactitol group vs Amitiza for non-Hispanic or non-Latino patients. Overall, there were no meaningful differences between the lactitol treatment group and the Amitiza group in the types of TEAEs reported in Hispanic or Latino and patients who were not Hispanic or Latino.

Study 302

In Study 302, 115/291 (39.5%) patients in the lactitol treatment group were Hispanic or Latino and 176/291 (60.5%) patients were not Hispanic or Latino. In the placebo group, 113/302 (37.4%) patients were Hispanic or Latino and 189/302 (62.6%) patients were not Hispanic or Latino.

In the Hispanic or Latino subgroup, 36/115 (31.3%) patients in the lactitol treatment group and 43/113 (38.1%) patients in the placebo group reported at least 1 TEAE. The most common TEAEs occurring in >3 Hispanic or Latino patients in the lactitol treatment group included urinary tract infection (9 patients), flatulence (7 patients), blood creatine phosphokinase increased (5 patients), and abdominal distension (4 patients). The most common TEAEs occurring in >3 Hispanic or Latino patients in the placebo group included urinary tract infection (10 patients). The other TEAEs occurred in ≤3 patients.

In the non-Hispanic or non-Latino subgroup, 107/176 (60.8%) patients in the lactitol treatment group and 93/189 (49.2%) patients in the placebo group reported at least 1 TEAE. The most common TEAEs occurring in >4 not Hispanic or Latino patients in the lactitol treatment group included flatulence (16 patients), upper respiratory tract infection (13 patients), nasopharyngitis (12 patients), diarrhea (11 patients), urinary tract infection (9 patients), blood creatine phosphokinase increased (7 patients), abdominal distension (6 patients), and back pain (6 patients). The most common TEAEs occurring in >4 not Hispanic or Latino patients in the placebo treatment group included urinary tract infection (16 patients), upper respiratory tract infection (9 patients), blood creatine phosphokinase increased (8 patients), diarrhea (8 patients), nasopharyngitis (8 patients), abdominal pain (5 patients), and flatulence (5 patients). The other TEAEs occurred in ≤4 patients.

The proportion of Hispanic or Latino patients with TEAEs was lower than in non-Hispanic or non-Latino patients for both the lactitol and placebo groups. The proportion of Hispanic or Latino patients with TEAEs was 6.8% lower in the lactitol group vs placebo, and in non-Hispanic or non-Latino patients was 11.6% higher in the lactitol group vs placebo. Overall, there were no meaningful differences between the lactitol treatment group and those in the placebo group in the types of TEAEs reported by ethnicity.

8.2.6. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Human carcinogenicity studies were not performed at the time of the NDA submission. Nonclinical carcinogenicity studies have been performed and are discussed in Section 5.5.3 Carcinogenicity.

Human Reproduction and Pregnancy

Studies of lactitol in pregnancy and lactating women were not conducted in the lactitol development program. Patients who were pregnant or lactating, or intended to become pregnant during the study were excluded from enrollment in the clinical development program. Women of childbearing potential were required to use an acceptable form of birth control as specified in the protocols.

The applicant stated two patients were confirmed to have become pregnant during Braintree-sponsored studies of lactitol. Lactitol was discontinued upon the diagnosis of pregnancy in each case.

Table 43: Pregnancy Cases During Lactitol Clinical Trials

Patient ID	Lactitol Exposure	Gestational timing	Outcome
(b) (6) Study BLI400-303	20 g daily	Preconception to 5 weeks EGA	Term-live birth no complications
(b) (6) Study BLI400-302	10 g daily	Preconception to 7 weeks EGA	Term-live birth no complications

Abbreviations: EGA,estimated gestational age
Source: Dr. Kristie Baisden's Division of Pediatric and Maternal Health Memorandum in DARRTS, dated 6/18/2019.

The available data from two exposure cases during clinical trials are not sufficient to evaluate for any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Nonclinical studies do not suggest that lactitol causes embryo-fetal toxicity.

The applicant states there were no reports of infant exposure to lactitol through breastfeeding. There are no available human data and animal data do not suggest lactitol adversely affects fertility. Refer to Dr. Kristie Baisden's Division of Pediatric and Maternal Health Memorandum, dated June 18, 2019, for further discussion.

Pediatrics and Assessment of Effects on Growth

The phase 3 clinical trials included in this submission were conducted in adults and therefore pediatric assessment of effects on growth were not conducted in these clinical trials. An Agreed iPSP was issued on September 20, 2018.

The Applicant conducted Study BLI400-201, a phase 2, open-label, multicenter study to evaluate the safety and efficacy of lactitol in adolescent patients with CIC. Patients were treated for 4 weeks with a daily dose of 21 grams of lactitol. Thirty-three adolescent patients were enrolled in Study BLI400-201. This study was not reviewed as part of this NDA for the adult indication.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

These categories are not applicable to this application.

8.2.7. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Lactitol has been marketed outside of the United States since 1985. Lactitol was first registered in Switzerland by Novartis Consumer Health S.A. in 1985 under the tradename Importal and was subsequently marketed in various European countries. Therefore, postmarketing safety data were reviewed from the Periodic Safety Update Report (PSUR) filed by the pharmaceutical company A.C.R.A.F. S.p.A. (ACRAF-Aziende Chimiche Riunite Angelini Francesco), covering the period between October 1, 2012 and September 23, 2015 and the PSUR filed by Novartis Consumer Health SA, covering the period between October 1, 2009 to September 30, 2012. The focus of the postmarketing data was whether the information raised concerns for QT prolongation, other proarrhythmic risk, and cardiac events given that the Applicant had not conducted a thorough QT study. To obtain additional information, we requested the Pharmacovigilance Risk Assessment Committee Rapporteur's Assessment from the European Medicines Agency to inquire about concerns of QT prolongation or other cardiac events, planned and/or ongoing clinical trials or non-interventional studies to further evaluate the proarrhythmic risk and risk minimization measures. This Pharmacovigilance Risk Assessment Committee assessment is discussed below.

In addition, the Division of Pharmacovigilance (DPV) evaluated adverse events with lactitol from the following data sources: PSUR AF.15.SC.005 filed by the Rome, Italy pharmaceutical company A.C.R.A.F. S.p.A. (ACRAF-Aziende Chimiche Riunite Angelini Francesco) covering the date period from October 1, 2012, to September 23, 2015; the PSUR filed by Novartis Consumer Health SA covering the date period from October 1, 2009, to September 30, 2012; and the FDA Adverse Event Reporting System (FAERS) database through September 22, 2019.

Pharmacovigilance Risk Assessment Committee Rapporteur's Assessment from the European Medicines Agency

This PSUR, finalized on May 13, 2016, contained the safety data regarding Portolac/ Portolac Eps/ Importal/ Importal Enfants/ Importal Jeunes Enfants/ Importal Ex-Lax/ Emportal/ Oponaf (Lactitol), collected by the HQ Pharmacovigilance Service of ACRAF S.p.A. between October 1, 2012 and September 23, 2015 (see below for DPV's evaluation of this PSUR).

As reported in the final assessment conclusions and actions, no new information has arisen during the reporting interval that would change the overall evaluation of benefit-risk for lactitol when used according to current product labelling information. The assessment did not raise any concerns in regards to QT prolongation, other proarrhythmic risk, or cardiac events. There are no proposed changes to the product information as a result of this PSUR. There is no Risk Management Plan in place.

Periodic Safety Update Report (PSUR) AF.15.SC.005 filed by the Rome, Italy pharmaceutical company A.C.R.A.F. S.p.A. (ACRAF-Aziende Chimiche Riunite Angelini Francesco).

This PSUR is dated November 18, 2015 and covers the period from October 1, 2012 to September 23, 2015. This report contains all the safety data regarding the brands Portolac/ Portolac Eps/ Importal/ Importal Enfants/ Importal Jeunes Enfants/ Importal Ex-Lax/ Emportal/Oponaf (Lactitol). The approved indications of the product differ from country to country, but are mainly symptomatic treatment of constipation and treatment of hepatic encephalopathy.

During the reporting period, 11 individual case safety reports (ICSRs) (2 serious; 9 non-serious) describing 19 adverse drug reactions were reported. The most involved SOC was gastrointestinal disorders (AEs n = 12) with diarrhea reported as the most frequent AE. Besides diarrhea, no events occurred with a frequency ≥3. The PSUR included narratives for the two serious ICSRs and one non-serious ICSR; DPV-I determined that the events described in these three ICSR narratives were not assessable or had an unlikely causal relationship to lactitol use. Furthermore, the PSUR briefly described five ICSRs of rash (n=3) or pruritus (n=2) that occurred prior to the reporting period; the two reports of pruritus had serious outcomes. One of these five ICSRs described a 6.5-month-old infant who experienced rash and pruritus after the second sachet of lactitol was administered; the narrative of this case suggested positive dechallenge and positive rechallenge with lactitol and had a possible causal relationship between lactitol and the events. The remaining four cases had unassessable causality for lactitol.

The PSUR indicates that based on medical judgement and scientific evaluation, no new safety concerns able to significantly impact the lactitol benefit/risk assessment were identified. The analysis of available data confirmed that findings on drug safety are substantially consistent with the information reported in the reference documents.

There were no emerging cardiac signals, including no signals of prolongation of the QT interval, evident from this review.

PSUR filed by Novartis Consumer Health SA

This PSUR covers the period from October 1, 2009 to September 30, 2012 for Importal/Emportal/Portolac. The total estimated number of patients treated with Importal/Emportal/Portolac was 11,854,687. There were 56 suspected adverse drug reactions reported and the most frequently reported SOC was gastrointestinal disorders. The PSUR included ICSR narratives for six reports that had a serious outcome. DPV assessed these six reports for a causal relationship with lactitol use; of the six, four were unassessable and two had a possible causal relationship with lactitol use and the event. One report with unassessable causality to lactitol involved the death of a 94-year-old patient who experienced dehydration, renal failure, decreased blood pressure, systemic inflammatory response syndrome, and peripheral edema; the Health Authority did not consider the patient's death to be related to the side effect of dehydration. DPV determined that three serious reports of pancreatitis, fulminant hepatitis, or abnormal weight gain had unassessable causal relationships between lactitol and the events. The two remaining serious cases had a possible causal relationship between lactitol and the reported events; however, these had limited information to rule out alternate etiologies for the events. One case described a 4-year-old boy with a history of epilepsy who had been

seizure-free for 3 years and experienced an epileptic seizure 36 hours after lactitol initiation. The second case described an elderly woman who experienced confusion, electrolyte derangements, diarrhea, and disorientation after taking lactitol, lorazepam, and acetaminophen/codeine.

The most frequently observed adverse reactions were reactions pertaining to incorrect product use (9 ADRs), 5 cases of drug inefficacy and 3 cases of abdominal distension. There were no emerging signals that could have an impact on the benefit/risk profile of the product Imporal/Emportal/Portolac. There were no concerns for QT prolongation or arrhythmias.

The FDA Adverse Event Reporting System (FAERS)

DPV searched the FAERS database for all adverse events with lactitol through September 22, 2019. DPV identified one FAERS case that described an elderly woman with chronic renal insufficiency on concomitant lactitol who experienced diarrhea and acute renal insufficiency following colchicine dose increase and had a serious outcome of hospitalization. This case had a probable causal association to colchicine, and it is possible that concomitant lactitol contributed to the diarrhea severity.

Expectations on Safety in the Postmarket Setting

Refer to Section 13 for postmarketing requirements and commitments.

8.2.8. Integrated Assessment of Safety

Because the phase 3 trials differed in the design and duration, safety was assessed in each individual trial and the data were not pooled for an integrated assessment. As described in this document, Study 302 was a placebo-controlled trial with a 6-month treatment duration, study 301 was an active-controlled trial with a 12-week treatment duration and an active comparator that has a different mechanism of action from lactitol, and Study 303 was an open-label trial with a 12-month treatment duration. Overall, types of AEs were generally similar across the trials.

