CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211801Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memo

Date:	9/11/2019
Reviewer:	Monisha Billings, DDS, MPH, PhD - Epidemiologist Division of Epidemiology I
Team Leader:	Patricia Bright, MSPH, PhD - Lead Epidemiologist Division of Epidemiology I
Deputy Director:	CAPT. Sukhminder K. Sandhu, PhD, MPH, MS - Supervisor Division of Epidemiology I
Subject:	ARIA Sufficiency Memo
Drug Name(s):	IBSRELA (Tenapanor)
Application Type/Number:	NDA 211801
Applicant/sponsor:	Ardelyx, Inc.
OSE RCM #:	2019-890

EXECUTIVE SUMMARY

Memo type	
-Initial	
-Interim	
-Final	x
Source of safety concern	
-Peri-approval	x
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	x
-No	
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

On May 23, 2019, the Division of Epidemiology – I (DEPI-I) coordinated a signal assessment meeting involving team members from the Division of Gastroenterology and Inborn Errors Products (DGIEP), Division of Biometrics VII (DB7), and Sentinel in the Office of Surveillance and Epidemiology. After an in-depth discussion, the team determined that the Active Risk Identification and Analysis (ARIA) system within Sentinel would be sufficient for detecting an inflammatory bowel disease (IBD) risk among irritable bowel syndrome (IBS) patients treated with Tenapanor.

1. BACKGROUND INFORMATION

1.1. Medical Product

IBSRELA (tenapanor hydrochloride), under review by the FDA (NDA 211801) is a locally acting inhibitor of the Sodium/Hydrogen Exchanger 3 (NHE3), indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults, with a recommended dosage of 50 mg, orally twice daily in adults. Irritable bowel syndrome with constipation is a functional gastrointestinal (GI) disorder characterized by recurrent abdominal pain related to defecation, with hard or infrequent stools. The worldwide prevalence of IBS has been estimated to be about 11% and the prevalence of IBS-C among the IBS subtypes is about 35%.[1] Biomarkers for this syndrome have not been identified and the Rome-IV diagnostic criteria are currently used for diagnosis.[2] The main goals of treatment of IBS-C is to improve symptoms, i.e., improve stool consistency, and increase frequency of bowel movements, and reduce abdominal pain.

By modulating sodium uptake in the intestinal tract and reducing sodium uptake, resulting in an increase in net fluid volume in the intestinal tract, tenapanor has been shown to produce softer and looser stools.

Pharmacologic properties of tenapanor indicate a theoretical safety concern for the development of inflammatory bowel disease (IBD) among those on tenapanor for IBS-C. IBD is a chronic, relapsing inflammatory disease of the intestine, presenting with symptoms of diarrhea, abdominal pain, rectal bleeding, weight loss, arthritis and fatigue (non-specific). The etiology of IBD is not clear. Genetics, dysregulated microbiome, environmental exposures including certain drugs all may be potential triggers of IBD. Colonoscopy with biopsy is the gold standard for diagnosis. One study found that those with IBS had a 15 times higher risk of IBD than those without IBS. The median time between diagnosis of IBS and IBD is 2.1 years and the average time is 2-3 years.[1,3] IBD is categorized as ulcerative colitis (UC) and Crohn's disease (CD).

1.2. Describe the Safety Concern

There is biologic plausibility for the development of inflammatory bowel disease (IBD) among those exposed to tenapanor based on the drug's mechanism of action, preclinical data, and an imbalance observed in some IBD symptoms in clinical trial data (see Table 1, Clinical Trials Section below), although the trial lacked confirmatory assessment with colonoscopy. The concern remains theoretic as confirmatory assessments with colonoscopies were not undertaken in the clinical trials, but there remains the potential for a serious chronic risk.

Drug's mechanism of action:

Tenapanor, an NHE3 inhibitor, is a secretagogue indicated for IBS-C; diarrhea is the most common adverse event in clinical trials, with the tenapanor arm reporting a higher risk of diarrhea than the placebo arm (RR=5.78, 95% CI: 3.55 – 9.44). It has been hypothesized that the drug may contribute to gut dysbiosis by blocking NHE3 and increasing intestinal lumen pH,

leading to intestinal inflammation and predisposing patients to IBD[4]. This is a theoretical risk which is yet to be confirmed in studies.