8.3. Conclusions and Recommendations

Based on our assessment of the safety data from the three phase 3 clinical trials, the safety profile of lactitol supports a favorable benefit/risk profile for the treatment of adults with CIC. The safety results of Study 302 will be described in the label since this trial is primarily relied upon for efficacy. Overall, the safety analyses of Studies 301 and 303 did not reveal any meaningful differences from Study 302. Any differences will be noted in the label. The most common adverse reactions in Study 302 included upper respiratory tract infection, flatulence, diarrhea, increased blood creatine phosphokinase, abdominal distention, and hypertension. The additional analyses of hypertension did not identify a concern for a causal relationship between lactitol and hypertension; however, the small numerical imbalance between lactitol and placebo will be described in the label.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not held for this application.

10 Pediatrics

The NDA submission was for an indication in adult patients. Pediatric postmarketing studies will be required under the Pediatric Research Equity Act.

11 Labeling Recommendations

Prescribing Information

Refer to the approved label for final language. The key revisions are described below.
In addition to the review team and consultants, the labeling was also reviewed by the Division of Medication Error Prevention and Analysis, and the Office of Prescription Drug Promotion. Their comments and recommendations have been incorporated into final labeling.

Section 2 Dosage and Administration

- The recommended adult dosage was revised from 21 g lactitol monohydrate to 20 grams lactitol and corresponding reduced dose to 10 grams lactitol (from 10.5 g lactitol monohydrate) throughout the label.
- Instructions for preparation and administration were revised to align with the revisions made to the bottle cap.

Section 4: Contraindications

- Known or suspected mechanical gastrointestinal obstruction and galactosemia will be listed as contraindications in the label.

Section 5 Warnings and Precautions

- (b) (4)

Section 6 Adverse Reactions

- The number of patients was revised to reflect the FDA safety population, which due to data integrity concerns, excluded patients enrolled at site 30 in Study 301, site 32 in Study 302 (McGuire sites), and site 25 in Study 303. Of note, Study 1 refers to Study 302 and Study 2 refers to Study 301 in labeling.
- The table of common adverse reactions was updated to include only safety data from Study 302 (placebo-controlled study), which aligns with the efficacy data reported in Section 14.
- Under the table of common adverse reactions, the label notes that the safety profile observed in Study 301 (non-inferiority trial) was generally similar. Any additional adverse events noted in Study 303 (open-label, long-term safety study) were described in text.

- In Section 6.2, (b) (4) The postmarketing section will describe hypersensitivity events, including rash and pruritus.

Section 7 Drug Interactions

- Section 7.1 Reduced Absorption of Other Oral Medication was added. The osmotic laxative effect of lactitol in the GI lumen may reduce the absorption of concomitantly administered oral medications. The revised label provides a recommendation to administer oral medications at least 2 hours before or 2 hours after lactitol. This recommendation has considered the usual time for stomach emptying and labeling information from other laxatives.

(b) (4)

Section 12 Clinical Pharmacology

- Section 12.3 Pharmacokinetics has been revised to describe the serum concentrations and PK parameters of lactitol at the recommended dose under fed conditions. The revised label also informs that C_{max} and AUC values increased greater than 2-fold under fasted conditions compared to fed conditions.

Section 14 Clinical Studies

- The section was revised to include efficacy data from only Study 302. (b) (4)
- For the primary efficacy population, the label describes all randomized subjects except subjects enrolled in both Study 301 and Study 302, site 32 (research site misconduct), site 6 (fire), and Subject (b) (6) and Subject (b) (6) (both subjects had re-enrolled at a different study site). This population matches the one submitted in the 5/21/2019 IR.
- Revisions were made to the description of the enrollment criteria to align with the pre-specified criteria in the protocol.
- Study 301 was described at a high-level, noting that lactitol was compared to an active control (lubiprostone 24 mcg twice daily), the primary endpoint was the same and that the frequency of CSBMs/week for lactitol was consistent with results from Study 302
- A statement describing the supportive information from the published literature was added to help strengthen the evidence relied on for product labeling: Studies of varying design describing the efficacy of lactitol in increasing the frequency of bowel movements during short-term treatment of less than 4 weeks in patients with symptoms of CIC have been published.

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not recommended.

13 Postmarketing Requirements and Commitment

We are waiving the pediatric study requirement for ages birth to less than 6 months because necessary studies are impossible or highly impracticable. This is because of the limited number of patients less than 6 months of age with functional constipation who require pharmacologic therapy and the complexities of studying this patient population.

The following are requested Pediatric Research Equity Act (PREA) PMRs:

1. A 12-week, randomized, double-blind, placebo-controlled, parallel-group study to assess the pharmacokinetics, efficacy, and safety of Pizensy (lactitol) for the treatment of functional constipation in pediatric patients 6 years to less than 17 years of age.

   Final protocol submission: 09/2020
   Trial completion: 03/2022
   Final report submission: 09/2022

2. An oral (gavage) toxicity study with lactitol in juvenile rats from postnatal day (PND) 14 through PND 91 to support clinical trials in patients 6 months to less than 6 years of age.

   Final protocol submission: 06/2020
   Study completion: 12/2020
   Final report submission: 03/2021

3. A 12-week, randomized, double-blind, placebo-controlled, parallel-group study to assess the pharmacokinetics, efficacy, and safety of Pizensy (lactitol) for the treatment of functional constipation in pediatric patients 6 months to less than 6 years of age.

   Final protocol submission: 09/2020
   Trial completion: 06/2023
   Final report submission: 12/2023

   The trial should enroll both toilet-trained and non-toilet-trained patients. The sample size and approach to endpoints in each of these subpopulations will be negotiated during the review of the protocol.

4. A long-term extension study to assess the safety of Pizensy (lactitol) for the treatment of functional constipation in pediatric patients 6 months to less than 17 years of age who participated in Study 1 or Study 3.

   Final protocol submission: 09/2020

Trial completion: 12/2024
Final report submission: 06/2025

The following FDAAA PMR will be requested:

5. *In vitro* studies to assess whether lactitol is a substrate, inhibitor, or inducer of metabolizing enzymes and transporters as outlined in the Guidance for Industry: In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (available at: *https://www.fda.gov/media/134582/download*). If *in vitro* studies suggest a potential for interaction, additional *in vivo* studies may be required.

   Draft Protocol submission: 05/2020
   Final protocol submission: 08/2020
   Trial completion: 05/2021
   Final report submission: 11/2021

   The Applicant has not conducted in vitro or in vivo studies to evaluate the drug interaction potential for lactitol. Although the absolute bioavailability of lactitol is expected to be low following oral administration, considerably measurable plasma concentrations were observed at the recommended oral dose of 20g lactitol. Currently, there is no information to adequately address the drug interaction potential for lactitol at these observed systemic concentrations. The results of the in vitro studies will be reviewed for further determination of whether in vivo drug interaction studies are needed.

14 Division Associate Director (Clinical/DGIEP) Comments

I concur with the recommendation of the review team to approve NDA 211291 for PIZENSY (lactitol) for the treatment of chronic idiopathic constipation (CIC) in adults. This is a 505(b)(2) application that relies, in part, upon published nonclinical and clinical studies to support the safety of lactitol and supplement the submitted efficacy data, respectively. Lactitol, a synthetic monosaccharide sugar derivative of lactose, is minimally absorbed systemically; it exerts osmotic effect by causing the influx of water into the small intestine leading to a laxative effect in the colon. Although there are several products that are FDA-approved for treatment of CIC (lubiprostone, linaclotide, plecanatide, and prucalopride), lactitol is the first product to be approved in this class. The recommended dosage is 20 grams orally once daily, preferably with meals. Its use is contraindicated in patients with mechanical gastrointestinal obstruction or galactosemia. Because the osmotic laxative effect of lactitol in the GI lumen may reduce the absorption of concomitantly administered oral medications, it is recommended that oral medications be administered at least 2 hours before or 2 hours after lactitol.

I agree with the review team that the totality of evidence, based on results from one large, multicenter, placebo-controlled trial in conjunction with supportive results from a non-inferiority (NI) trial in the same population and published literature, supports a conclusion that the effectiveness of lactitol has been established in the intended adult population with CIC. The placebo-controlled trial demonstrated robust primary efficacy results for lactitol. The primary endpoint was the proportion of patients who were weekly responders for at least 9 weeks out of

the first 12-week treatment period, with at least 3 of those weeks occurring in the last 4 weeks of the first 12-week treatment period. A weekly responder was defined as having ≥3 CSBMs and an increase from baseline of >1 CSBM for that given week. Additional exploratory analyses for the long-term treatment effect and change in number of CSBMs supported results of the primary endpoint. Although the submission included two adequate and well-controlled trials, the NI trial with lubiprostone as an active comparator could not be relied on as one of two adequate and well-controlled trials to establish effectiveness due to (1) uncertainty regarding the appropriateness of the selected NI margin based on clinical trial results from a drug in a different class (linaclotide) and (2) borderline study results with respect to the proposed NI margin. Since lactitol has been marketed widely in several other countries for many years, the published literature on lactitol trials and a meta-analysis of placebo response rates for recent CIC trials were relied upon, in part, to supplement the efficacy data submitted in the NDA.

The most common adverse reactions observed in clinical trials include upper respiratory tract infection, flatulence, diarrhea, increased blood creatinine phosphokinase, abdominal distension, and increased blood pressure. Severe diarrhea occurred in 1% of lactitol-treated patients, compared to none in the placebo group, during the placebo-controlled trial. None of these patients experienced electrolyte imbalance or complications due to severe diarrhea. Because a thorough QT study had not been conducted, the review team assessed all available premarket cardiac safety data and postmarket safety experience from other countries to determine whether lactitol may have an effect on QT prolongation or predispose patients to other proarrhythmic risks/cardiac events. Given that lactitol is minimally absorbed systemically and a comprehensive review of available premarket and postmarket safety data did not reveal cardiac-related safety concerns, it was determined that a thorough QT study is not needed for this product.

I concur with the review team that data submitted in this NDA support the conclusion that the benefits of treatment with lactitol outweigh the identified risks in the intended population. A REMS will not be required. A FDAAA PMR will require *in vitro* studies to assess whether lactitol is a substrate, inhibitor, or inducer of metabolizing enzymes and transporters. If *in vitro* studies suggest a potential for interaction, additional *in vivo* studies may be required. In addition, PREA PMR studies will assess: 1) the PK, efficacy, and safety of lactitol in pediatric patients with functional constipation 6 to less than 17 years of age; 2) the effect of repeat dosing in juvenile rats (dosing to be initiated on postnatal day 14) to support dosing in pediatric patients 6 months to less than 6 years of age; 3) the PK, efficacy, and safety of lactitol in pediatric patients with functional constipation 6 months to less than 6 years of age (including both toilet-trained and non-toilet-trained patients); and 4) the long-term safety of ongoing treatment in pediatric patients with functional constipation 6 months to less than 17 years of age who completed controlled trials.

15 Appendices

15.1. References

See footnotes.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Studies BLI400-201, BLI400-301, BLI400-302, BLI400-303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: BLI400-201: 4 investigators, BLI400-301: 50 investigators, BLI400-302: 52 investigators, BLI400-303: 25 investigators Braintree Laboratories, Inc. certifies that they have not entered into any financial arrangement with the clinical investigators listed in the provided tables.		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT AND FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET
Review of Mice Carcinogenicity Study Results

P/T REVIEWER: Tamal Chakraborti, PhD

DATE: 10/16/2018

NDA: 211281

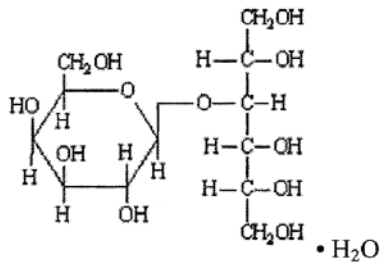
DRUG CODE #: BLI400

CAS #: 81025-04-9

DIVISION: DGIEP

DRUG NAME: Lactitol Monohydrate

CHEMICAL STRUCTURE:



SPONSOR: Braintree Laboratories, Inc.