Preclinical data[i]

Preclinical studies have shown that in mice with targeted deletion of the NHE3 gene have a shortened lifespan due to a syndrome of chronic diarrhea, abdominal distention, metabolic acidosis and hyponatremia.[5] NHE3 knock-out mice also develop distal colitis characterized by neutrophil infiltration and depletion of goblet cells. Alkalization of the gut may alter the microbiome in these animals.[6] NHE3 knock-out animals develop spontaneous IBD and have more severe experimental IBD.[6-8] Studies have also reported mice with infectious colitis and IBD to have reduced expression of NHE3.[9-12] In rats, a decrease in goblet cells at doses of ≥0.1mg/Kg/day of tenapanor (14-day repeat toxicity) has been reported. Diarrhea and dehydration with rectal necrosis, cecal hemorrhage, and in some death at ≥30 mg/Kg/day (28-day repeat dose) has been found.

Human studies

In humans, patients with inactivating mutations in the NHE3 gene develop congenital sodium diarrhea in infancy, and if they survive, are predisposed to inflammatory bowel disease when older.[4] It has been shown that patients with inactivating mutations in NHE3 or activating mutations in guanylate cyclase share a phenotype of congenital sodium diarrhea and IBD.[4] Further, it has been found that patients with IBD have decreased expression of NHE3.[13]

Clinical trials

Two pivotal (randomized, double-blind, placebo-controlled) phase 3 studies and three safety analysis datasets (Core IBS-C, ESRD, CKD) were submitted by the sponsor. In these clinical studies, the most common adverse event leading to discontinuation of tenapanor was diarrhea.

Rectal bleeding, as a potential symptom of IBD was an adverse event (AE) of interest in <2% of tenapanor-treated patients, at an incidence greater than placebo during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 treatment period, although it can also be a symptom of other processes.

There were seven cases of rectal bleeding in the tenapanor arm and one in the placebo arm. Rectal bleeding began 2-64 days after starting the drug in the clinical trials, with onset after 1-2 months in the majority of the patients and after 2 days in one patient. Colonoscopy was not performed in all eight cases of rectal bleeding since the trial protocol did not specify colonoscopy to be performed in new-onset cases of rectal bleeding; only one subject in the tenapanor arm and one in the placebo arm had a colonoscopy. Therefore, the clinical program could not confirm the safety concern.

Further, of the seven cases of rectal bleeding in the tenapanor arm, four had blood and diarrhea, after starting the drug, suggestive of IBD. The one patient who had a colonoscopy, was least

[i] Adapted from Elizabeth Mannick Clinical Review, DGIEP.

affected with no diarrhea, had only microscopic blood in stool, and colonoscopy was negative for colitis/IBD.

Table 1: AEs in Clinical Trials for IBS-C [ii]

Adverse Event	Tenapanor	Placebo	Relative Risk (RR)	Risk Difference (RD)
Rectal Bleeding: All IBS-C	7/1343 (0.52%)	1/738 (0.14%)	3.85 (95% CI: 0.47- 31.20)	0.004 (95% CI: -0.0008 - 0.009)
Rectal Bleeding: Study 301	4/309 (1.29%)	0/301 (0%)	-	0.13 (95% CI: 0.0003 - 0.026)
Rectal Bleeding: Study 302	3/293 (1.02%)	1/293 (0.34%)	3.00 (95% CI: 0.31- 28.67)	0.007 (95% CI: -0.006 - 0.02)

Safety Signal Classification

Based on the aforementioned evidence, there is a potential risk of IBD with exposure to tenapanor among IBS-C cases.

Labelling

Section 6.1 Adverse Reactions, Clinical Trials Experience of the proposed label for tenapanor reports:

"Less Common Adverse Reactions

Adverse reactions reported in less than 2% of IBSRELA-treated patients and at an incidence greater than placebo during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 were: rectal bleeding and abnormal gastrointestinal sounds."

Product Class - Linaclotide label reports rectal hemorrhage in postmarketing experience.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

[ii] Adapted from Elizabeth Mannick SAM Presentation, DGIEP. RR and RD computed by DEPI-I.

1.4. Statement of Purpose

The regulatory goal of ARIA is signal detection (i.e. postmarketing surveillance) to evaluate whether postmarket data indicate an IBD risk among IBS patients treated with tenapanor.

(b) (4)

[redacted]

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6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

The tools in ARIA are sufficient to assess an IBD risk among IBS patients treated with tenapanor.

7 NEXT STEPS

This study was determined to be ARIA sufficient and will be conducted in the Sentinel system. FDA will monitor the accrual of tenapanor exposure to identify when adequate exposure has been captured in Sentinel to allow for the assessment.

8 REFERENCES

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 7, 2019

To: Mary Chung, Regulatory Project Manager, (DGIEP)

Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for IBSRELA (tenapanor) tablets, for oral use

NDA: 211801

In response to DGIEP's consult request dated November 1, 2018, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for the original NDA submission for Ibsrela.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DGIEP on July 30, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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MEETA N PATEL
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 7, 2019
To:	Dragos Roman, MD Acting Director **Division of Gastroenterology and Inborn Error Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	IBSRELA (tenapanor)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 211801
Applicant:	Ardelyx, Inc.

1 INTRODUCTION

On September 12, 2018, Ardelyx, Inc., submitted for the Agency's review a New Drug Application (NDA) New Molecular Entity (NME) 211801 IBSRELA (tenapanor) tablets, for oral use. The Applicant proposes IBSRELA (tenapanor) tablets for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) on July 3, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for IBSRELA (tenapanor) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft IBSRELA (tenapanor) tablets MG received on September 12, 2018, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on July 31, 2019.
- Draft IBSRELA (tenapanor) tablets Prescribing Information (PI) received on September 12, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 31, 2019.
- Approved TRULANCE (plecanatide) tablets, for oral use labeling dated January 19, 2017.
- Approved LINZESS (linaclotide) capsules, for oral use labeling dated March 8, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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DMPP-OPDP review of tenapanor (IBSRELA) NDA 211801 MG

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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2018288
IND/NDA/BLA Number/ Referenced IND for NDA/BLA:	NDA 211801/ Referenced IND 108732
Applicant/Applicant:	Ardelyx, Inc.
Established Name/Trade Name:	Tenapanor/IBSRELA
Indication:	Treatment of irritable bowel syndrome with constipation (IBS-C) in adults.
Meeting Type/Deliverable:	NDA Review
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Clinical Reviewer	Betsy (Elizabeth) Mannick
Clinical Team Leader (TL)	Tara Altepeter
Review Division Project Manager:	Mary Chung
COA Reviewer:	Susan Pretko
COA TL:	Sarrit Kovacs
COA Associate Director:	Elektra Papadopoulos
Date Consult Request Received:	09/21/2018
Date COA Review Completed:	07/17/2019

Please check all that apply: ☐Rare Disease/Orphan Designation
☐Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Gastroenterology and Inborn Errors Products (DGIEP) regarding NDA 211801. The applicant has completed phase 3 of their drug development program and has submitted a section 505(b)(1) NDA. The proposed indication is treatment of adult patients with irritable bowel syndrome with constipation (IBS-C).

The applicant proposed labeling claims based on the following patient-reported outcome (PRO) instruments used in their phase 3 clinical trials (Study TEN-01-301 and TEN-01-302, or studies 301 and 302, respectively) in adult patients ages 18-75 years that meet the definition of IBS-C using Rome III Criteria for the diagnosis of IBS.