LABORATORY: (b) (4)

CARCINOGENICITY STUDY REPORT DATE: June 29, 2018

THERAPEUTIC CATEGORY: Laxative

PHARMACOLOGICAL CLASSIFICATION: Osmotic laxative

MUTAGENIC/GENOTOXIC: Lactitol was reported to be non-genotoxic in the Ames test, chromosome aberration test with Chinese hamster lung cells and in the in vivo oral mouse bone marrow micronucleus test.

MOUSE CARCINOGENICITY STUDY:

STUDY DURATION (Weeks): 26

STUDY STARTING DATE: October 17, 2016

STUDY ENDING DATE: October 12, 2017

MOUSE STRAIN: Tg.rasH2

ROUTE: Oral (Gavage)

DOSING COMMENTS: Doses were selected based on the Exec CAC recommendations (Exec CAC meeting minutes dated 9/21/2016). The Committee recommended doses of 0 (water), 225, 675, and 2000 mg/kg/day, by oral gavage, in both males and females. The recommended high dose was based on limit dose considerations. The recommended mid and low doses are 675 and 225 mg/kg/day, respectively.

NUMBER OF MICE:

- Control-1 (C1): 25/sex
- Positive Control: 25/sex
- Low Dose (LD): 25/sex
- Middle Dose (MD): 25/sex
- High Dose (HD): 25/sex

MOUSE DOSE LEVELS:

- Low Dose: 225 mg/kg/day
- Middle Dose: 675 mg/kg/day
- High Dose: 2000 mg/kg/day

BASIS FOR DOSES SELECTED: Dose selection was based on the Exec CAC recommendations (Exec CAC meeting minutes dated 9/21/2016). The Committee recommended doses of 0 (water), 225, 675, and 2000 mg/kg/day, by oral gavage, in both males and females. The recommended high dose was based on limit dose considerations.

PRIOR FDA DOSE CONCURRENCE: Yes (Exec CAC meeting minutes dated 9/21/2016).

MOUSE CARCINOGENICITY: Negative.

MOUSE TUMOR FINDINGS: There were no significant drug-related tumor findings in male or female Tg.rasH2 mice.

MOUSE STUDY COMMENTS:

- The Exec CAC concurred that there were no drug-related neoplasms in the 26-week mouse carcinogenicity study in either males or females (Exec CAC meeting minutes dated 10/18/2018).

- The Exec CAC concurred that the study conduct was adequate, noting prior approval of the protocol (Exec CAC meeting minutes dated 10/18/2018).

Study title: 26-Week Oral (Gavage) Carcinogenicity Study in the Tg.rasH2 Mouse	
Study no.:	2062-014
Study report location:	EDR 4.2.3.4.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 17, 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lactitol monohydrate, Lot No. 11462RD, 100%
CAC concurrence:	Yes.

Key Study Findings:

- In a 26-week oral (gavage) carcinogenicity study in Tg.rasH2 mice, animals were treated daily with lactitol monohydrate at 0 (water), 225, 675, and 2000 mg/kg/day.
- There were no significant treatment-related effects on mortality.
- There were no significant treatment-related effects on body weight or food consumption.
- There were no significant treatment-related tumor findings in male or female Tg.rasH2 mice treated with lactitol monohydrate at daily oral doses up to 2000 mg/kg/day.
- There were no significant treatment-related non-neoplastic findings.
- Tumor findings in MNU treated (positive control) animals showed a carcinogenic response consistent with the expected effect of MNU in Tg.rasH2 mice, which confirmed the responsiveness of the Tg.rasH2 transgenic mouse to a known carcinogen.

Adequacy of Carcinogenicity Study

- The Exec CAC concurred that the study conduct was adequate, noting prior approval of the protocol (Exec CAC meeting minutes dated 10/18/2018).

Appropriateness of Test Models

- Per the ICH Guidance S1B, Tg.rasH2 mouse is an acceptable model for the evaluation of the carcinogenic potential of pharmaceuticals.

Evaluation of Tumor Findings

- The Exec CAC concurred that there were no drug-related neoplasms in the 26-week mouse carcinogenicity study in either males or females (Exec CAC meeting minutes dated 10/18/2018).

- Tumor findings in MNU treated (positive control) animals showed a carcinogenic response consistent with the expected effect of MNU in Tg.rasH2 mice, which confirmed the responsiveness of the Tg.rasH2 transgenic mouse to a known carcinogen.

Methods:	
Doses:	0, 225, 675 and 2000 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	10 mL/kg
Route of administration:	Oral (gavage)
Formulation/Vehicle:	Water

Basis of dose selection:	The recommended high dose was based on limit dose considerations.
Species/Strain:	CByB6F1-Tg(HRAS)2Jic Hemizygous [RasH2] transgenic mice
Number/Sex/Group:	25/sex/group
Age and body weight:	Animals were approximately 5 weeks of age with a weight range of 20.8 to 24.8 g for males and 17.2 to 20.4 g for females at the initiation of the treatment.
Animal housing:	Animals were housed in individual cage.
Paradigm for dietary restriction:	Not Applicable (N/A)
Dual control employed:	No
Positive control:	Single Intraperitoneal injection N-Nitroso-N-methylurea (also known as N-methyl-N-nitrosourea, NMU, or MNU) at 75 mg/kg
Interim sacrifice:	No
Satellite groups:	None
Deviation from study protocol:	Protocol deviations did not affect the quality or integrity of the study.

The following table (from page 14 of the report) shows the study design.

Table 44: Study Design and Group Assignments

Table C. Group Assignments

Group Number	Dose Level (mg/kg/day)	Number of Animals	
		Male	Female
1	0	25	25
2	225	25	25
3	675	25	25
4	2000	25	25
5	Positive Control (NMU)[a]	25	25

[a]N-Nitroso-N-methylurea (NMU) was administered on Day 1 only via intraperitoneal injection at a dose level of 75 mg/kg.

Observations and Results:

Mortality: Mortality was observed twice daily. There were no lactitol-related unscheduled deaths. All deaths were sporadic across groups without any dose relationship and the causes of death were variable and were not considered treatment related. The survival rate at Week 27 is shown in the table (from page 21 of the report) below.

Table 45: Survival Rate (Week 27)

Table H. Survival Rate The Number of Animals Surviving to the Scheduled Terminal Necropsy (Week 27)*			
Dose Level (mg/kg/day)	**Male**	**Female**	**Overall (M+F)**
0 (Vehicle)	24 (96%)	25 (100%)	49 (98%)
225	23 (92%)	24 (96%)	47 (94%)
675	25 (100%)	24 (96%)	49 (98%)
2000	24 (96%)	25 (100%)	49 (98%)
75 mg/kg (Positive Control)[a]	15 (60%)	16 (64%)	31 (62%)
*Respective survival percentage calculations are included in parentheses. [a]NMU was administered intraperitoneally once, on Day 1.			

The cause of death is shown in the table below (from pages 25 of the report).

Table 46: Unscheduled Euthanasia and/or Deaths During the Study

Table K. Unscheduled Euthanasia and/or Deaths During the Course of the Study				
Animal Number/ Sex	Dose Level (mg/kg/day)	Fate/ Animal Disposition	Fate Day	Cause of Death/Euthanasia
1023/M	0	EE	177	hemangiosarcoma/hemangioma
2014/M	225	EE	117	undetermined
2025/M	225	EE	96	hemangiosarcoma/hemangioma
4015/M	2000	EE	134	lung tumor
5001/M	NMU	EE	110	lymphoid tumor
5004/M	NMU	FD	77	undetermined
5005/M	NMU	EE	122	stomach, nonglandular; carcinoma, squamous cell
5007/M	NMU	EE	170	stomach, nonglandular; carcinoma, squamous cell
5009/M	NMU	EE	155	stomach, nonglandular; carcinoma, squamous cell
5015/M	NMU	FD	106	stomach, nonglandular; carcinoma, squamous cell
5016/M	NMU	FD	106	undetermined
5017/M	NMU	EE	143	lymphoid tumor
5019/M	NMU	FD	105	stomach, nonglandular; carcinoma, squamous cell
5025/M	NMU	EE	108	lymphoid tumor
2506/F	225	FD	172	lung tumor
3525/F	675	EE	146	hemangiosarcoma/hemangioma
5509/F	NMU	FD	165	undetermined
5510/F	NMU	FD	78	undetermined
5511/F	NMU	FD	94	lymphoid tumor
5514/F	NMU	EE	176	accidental injury
5516/F	NMU	FD	118	stomach, nonglandular; carcinoma, squamous cell
5517/F	NMU	EE	176	skin tumor
5520/F	NMU	EE	141	skin; carcinoma, squamous cell
5522/F	NMU	FD	106	lymphoid tumor
5523/F	NMU	FD	140	undetermined
M-Male F-Female NMU: N-Nitroso-N-methylurea (Positive Control)			EE-Euthanized *in extremis* FD-Found Dead	

The following Figures (66, 67 of the report) show the survival curves for males and females.

Figure 3: Summary of Survival Estimates- Male

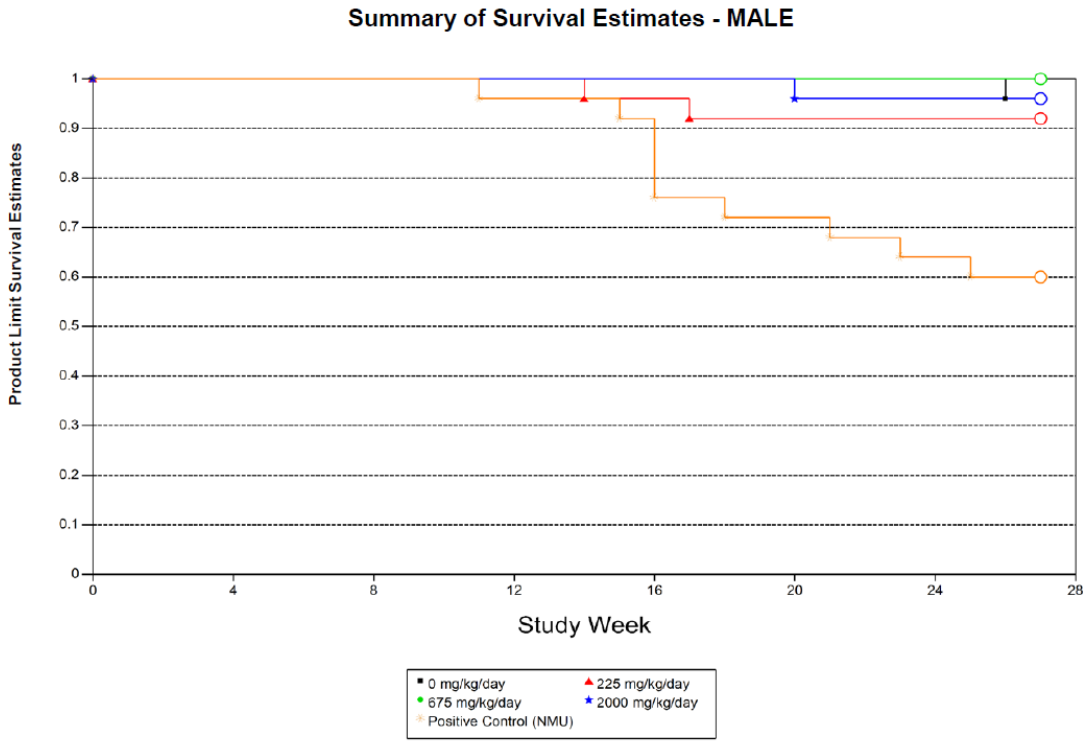
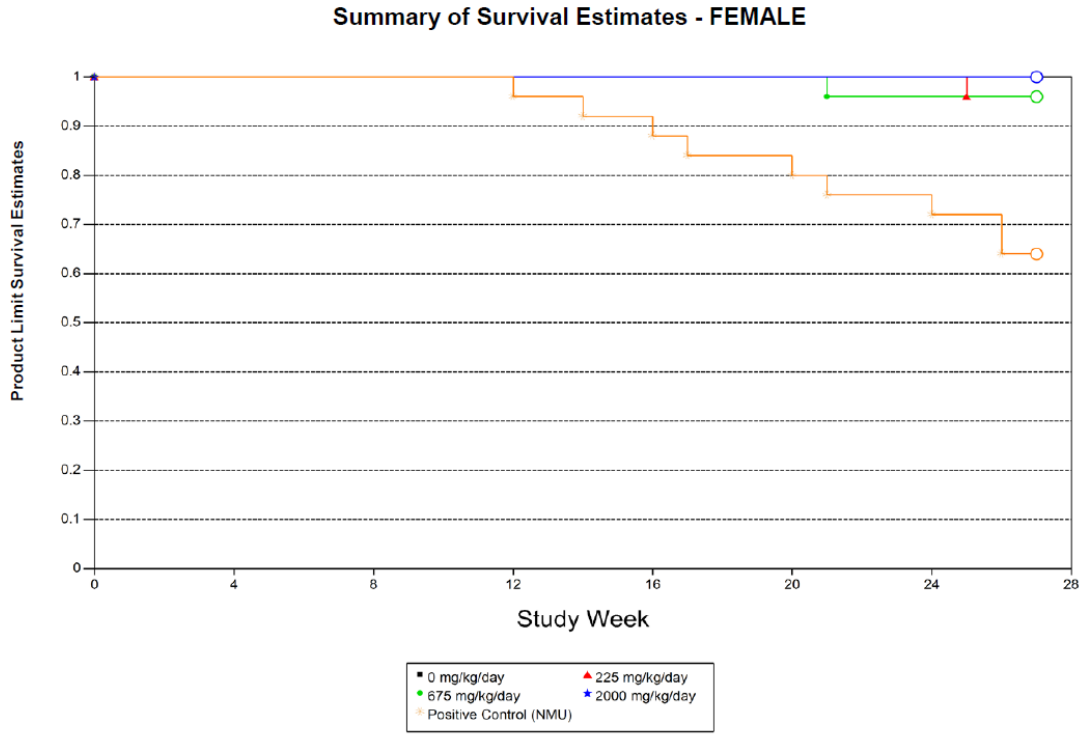


Figure 4: Summary of Survival Estimates- Female



Clinical Signs: Clinical signs were observed once weekly. There were no treatment-related clinical signs or incidence of masses/nodules.

Body Weights: Body weights were recorded at two days after receipt, Day -1, weekly for Weeks 1 through 14, and every two weeks thereafter. There were no significant treatment-related effects on body weights in either sex. The mean initial (Week 1) and final (Week 26) body weights of control males were 22.8 and 31.1 g, respectively. The mean initial (Week 1) and final (Week 26) body weights of control females were 13.86 and 23.03 g, respectively. Final body weights of treated males were 96.53%, 98.42% and 99.58% of control at 225, 675 and 2000 mg/kg/day, respectively. Final body weights of treated females were 99.17%, 101.3% and 101.9% of control at 225, 675 and 2000 mg/kg/day, respectively. The following table shows the body weights and body weight gain in males and females at Week 26.

Table 47: Body Weights and Body Weight Gain in Males and Females at Week 26

	0 mg/kg/day	225 mg/kg/day	675 mg/kg/day	2000 mg/kg/day
Male				
Week 1	22.8	23.26	22.98	23.05
Week 26	31.1	30.02	30.61	30.97
% of Control, Wk 26	100.00	96.53	98.42	99.58
ΔWk 26-Wk 1	8.3	6.76	7.63	7.92
BW Gain, % of Initial BW	36.40	29.06	33.20	34.36
BW Gain, % Of Control	100	79.84	91.21	94.39
Female				
Wk 1	13.86	18.72	18.06	19.12
Wk 26	23.03	22.84	23.33	23.48
% of Control, Wk 26	100.00	99.17	101.30	101.95
ΔWk 26-Wk 1	9.17	4.12	5.27	4.36
BW Gain, % of Initial BW	66.16	22.01	29.18	22.80
BW Gain, % Of Control	100	33.26	44.10	34.47

Abbreviations: BW, body weight

Growth curves are shown below (from pages 69, 70 of the report).

Figure 5: Mean Body Weight Values- Male

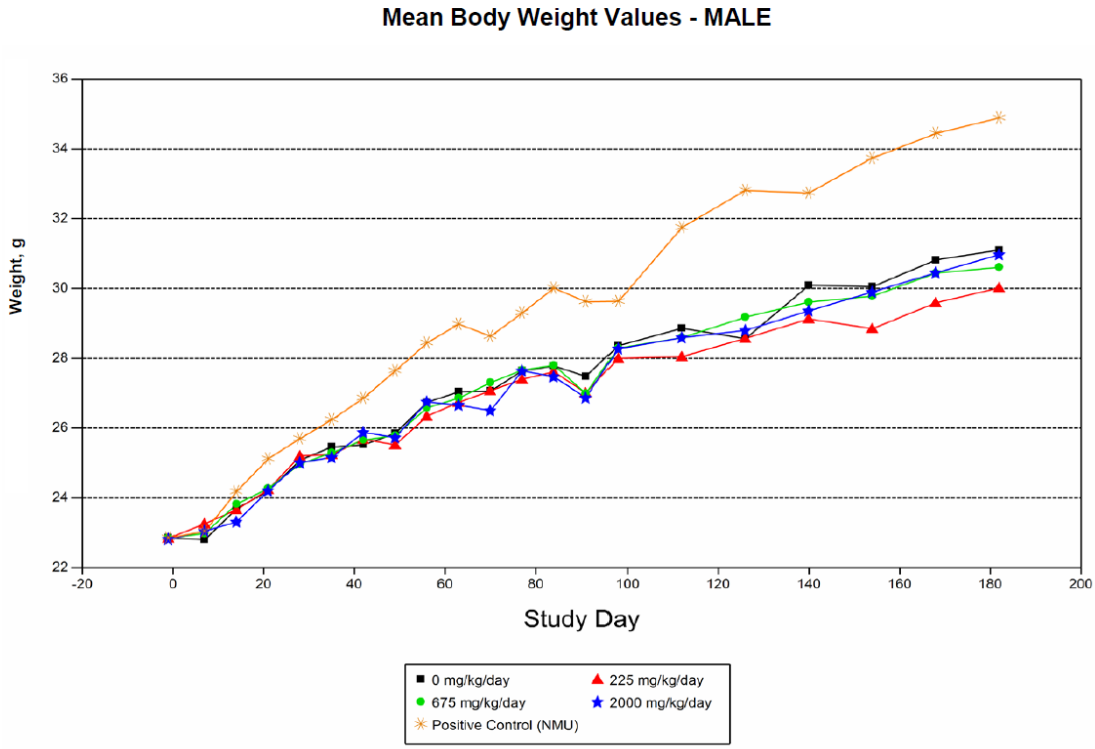
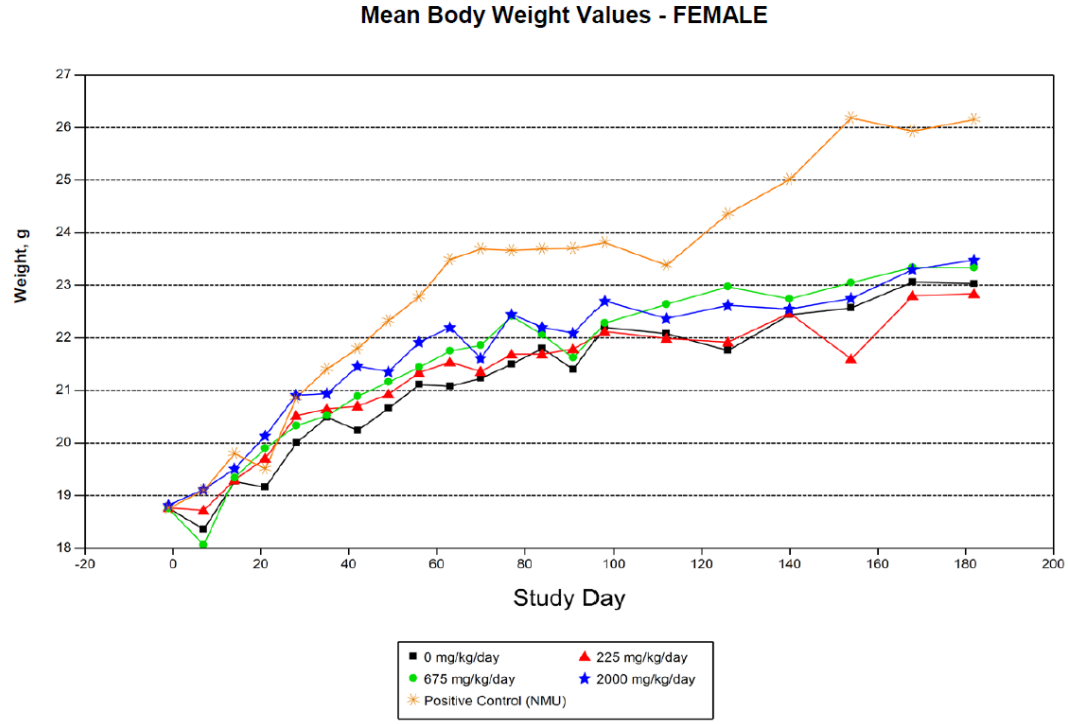


Figure 6: Mean Body Weight Values- Female



Feed Consumption: Food consumption was recorded weekly for the first 14 weeks and every two weeks thereafter. The mean initial (Week 1) and final (Week 26) food consumption of control males were 4.01 and 3.83 g/animal/day, respectively. The mean initial (Week 1) and final (Week 26) food consumption of control females were 2.92 and 3.03 g/animal/day, respectively. There were no significant treatment related effects on food consumption.

Clinical Pathology: Hematology was conducted at necropsy. There were no significant treatment-related meaningful changes in hematology parameters.

Gross Pathology: Gross pathology was conducted at necropsy. There were no significant treatment-related gross pathology findings.

Histopathology:

Peer Review: Yes

Neoplastic: There were no drug-related neoplasms in the 26-week mouse carcinogenicity study in either males or females. Tumor findings in MNU treated (positive control) animals showed a carcinogenic response consistent with the expected effect of MNU in Tg.rasH2 mice, which confirmed the responsiveness of the Tg.rasH2 transgenic mouse to a known carcinogen.

Non-Neoplastic: There were no significant treatment-related non-neoplastic findings.

Toxicokinetics: Not performed

Dosing Solution Analysis: Dosing formulations prepared for the study were evaluated for homogeneity and concentration. Appropriate samples were collected from top, middle and bottom portions of the formulations for analyses of homogeneity (at Week 1) and concentration (Weeks 1, 8, 15, 22 and 26), respectively. All homogeneity and concentration samples were within the ±10% of the nominal concentration and ≤10% of acceptance criterion.

15.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.4.1. Bioanalytical Method Validation and In-Study Report

The Applicant applied HPLC with Mass Spectrometric to determine lactitol concentrations in the plasma. The performance and the assay validation parameters are summarized in Table 48. The validated bioanalytical method was used to measure lactitol concentrations in PK samples collected from the submitted clinical studies. The bioanalytical method validation is acceptable. The in-study bioanalytical report for study BLI400-101 is also acceptable.

Table 48: Bioanalytical Method Validation and In-Study Report

Method HPLC with Mass Spectrometric Detection (Zn-1001 Bioanalytical study report)	HPLC-MS/MS → m/z 351 189 lactitol → m/z 350 169 internal standard
Compound (parent)	Lactitol
Internal Standard	Sucrose-(glucose-1-^{13}C)
Matrix	Human EDTA K_2 Plasma
Regression Method:	Linear Regression
Calibration range	25-10,000 ng/mL
Sample Volume	50 µL
Intra-run Accuracy for LLOQ Intra-run Precision for LLOQ	-0.4% 2.9%
Intra-run Accuracy for QCs Intra-run Precision for QCs Inter-run Accuracy for QCs Inter-run Precision for QCs	-11.2 to 8.5% 0.6 to 5.8% 2.2 to 6.4% 1.6 to 4.3%
Bench Top Stability	25 hours QCs 1.2 to 8.6% 62 hours QCs 2.9% to 6.2%
Refrigerated Stability (5°C)	73 hours QCs 3.5% to 5.6%
Freeze/Thaw Cycle Stability (-70°C)	3 Cycles QCs 1.9 to 2.8%
Long Term Storage Stability (-70°C)	18 days QCs 2.7 to 3.7% 124 days QCs 2.3 to 2.9%
Whole Blood Stability (Wet Ice)	0 hours QCs 3.3 to 4.6% 2 hours QCs 1.2 to 3.5%
Autosampler Stability (5°C)	QCs 2.5 to 5.3%
Reinjection Reproducibility	Analytical Run 10 Calibration and QC Sample Results 2.2% to 4.5%
Recovery (QC low, mid and high)	92.9 to 117%
Matrix Effect (hemolytic, lipemic)	Six different (individual, non-pooled) lots, in singlicate, at high and low level: -1.9% to 4.0%,
Assay Selectivity	Ten different (individual, non-pooled) lots of blank plasma were fortified at the concentration of the LLOQ standard lactitol: 0.004% to 11.0%, IS: 0.7 to 2.33%
Injection Carryover	No significant carryover was observed with reagent and plasma blanks injected after ULOQ standards using IS.
Conclusion	Method validation is acceptable.
In study report for study BLI400-101 ((BLI400-101 Bioanalytical analysis report): Number of samples: 480 (two aliquots of each sample) Date(s) of receipt: November 22, 2016 and January 18, 2017 Date of Analysis: December 9, 2016 to January 27, 2017 Reviewer comment: The long-term stability data could support sample storage for up to 124 days. The interval between the time when the first subject was dosed (Nov 1st, 2016) and the time when the last sample was analyzed (Jan 27th, 2017) was less than 90 days; therefore, the currently available long-term stability data is acceptable to support the PK results of study BLI400-101.	

18 runs: 16 runs for samples running and 2 runs for incurred sample reanalysis.

Calibration curve 10 runs: accuracy was 4.9 to 6.3%
QCs 18 runs: accuracy was 3.9 to 6.4%
Reproducibility of Incurred samples: accuracy was -13.9 to 15.9%

A total of 480 human plasma samples were analyzed for lactitol using a validated method. Reproducibility of incurred samples was performed, and the results met acceptance criteria. The results from calibration standards and quality control samples demonstrated acceptable performance of the method for all reported concentrations.

15.4.2. Individual Study Report

Study BLI400-101

Title: A Comparison of the Pharmacokinetics of Lactitol in Fasting and Fed Conditions in Healthy Volunteers

Study Date: 11/01/2016 - 11/17/2016

Study Design:

Study BLI400-101 was an open label, single dose, cross over, two-treatment (fed vs fasted), two-period, and two-sequence study in healthy subjects. A total of 16 healthy adult subjects (8 males and 8 females) were enrolled to receive two single-dose administrations of BLI400.

- Dose administration:

Both doses were administered after a minimum 10-hour overnight fast. The fed portion of the study was conducted by ingestion of an FDA-recommended standard high-calorie and high-fat meal. The study drug was administered 30 minutes after the meal. The two drug administrations were separated by a washout period of at least 7 days.

- Study population:

The study was conducted in 16 healthy Caucasian and African American subjects with a range of age from 23 to 59 years, a range of body mass index from 20.1 to 31.9 kg/m^2, a range of height from 151.8 to 180.3 cm, and a range of body weight from 62.7 to 98.9 kg.

- Investigational drug:

The investigational drug product was BLI400 Lactitol Monohydrate NF Powder for Reconstitution, Braintree Laboratories, Inc., Lot RD1114, Manufacture Date of 14 October 2016. Each dose uses two 10.5 g packets administered with 8 oz of water.

- Pharmacokinetics (PK)

Blood samples (4 mL) were drawn at predose (0 hour) and at 10, 20, 30 and 60 minutes (within ± 3 minutes) and then at 2, 4, 6, 8, 10, 12, 16, 18, 20 and 24 hours (within ± 30 minutes) after administration of the investigational product. Drug concentrations were determined using the validated LC/MS/MS method with a lower limit of quantitation of 25 ng/mL.

- Study Results:

The PK results are described in Section 6.3.1.

Study BLI400-302

Title: A Safety and Efficacy Evaluation of BLI400 Laxative in Constipated Adults

Study Date: 06/07/2016-06/19/2017

Study Design:

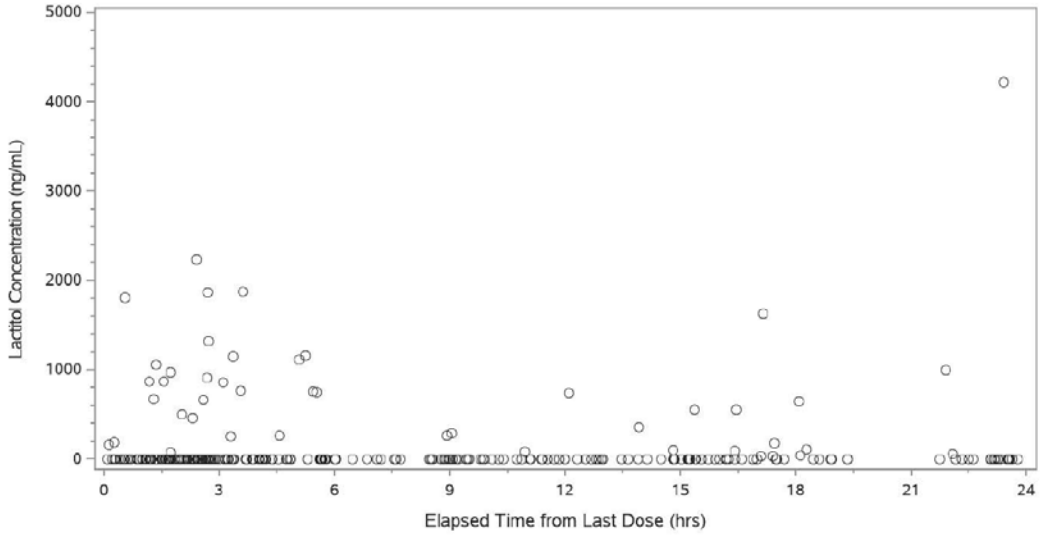
This study was a randomized, double-blind, parallel, placebo-controlled phase 3 study to evaluate efficacy and safety of BLI400 in adult CIC patients. CIC patients were treated with BLI400 (lactitol) powder (21 g) once daily for 6 months. Plasma lactitol levels were measured in a subset of patients at V1, V3–V8, and the end of study. See Sections 7 and 8 for summaries of objectives, study design, and patients population information.

PK results:

- **Overall PK results in study BLI400-302**

Figure 7 shows plasma lactitol concentrations from the PK subset of patients at various study visits. The majority of PK samples had drug concentrations lower than the assay sensitivity (25 ng/mL). Approximately 23% to 30% of patients treated with BLI400 and who provided PK samples had measurable plasma lactitol concentrations ranging from 26 ng/mL to 5,500 ng/mL over the course of the study. The observed drug concentrations in Study BLI400-302 were within the range of drug concentrations observed in Study BLI400-101 in which subjects received single dose of 21g BLI400. Overall, there is no evidence suggesting a potential for drug accumulation during the 6-month treatment period.

Figure 7: Plasma Lactitol Concentrations in Study BLI400-302

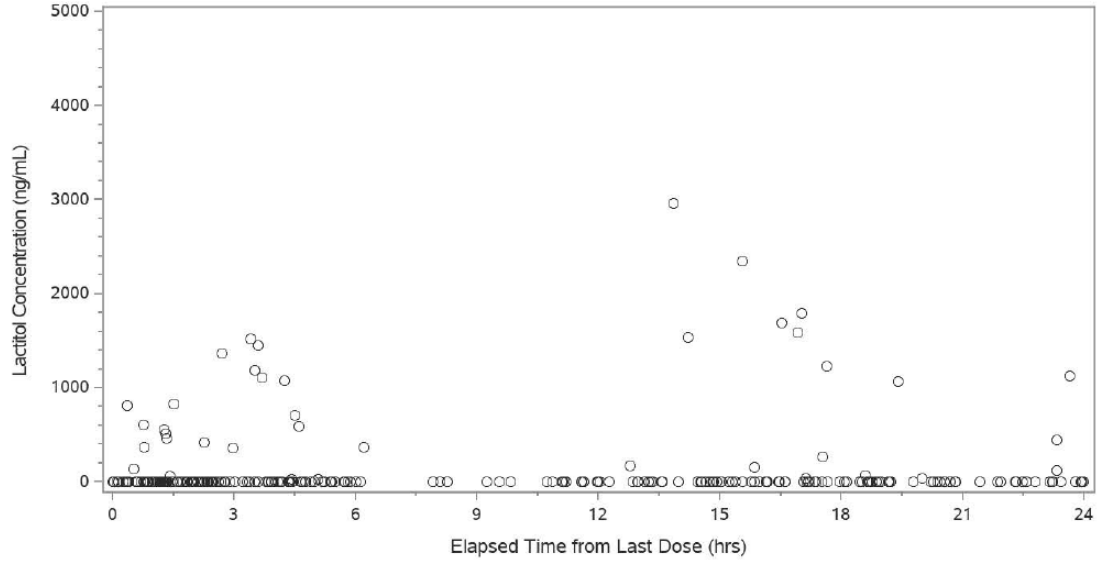


Source: Information Request (IR) Response 22Aug2019, Figure 1.1.
Note that the timepoint in the plot may not accurately represent the actual time after the last dose administration. See “Reviewer’s note on the limitation of the PK data” below for more information.

- **Effect of renal impairment on PK in CIC patients**

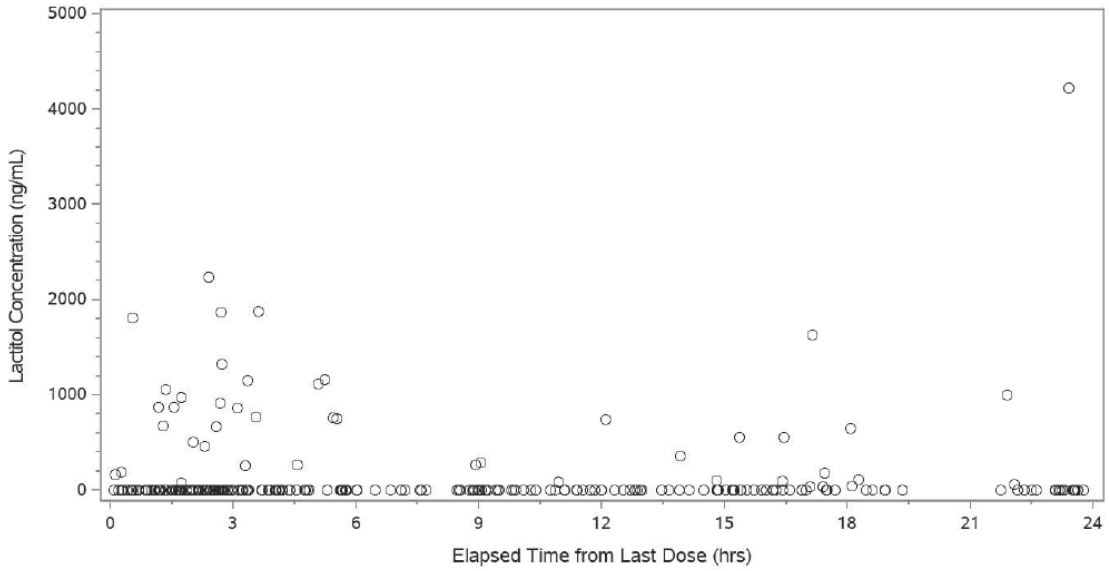
The observed drug concentrations in subjects with renal impairment are shown in Figure 8. The observed drug concentrations in subjects without renal impairment are shown in Figure 9. It is noted that patients with renal impairment appeared to be more likely to have a measurable plasma lactitol concentration. However, the range of the observed drug concentrations in renal impairment subjects is within the observed drug concentrations in non-renal impairment subjects. The comparison of the mean drug exposures among subgroups of patients by their GFR values does not suggest that renal impairment had a clear trend of increased serum lactitol concentrations across the study visits (Table 49).

Figure 8: Plasma Lactitol Concentrations in Renal Impairment CIC Patients



Abbreviations: CIC, chronic idiopathic constipation
Note that the timepoint in the plot may not accurately represent the actual time after the last dose administration. See “Reviewer’s note on the limitation of the PK data” below for more information.
Source: IR response 22Aug2019, Figure 1.12.

Figure 9: Plasma Lactitol Concentrations in Non-Renal Impairment CIC Patients



Abbreviations: CIC, chronic idiopathic constipation
Note that the timepoint in the plot may not accurately represent the actual time after the last dose administration. See "Reviewer's note on the limitation of the PK data" below for more information.
Source: IR response 22Aug2019, Figure 1.13.

Table 49: Comparison of Plasma Lactitol Concentrations by Subjects GFR Values

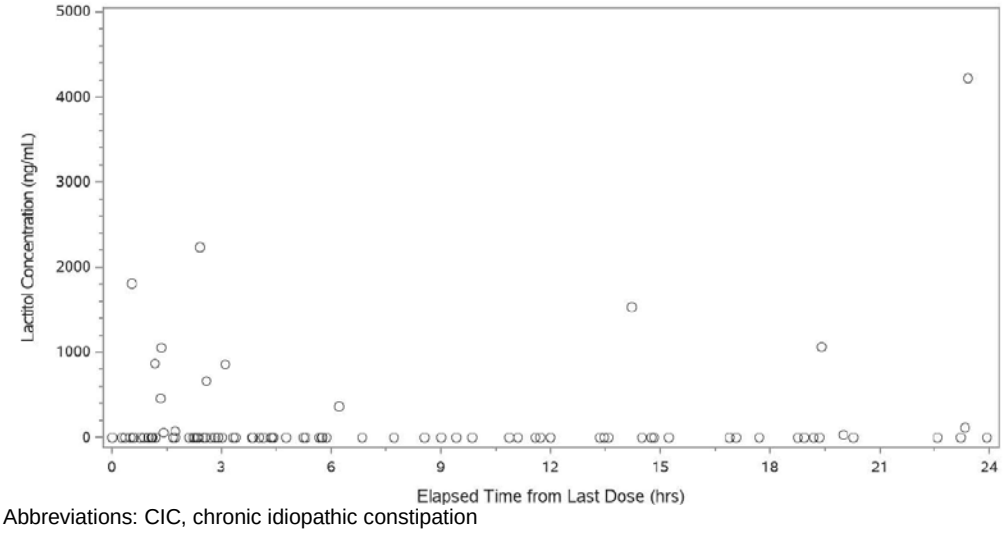
		V1	V3	V4	V5	V6	V7	V8
Non-renal[1] (GFR≥90)	N	0	11	9	12	9	9	8
	Mean		574	546	813	1453	779	606
	SD		(673)	(429)	(660)	(1184)	(499)	(368)
Renal[1] (GFR<90)	N	1	11	12	8	10	8	7
	Mean	135	1025	550	809	756	798	625
	SD		(1543)	(556)	(658)	(824)	(978)	(472)
Renal[2] (GFR<60)	N	0	2	3	3	2	4	2
	Mean		2814	604	1043	1238	980	791
	SD		(3813)	(375)	(694)	(1572)	(1332)	(494)

Abbreviations: GFR, glomerular filtration rate; SD, standard deviation
Source: IR response 22Aug2019 cover letter, Table 1

- **Effect of hepatic impairment on PK in CIC patients**

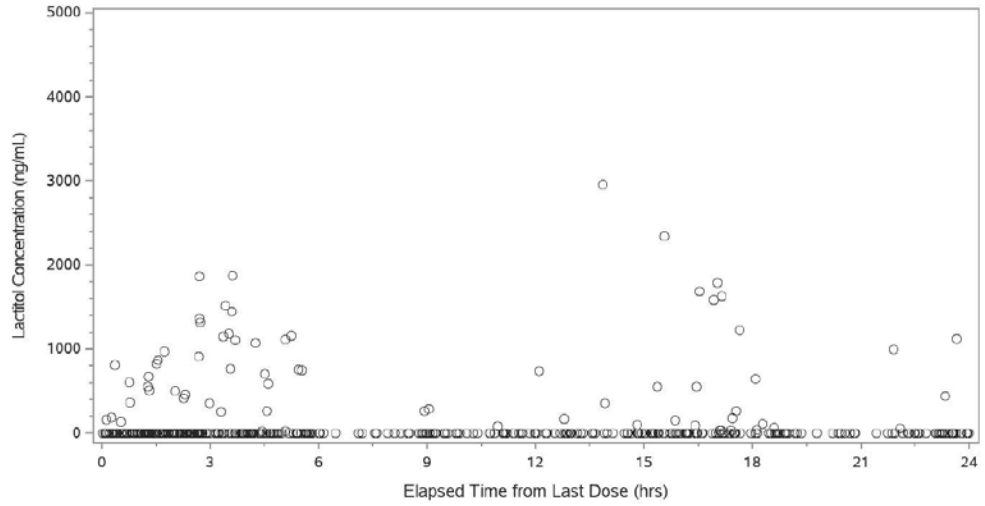
The observed drug concentrations in subjects with hepatic impairment are shown in Figure 10. The observed drug concentrations in subjects without hepatic impairment are shown in Figure 11. Except for one observation at drug concentration of approximately 4,000 ng/mL, the observed drug concentrations in hepatic impairment subjects were within the range of the observed drug concentrations in non-hepatic impairment subjects. One patient ([redacted] (b) (6)) among the four patients with hepatic impairment had measurable lactitol levels at multiple visits. The highest observed concentration, 1,140 ng/ml at V8, was within the range of the observed concentration among the study population. The comparison of the mean drug exposures between hepatic and non-hepatic impairment subjects does not suggest hepatic impairment had a clear trend of increased plasma lactitol concentrations across the study visits (Table 50).

Figure 10: Lactitol Plasma Concentrations by Sampling Time in Hepatic Impairment CIC Patients



Abbreviations: CIC, chronic idiopathic constipation
Note that the timepoint in the plot may not accurately represent the actual time after the last dose administration. See "Reviewer's note on the limitation of the PK data" below for more information.
Source: IR response 22Aug2019, Figure 1.14.

Figure 11: Plasma Lactitol Concentrations in Non-Hepatic Impairment CIC Patients



Abbreviations: CIC, chronic idiopathic constipation
Note that the timepoint in the plot may not accurately represent the actual time after the last dose administration. See "Reviewer's note on the limitation of the PK data" below for more information.
Source: IR response 22Aug2019, Figure 1.15.

Table 50: Comparison of Plasma lactitol Concentrations in Hepatic Impairment and Non-Hepatic Impairment CIC Patients

		V1	V3	V4	V5	V6	V7	V8
Non Hepatic	N	1	19	17	17	14	14	11
	Mean	135	782	616	883	1003	767	538
	SD		(1219)	(498)	(656)	(750)	(752)	(348)
Hepatic Impairment	N	0	3	4	3	5	3	4
	Mean		908	259	406	1320	884	828
	SD		(1160)	(404)	(422)	(1728)	(803)	(525)

Abbreviations: CIC, chronic idiopathic constipation; SD, standard deviation
Source: IR response 22Aug2019 cover letter, Table 2

Reviewer's note on the limitation of the PK data: In response to the FDA's information request, the Applicant explained that the actual time of PK sampling following the last dose administration was not accurately captured or reported in Study BLI400-302. The Applicant noted that the drug concentrations observed in the 12 to 24 hour period were believed to be a result of study medication doses entered into the e-Diary in the evening, after the alarm notified subjects that they had not made an entry (alarms were programmed for 7:00PM, 7:30PM and 8:00PM). Although patients were instructed to take their daily medication dose in the morning, they were allowed to enter the dosing information up until approximately midnight of that day. Therefore, the PK time in the plots shown above may not reflect the actual time following the last dose administration and caution should be taken in the interpretation of the PK results.

- **Drug-drug interactions**

The Applicant did not conduct any in vitro or in vivo drug-drug interaction studies for lactitol. In Study BLI400-302, the Applicant conducted analysis based on treatment-emergent adverse events in patients taking concomitant narrow therapeutic index drugs to evaluate potential drug-drug interaction with lactitol. The narrow therapeutic index drugs include carbamazepine, digoxin, levothyroxine, lithium, phenytoin, theophylline, and warfarin. No adverse events attributable to drug-drug interaction with lactitol were identified based on this analysis.

As a sugar alcohol, lactitol is poorly absorbed, is osmotically active in the GI lumen, and consequently may affect the absorption of co-administered oral drugs, especially for BCSIII drugs that possess poor intestinal permeability. In phase 3 studies, there was an observation of higher adverse events related to hypertension in the drug treatment group (N=9) compared to the placebo group (N=2) among approximately 20 patients with hypertension. There were 7 patients with an AE of hypertension (i.e., increased blood pressure) who were taking anti-hypertensives at the time of the AE. The co-administrated anti-hypertension drugs include lisinopril (patients N=4), hydrochlorothiazide (N=2), losartan (N=3), and atenolol (N=2). All these four drugs belong to BCSIII drugs. The reduction of drug exposure of BCSIII hypertension drugs by lactitol could be a potential reason that resulted in the increased blood pressure in patients who experienced hypertension AE. See Section 6.3.2.4 for more information.

15.5. Additional Information on the Analysis Populations

The count of 623 randomized patients from the CSR also excluded one patient randomized to lactitol (Subject (b) (6)). According the Response to Filing Communication (02/11/2019) and the Response to Information Request (03/26/2019), Subject (b) (6) was a screen failure at site (b) (6). This subject later enrolled at site (b) (6) as Subject (b) (6), was randomized to lactitol, and discontinued after being identified as a duplicate subject. The Applicant excluded this patient from the ITT, mITT, FDA-ITT, FDA-mITT, and safety populations.

There were 20 patients in the Applicant's randomized population who were excluded from the ITT population (n=603):

- Twelve patients excluded due to confirmed research misconduct at site 32
- Five patients excluded due to a fire at site 6 (however, safety information was available for 3 subjects)
- Two patients excluded due to participating in multiple investigational studies
- One patient was randomized in error (kit never dispensed).

There were 27 patients from the Applicant's randomized population who were excluded from the mITT population in the CSR (n=596):

- Twenty patients excluded from the ITT population described above as well as 7 additional patients.
- Six patients were excluded due to not having any entries in the BM diary after randomization
- One patient was randomized in error and did not meet the BM entry criteria (she had an average of 5 CSBMs per week during the baseline period).

There were 7 patients from the Applicant's randomized population who were excluded from the total safety population; 2 patients excluded due to participating in multiple investigational studies, 2 patients did not take any study medication, 2 patients were excluded due to a fire at site 6 which destroyed all study records, and 1 patient was randomized in error (kit never dispensed).

The FDA primary analysis population includes all randomized subjects except subjects enrolled in both Study 301 and Study 302, subjects enrolled at site 32 (research site misconduct) and site 6 (fire). Additionally, both Subject (b) (6) and Subject (b) (6) (who had re-enrolled at different study sites) were only counted in the original site they had enrolled, which lead to efficacy data from both subjects being excluded from the efficacy analyses. The FDA primary analysis population was not defined in either of the Applicant's CSRs, but was defined post-hoc after identifying that Subject (b) (6) (lactitol) had re-enrolled, on her own accord, at site (b) (6) after the fire at site 6 led to all patients from site 6 being discontinued from the study. The review team decided that patients should only be included in the efficacy analysis based on the first site of enrollment. In addition, the Applicant's CSRs used a different definition for the mITT population than in the protocol and SAP. The mITT population, as defined in the CSR, includes randomized patients who took study drug and had made an entry in the BM diary post-baseline, but the SAP defined the mITT as all randomized patients who took study drug. Several patients participated in the study for months without any post-baseline diary entries. Additionally, the ITT population excluded two randomized patients who had enrolled in multiple investigational studies. Due to the data quality issues with the Applicant's defined study populations, a new study population, the FDA primary analysis population, was defined and is used as the primary analysis population in this review. Note that Subjects (b) (6) and (b) (6) are included in the FDA primary analysis population, but are excluded from safety analyses and had been excluded from the ITT population due to enrolling in multiple investigational studies.

15.6. Sensitivity Analyses for Randomized Patients Not Included in the Primary Analysis Population

The primary analyses excluded all patients that had previously enrolled in Study 301, consistent with the FDA recommendation in the 8/28/2018 refuse to file letter that patients who enrolled in more than one phase 3 study should be included in the efficacy analysis only for the first study in which they enrolled. There were 10 (8 BLI400 and 2 placebo) ITT patients excluded from the ITT analysis due to enrollment in both studies 301 and 302. In addition, 20 randomized patients (8 BLI400, 10 placebo, and 2 unknown treatment assignments) were excluded from the ITT population in the CSR; 12 (5 BLI400 AND 7 placebo) patients were excluded due to confirmed research misconduct at site 32; 5 (2 BLI400, 1 placebo, and 2 unknown treatment assignments) patients were excluded due to a fire at site 6; 2 (1 BLI400 and 1 placebo) patients were excluded due to participating in multiple investigational studies; and 1 placebo patient was randomized in error (kit never dispensed). There was one additional patient (Subject (b) (6)

Subject (b) (6)) that had been a screen failure at Site (b) (6) but later re-enrolled at Site (b) (6) and was randomized to BLI400. This patient was discontinued from the study after it was discovered that the patient was a duplicate patient. That patient was not included in the Applicant's count of 623 randomized patients.

An additional analysis including data from all ITT patients (including subjects previously enrolled in Study 301) as defined in the CSR is included in the table below. Also included are two sensitivity analyses which impute missing values for the randomized individuals excluded from the ITT population under the worst-case scenario for treatment efficacy. All BLI400 patients excluded from the ITT population are imputed as non-responders and all placebo patients excluded from the ITT population are imputed as responders. The first scenario assumes that patients with missing treatment assignments were randomized to BLI400. The second scenario assumes that patients with missing treatment assignments were randomized to placebo. All three analyses are still significant, indicating that the randomized patients excluded from the efficacy analyses would not alter our efficacy conclusions. Note that Subject (b) (6) was counted twice in the randomized patient population and is considered a non-responder at site 6 and a responder at site (b) (6).

Table 51: Sensitivity Analyses With Subjects Excluded From the Primary Efficacy Analyses

		BLI400	Placebo
All ITT Patients (Including Duplicate Subjects from 301)	N	299	304
	Responders (%)	77 (25.8)	39 (12.8)
	Treatment Difference (95% CI)	12.9 (6.7, 19.1)	
WC Imputation for all Randomized Patients (Missing Treatment Assignments are Assigned BLI400)	N	310	314
	Responders (%)	77 (24.8)	49 (15.6)
	Treatment Difference (95% CI)	9.2 (3.0, 15.5)	
WC Imputation for all Randomized Patients (Missing Treatment Assignments are Assigned Placebo)	N	308	316
	Responders (%)	77 (25.0)	51 (16.1)
	Treatment Difference (95% CI)	8.9 (2.5, 15.2)	

Abbreviations: CI, confidence interval; ITT, intent to treat; WC, worst case
Source: Reviewer's analysis created from ADEFF.xpt and ADSL.xpt

15.7. Supplementary Tables

Table 52: Study 301 Recoded Terms

Applicant's AE Code (number of events recoded)	Reviewer's Recoded Term
Abdominal discomfort (2)	Abdominal pain
Nasopharyngitis (2)	Upper respiratory tract infection
Red blood cells urine (1)	Haematuria
Rash maculo-papular (1)	Rash
Tension headache (1)	Headache
Type 2 diabetes mellitus (1)	Diabetes mellitus
Otitis media (2)	Ear infection

Table 53: Study 302 Recoded Terms

Applicant's AE Code (number of events recoded)	Reviewer's Recoded Term
Abdominal discomfort (2)	Abdominal pain
Abdominal pain upper (10)	Abdominal pain
Viral upper respiratory tract infection (3)	Upper respiratory tract infection
Nasopharyngitis (24)	Upper respiratory tract infection
Blood creatine phosphokinase MB increased (1)	Blood creatine phosphokinase increased
Gastroenteritis viral (4)	Gastroenteritis
Glucose urine present (1)	Glycosuria
Blood urine present (2)	Haematuria
Red blood cells urine positive (3)	Haematuria
Blood potassium increased (6)	Hyperkalaemia
Blood potassium decreased (4)	Hypokalaemia
Blood calcium increased (1)	Hypercalcaemia
Mean cell haemoglobin concentration decreased (3)	Mean cell haemoglobin decreased

Table 54: Study 301 Schedule of Events

Procedures	Visit 1	Screening *Days (-1 through -14)*	Visit 2 *Day 0*	Visits 3 - 4 *Days: 28, 56, +/-2 days*	Visit 5/ ET *Day 84 +4 days*	Day 98 ☎ *+/- 3 days*
Informed Consent	X					
Inclusion/Exclusion Criteria Review	X					
Medical History	X					
Physical Examination	X				X	
Vital Signs	X		X	X	X	
ECG	X		X	X	X	
Review of Concomitant Medication	X		X	X		
Urine Pregnancy Test (if applicable)	X		X		X	
Dispense Electronic Diary	X		X			
Subject Completes Diary		X		X	X	
Randomize Eligible Subjects			X			
Blood Samples for Chemistry & Hematology Testing			X	X	X	
Urine Sample for Urinalysis			X	X	X	
Dispense Rescue Bisacodyl	X	X	X	X		
Dispense Study Drug			X	X		
Study Drug and Rescue Bisacodyl Accountability			X	X	X	
Assess Safety			X	X	X	X

Abbreviations: ECG, electrocardiogram
Source: Applicant's submission, NDA 211281, Study 301 CSR, page 18/77.

Table 55: Study 302 Schedule of Events

Procedures	Visit 1 Screening	Visit 2 *Day 0*	Visits 3 - 7 *Days: 28, 56, 84, 112, 140* *+/-2 days*	Visit 8/ ET *Day 180* *+4 days*	Day 194 ☎ *+/- 3 days*
Informed Consent	X				
Inclusion/Exclusion Criteria Review	X				
Medical History	X				
Physical Examination	X			X	
Vital Signs	X	X	X	X	
Electrocardiogram	X			X	
Review of Concomitant Medication	X	X	X	X	X
Dispense Electronic Diary	X	X	X		
Review Diary Compliance		X	X		
Blood Samples for Chemistry & Hematology Testing[2]	X		X	X	
Urine Sample for Urinalysis*	X		X	X	
Dispense Rescue Bisacodyl	X	X	X		
Randomize Eligible Subjects		X			
Dispense Study Drug[1]		X	X		
Study Drug and Rescue Bisacodyl Accountability		X	X	X	
Assess Safety		X	X	X	X

**Serum pregnancy testing was performed at Visit 1 (Screening), Visit 5 (Day 84) and Visit 8 (Day 180) only.*

Source: Applicant's submission, NDA 211281, Study 302 CSR, page 20/96.

Table 56: Study 303 Schedule of Events

Procedures	Visit 1 Day 0	Visit 2 Month 2 *+/- 4 days*	Visit 3 Month 4 *+/- 4 days*	Visit 4 Month 6 *+/- 4 days*	Visit 5 Month 9 *+/- 4 days*	Visit 6 Month 12/ ET *+/- 4 days*	☎Day 374 *+/- 4 days*
Informed Consent	X						
Inclusion/Exclusion Criteria Review	X						
Medical History	X						
Physical Examination	X					X	
Vital Signs	X	X	X	X	X	X	
Electrocardiogram	X	X				X	
Review of Concomitant Medication	X	X	X	X	X	X	X
Urine Pregnancy Test (if applicable)	X						
Enroll Eligible Subjects	X						
Subject to Complete PAC-QOL, PAC-SYM	X	X	X	X	X	X	
Blood Sample for Chemistry Testing	X	X	X	X	X	X	
Blood Sample for Hematology Testing	X	X	X	X	X	X	
Urine Sample for Urinalysis	X	X	X	X	X	X	
Blood Sample for Serum Pregnancy Testing				X		X	
Dispense Study Drug and Rescue Bisacodyl	X	X	X	X	X		
Study Drug and Rescue Bisacodyl Accountability		X	X	X	X	X	
Assess Safety		X	X	X	X	X	X

Abbreviations: PAC-SYM, patient assessment of constipation symptom; PAC-QOL, patient assessment of constipation quality of life
Source: Applicant's submission, NDA 211281, Study 303 CSR, page 14/56.

Electrocardiograms (ECGs), QT Interval

Study 301

Visit 3

There were 4 (1.8%) patients in the lactitol arm and 6 (2.7%) patients in the Amitiza arm with a normal QTc at baseline (≤450 msec) that increased to >450 msec at Visit 3. There were no patients in either the lactitol or Amitiza treatment groups with a normal QTc at baseline (≤450 msec) that increased to >500 msec at Visit 3. Table 57 below describes the patients who had a normal QTc at baseline and increases in the QTc to >450 ms were observed at Visit 3.

Table 57: Patients With QTc Interval Change From Normal (≤450 ms) at Baseline to >450 ms at Visit 3 (Safety Population): Study 301

USUBJID	Age (Years)	Sex	Arm	QTc Interval (msec), Baseline	QTc Interval (msec), Visit 3	Change (msec)
BLI400301 (b) (6)	44	M	BLI400	446	456	10
BLI400301	19	F	BLI400	442	451	9
BLI400301	29	F	BLI400	428	455	27
BLI400301	79	F	BLI400	420	452	32
BLI400301	56	F	Lubiprostone	401	456	55
BLI400301	41	F	Lubiprostone	443	453	10
BLI400301	68	F	Lubiprostone	413	455	42
BLI400301	46	F	Lubiprostone	429	455	26
BLI400301	56	F	Lubiprostone	448	454	6
BLI400301	38	F	Lubiprostone	436	461	25

Source: Reviewer's analysis using Applicant's data, NDA 211281, Study 301, ADEG dataset, module 5.3.5.1.

Visit 4

There were 4 (1.8%) patients in the lactitol arm and 2 (0.9%) patients in the Amitiza arm with a normal QTc at baseline (≤450 msec) that increased to >450 msec at Visit 4. There were no patients in either the lactitol or Amitiza arms with a normal QTc at baseline (≤450 msec) that increased to >500 msec at Visit 4.

Table 58: Patients With QTc Interval Change From Normal (≤450 ms) at Baseline to >450 ms at Visit 4 (Safety Population): Study 301

USUBJID	Age (Years)	Sex	Arm	QTc Interval (msec), Baseline	QTc Interval (msec), Visit 4	Change (msec)
BLI400301 (b) (6)	44	M	BLI400	446	474	28
BLI400301	65	F	BLI400	432	456	24
BLI400301	41	F	BLI400	447	464	17
BLI400301	51	F	BLI400	441	454	13
BLI400301	21	F	Lubiprostone	446	457	11
BLI400301	41	F	Lubiprostone	446	452	6

Source: Reviewer's analysis using Applicant's data, NDA 211281, Study 301, ADEG dataset, module 5.3.5.1.

Visit 5

There were 2 (0.9%) patients in the lactitol arm and 2 (0.9%) patients in the Amitiza arm with a normal QTc at baseline (≤450 msec) that increased to >450 msec at Visit 5. There was 1 (0.5%) patient in the lactitol arm and no patients in the Amitiza arm with a normal QTc at baseline (≤450 msec) that increased to >500 msec at Visit 5.

Table 59: Patients With QTc Interval Change From Normal (≤450 ms) at Baseline to >450 ms at Visit 5 (Safety Population): Study 301

USUBJID	Age (Years)	Sex	Arm	QTc Interval (msec), Baseline	QTc Interval (msec), Visit 5	Change (msec)
BLI400301 (b) (6)	48	F	BLI400	433	451	18
BLI400301	34	F	BLI400	428	511	83
BLI400301	45	F	Lubiprostone	445	454	9
BLI400301	30	F	Lubiprostone	425	453	28

Source: Reviewer's analysis using Applicant's data, NDA 211281, Study 301, ADEG dataset, module 5.3.5.1.

Early Termination Visit

There were 3 (1.4%) patients in the lactitol arm and no patients in the Amitiza arm with a normal QTc at baseline (≤450 msec) which increased to >450 msec at early termination. These 3 patients did not withdraw from the trial due to heart problems. There were no patients in the lactitol arm with a normal QTc at baseline (≤450 msec) which increased to >500 msec at early termination.

Table 60: Patients With QTc Interval Change From Normal (≤450 ms) at Baseline to >450 ms at Early Termination (Safety Population): Study 301

USUBJID	Age (Years)	Sex	Arm	Analysis relative day	QTc Interval (msec), Baseline	QTc Interval (msec), early termination	Change (msec)
BLI400301 (b) (6)	25	F	BLI400	24	446	456	10
BLI400301	59	F	BLI400	34	437	451	14
BLI400301	37	F	BLI400	41	398	453	55

Source: Reviewer's analysis using Applicant's data, NDA 211281, Study 301, ADEG dataset, module 5.3.5.1.

Study 302

Table 61: Patients With QTcF Interval Change From Normal (≤450 ms) at Baseline to >450 ms at Visit 8 (FDA Safety Population): Study 302

USUBJID	Age (Years)	Sex	Arm	QTcF Interval, aggregate (msec), Baseline	QTcF Interval, aggregate (msec), Visit 8	Change (msec)
BLI400302 (b) (6)	30	F	BLI400	427	451	24
BLI400302	37	F	BLI400	408	457	49
BLI400302	62	F	BLI400	442	463	21
BLI400302	59	F	BLI400	425	464	39
BLI400302	81	F	BLI400	435	457	22
BLI400302	37	F	Placebo	429	452	23
BLI400302	69	F	Placebo	441	453	12
BLI400302	40	F	Placebo	433	453	20
BLI400302	67	M	Placebo	436	475	39
BLI400302	51	F	Placebo	428	461	33
BLI400302	26	F	Placebo	446	461	15
BLI400302	41	F	Placebo	416	457	41

Source: Reviewer's analysis using Applicant's data, NDA 211281, Study 302, ADEG dataset, module 5.3.5.1.

Hypertension

Of note, the trials were not prospectively designed to evaluate BP, which limited our ability to adequately evaluate the relationship between lactitol and hypertension. There are several elements that may affect BP measurements, such as proper cuff size and placement, wrapping the cuff over clothing, time of day, and patient position; the BP measurements were not standardized in the trial. In addition, the protocols did not specifically exclude patients with hypertension and many patients had hypertension or associated risk factors at baseline. The protocols did not specify the criteria for classifying blood pressure changes as AEs, which likely resulted in variation across sites' and investigators' reporting of blood pressure-related AEs. Therefore, it was difficult to determine whether changes in BP were truly related to lactitol. These limitations were considered in the determination of whether a causal relationship exists between lactitol and hypertension. Refer to Section 15.4.2 above for a discussion of potential drug-drug interactions.

The case report forms and narratives were reviewed for the 3 patients (BLI400301-(b) (6), BLI400302-(b) (6), and BLI400302-(b) (6)) who had no baseline cardiovascular risk factors. Although no risk factors were reported at baseline, the baseline BPs for these patients would be considered elevated (systolic BP 120-129 mm Hg and diastolic BP <80 mm Hg) or hypertensive (systolic BP ≥130 mm Hg or diastolic BP ≥80 mm Hg) based on the clinical practice guidelines from the American College of Cardiology/American Heart Association Task Force.[21] For these 3 patients, other confounding factors were identified (e.g., elevated blood creatine kinase, glucose tolerance impairment) or the available information was incomplete. Therefore, the team could not establish a relationship between lactitol use and hypertension.

In the phase 3 trials, there were 7 lactitol-treated patients who had an AE of hypertension or blood pressure increased and were taking anti-hypertensives at the time of the AE (refer to Item 8 – Table 1, IR response received May 21, 2019). These patients had a reported history of hypertension.

[21] Whelton, PK, Carey, RM, Aronow, WS et al.
2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018 May 15;71(19):e127-e248.

Table 62: Summary of Patients with Baseline Systolic Blood Pressure <130 mm Hg and Diastolic Blood Pressure <80 mm Hg[1] and Increases in Systolic or Diastolic Blood Pressure by 10 or 20 mm Hg at Any Visit During Study 302 (FDA Safety Population)

	Lactitol n/N (%) (N=291)[2]	Placebo n/N (%) (N=302)[2]
Baseline systolic BP <130 mm Hg and diastolic BP <80 mm Hg[1]	131 (45.0%)	144 (47.7%)
Blood Pressure Parameter (systolic or diastolic) Change from Baseline		
DBP Chg>10 mm Hg	50 (38.2%)	55 (38.2%)
SBP Chg>10 mm Hg	69 (52.7%)	73 (50.7%)
SBP Chg>20 mm Hg	28 (21.4%)	32 (22.2%)

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure
[1] Based on the clinical practice guidelines from the American College of Cardiology/American Heart Association Task Force.
[2] Total N is FDA safety population excluding data from site 32.

In addition, a similar analysis was performed for all patients, regardless of whether the baseline BP was normal, using the FDA safety population. The results are summarized below.

Table 63: Summary of All Patients With Increases in Systolic or Diastolic Blood Pressure by 10 or 20 mm Hg at Any Visit During Study 302 (FDA Safety Population)

Blood Pressure Parameter (systolic or diastolic) Change from Baseline	Lactitol n/N (%) (N=291)[1]	Placebo n/N (%) (N=302)[1]
DBP Chg>10 mm Hg	85 (29.2%)	89 (29.5%)
SBP Chg>10 mm Hg	125 (43.0%)	140 (46.4%)
SBP Chg>20 mm Hg	48 (16.5%)	53 (17.5%)

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure
[1] Total N is FDA safety population excluding data from site 32.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Tamal Chakraborti, Ph.D.	ODE 3/DGIEP	Sections: Section 5	_X_ Authored ___ Approved
	Signature: Tamal K. Chakraborti -S Digitally signed by Tamal K. Chakraborti -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300143215, cn=Tamal K. Chakraborti -S Date: 2020.02.07 10:51:21 -05'00'			
Nonclinical Supervisor	Sushanta Chakder, Ph.D.	ODE 3/DGIEP	Sections: 5	___ Authored _X_ Approved
	Signature: Sushanta K. Chakder -S Digitally signed by Sushanta K. Chakder -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300144003, cn=Sushanta K. Chakder -S Date: 2020.02.07 11:38:12 -05'00'			
Associate Director, Nonclinical	Ronald Wange, Ph.D.	OND IO	Sections: 5	___ Authored _X_ Approved
	Signature: Ronald L. Wange -S Digitally signed by Ronald L. Wange -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300236480, cn=Ronald L. Wange -S Date: 2020.02.07 11:49:29 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Jie (Jenny) Cheng, Ph.D.	OTS/OCP/DIIP	Sections: 6, 15.4	_X_ Authored ___ Approved
	Signature: Jie Cheng -S (Affiliate) Digitally signed by Jie Cheng -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013573366, cn=Jie Cheng -S (Affiliate) Date: 2020.02.07 12:06:41 -05'00'			
Clinical Pharmacology Team Leader	Jie (Jack) Wang, Ph.D.	OTS/OCP/DTPM	Section: 6, 15.4	___ Authored _X_ Approved
	Signature: Jie Wang -S Digitally signed by Jie Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jie Wang -S, 0.9.2342.19200300.100.1.1=2000739081 Date: 2020.02.07 12:20:36 -05'00'			
Clinical Pharmacology Division Deputy Director	Doanh Tran, Ph.D.	OTS/OCP/DCEP	Sections: 6, 15.4	___ Authored _X_ Approved
	Signature: Doanh C. Tran -S Digitally signed by Doanh C. Tran -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Doanh C. Tran -S, 0.9.2342.19200300.100.1.1=1300378169 Date: 2020.02.07 12:49:25 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Irena Lavine, M.D.	ODEIII/DGIEP	Sections: 2, 3, 7.1, 8, 15.2, 15.7	_X_ Authored ___ Approved
	Signature: Irena G. Lavine -S Digitally signed by Irena G. Lavine -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001356661, cn=Irena G. Lavine -S Date: 2020.02.10 15:36:26 -05'00'			
Clinical Team Leader	Juli Tomaino, M.D.	ODEIII/DGIEP	Authored Sections: 1.1, 1.2, 1.3 Approved: All sections	_X_ Authored _X_ Approved
	Signature: Juli A. Tomaino -S Digitally signed by Juli A. Tomaino -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001149989, cn=Juli A. Tomaino -S Date: 2020.02.11 09:11:02 -05'00'			
Division Associate Director (Clinical)	Jessica Lee, M.D., M.M.Sc.	ODEIII/DGIEP	Authored Section: 14 Approved: All sections	_X_ Authored _X_ Approved
	Signature: Jessica J. Lee -S Digitally signed by Jessica J. Lee -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jessica J. Lee -S, 0.9.2342.19200300.100.1.1=2000596373 Date: 2020.02.11 10:20:39 -05'00'			
ODEIII Deputy Director	Victor Crentsil, M.D., M.H.S.	ODEIII	Sections: All sections	___ Authored _X_ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Paul Imbriano, Ph.D.	ODE III/DB III	Sections: 7.2, 8.1, 15.5, 15.6	_X_ Authored ___ Approved
	Signature: Paul M. Imbriano -S Digitally signed by Paul M. Imbriano -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001738951, cn=Paul M. Imbriano -S Date: 2020.02.10 15:10:07 -05'00'			
Statistical Team Leader	George Kordzakhia, Ph.D.	ODE III/DB III	Approved Sections: 7.2, 8.1, 15.5, 15.6	__ Authored _X_ Approved
	Signature: George Kordzakhia -S Digitally signed by George Kordzakhia -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300390764, cn=George Kordzakhia -S Date: 2020.02.10 16:13:05 -05'00'			
Division Deputy Director (OB/DBIII)	Gregory Levin, Ph.D.	ODE III/DB III	Sections: 1, 7, 8, 15.5, 15.6	___ Authored _X_ Approved
	Signature: Gregory P. Levin -S Digitally signed by Gregory P. Levin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001127703, cn=Gregory P. Levin -S Date: 2020.02.10 16:47:38 -05'00'			

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/s/

ANDREW R KELLEHER
02/12/2020 01:54:05 PM

VICTOR CRENTSIL
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