Table 1. COA(s) included in the applicant's Integrated Summary of Efficacy (ISE) Report

COA Name (COA Type)	Concept(s)/Endpoints(s)	Endpoint Position[1]	Copy of COA
IBS Symptom eDiary/Interactive Voice Response System (IVRS)(PRO)	6/12-week Overall combined responder rate (Complete Spontaneous Bowel Movements (CSBMs) and abdominal pain)	Primary	Appendix 1
IBS Symptom eDiary/ IVRS(PRO)	1. 6/12-week CSBM responder rate 2. 6/12-week abdominal pain responder rate 3. 9/12-week overall combined responder rate 4. 9/12-week CSBM responder rate 5. 9/12-week abdominal pain responder rate	Key Secondary	Appendix 1
IBS Symptom eDiary/ IVRS(PRO)	1. Durable overall responder rates 2. Durable CSBM responder rates 3. Durable abdominal pain responder rate 4. Weekly overall responder rate 5. Weekly CSBM responder rate 6. Weekly abdominal pain responder rate 7. Weekly proportion of subjects with ≥3 CSBMs 8. Average weekly CSBMs 9. Average weekly SBMs 10. Average weekly stool consistency (using the Bristol Stool Form Scale) 11. Average weekly straining score 12. 6/12- and 9/12-week overall abdominal discomfort responder rate 13. 6/12- and 9/12-week overall abdominal bloating responder rate 14. 6/12- and 9/12-week overall abdominal cramping responder rate 15. 6/12- and 9/12-week overall abdominal fullness responder rate 16. Weekly abdominal discomfort responder rate 17. Weekly abdominal bloating responder rate 18. Weekly abdominal cramping responder rate 19. Weekly abdominal fullness responder rate 20. Average weekly abdominal pain score 21. Average weekly abdominal discomfort score 22. Average weekly abdominal bloating score 23. Average weekly abdominal cramping score 24. Average weekly abdominal fullness score	Other Secondary	Appendix 1

[1] Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.

	25. Weekly IBS severity score 26. Weekly constipation severity score 27. Weekly adequate relief of IBS symptoms 28. Weekly degree of relief of IBS symptoms score		
Bristol Stool Form Scale (BSFS)	Stool Consistency	Secondary	Appendix 2

The applicant obtained statistically significant results for the pre-specified primary endpoint in each of the two phase 3 clinical trials (Study 301 and Study 302) but did not reach a statistically significant result on the first key secondary endpoint in Study 301. The Division requested COA Staff input on the other secondary endpoints that may be reasonable to include in the labeling based on whether the data are adequate and clinically meaningful.

The Division's COA consult request form and the applicant's proposed draft labeling only focus on IBS symptoms captured by the IBS Symptom eDiary/IVRS; therefore, the present COA review focuses only on those IBS symptoms and not on any of the exploratory endpoints in the phase 3 clinical trials.

The following is a high-level summary of conclusions based on the present COA review:

- The applicant has not provided sufficient evidence to (b) (4) [redacted]
- The applicant's submitted data appears to sufficiently demonstrate meaningful within-patient change based on the IBS disease severity and Constipation severity anchors for change in average weekly complete spontaneous bowel movements (CSBMs), decrease in abdominal pain score, change in average weekly SBMs, and change in stool consistency from baseline to week 12. This reviewer defers to the Division regarding acceptability of the applicant's proposed labeling claims.
- This reviewer does not agree that the anchor-based data are sufficient to demonstrate meaningful within-patient change in the average (b) (4) [redacted] from baseline to week 12.

B. CLINICAL OUTCOME ASSESSMENT REVIEW

1 BACKGROUND AND MATERIALS REVIEWED

Regulatory Background

The applicant submitted the original NDA application under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act on September 12, 2018.

COA Tracking ID: C2018288
NDA Number/Referenced IND: NDA 211801 // Referenced IND 108732

Previous COA Reviews

There are no previous COA Reviews for the referenced IND. The following are previous COA reviews that are relevant for the proposed indication.

- C2017264_NDA 208745 (Trulance (plecanatide))_DGIEP (IBS-C)_Kovacs_Finalized in DARRTS 11/13/2017 (DARRTS Reference ID: 4180545).
- C2017053_IND 126560 (Linzess (linaclotide))_DGIEP (IBS-C)_Kovacs_Finalized in DARRTS 11/20/2017 (DARRTS Reference ID: 4174640).
- AT 2016-046_NDA 208745 (Trulance (plecanatide))_DGIEP (CIC)_Kovacs_Finalized in DARRTS 11/22/2016 (DARRTS Reference ID: 4017868)
- AT 2015-152_NDA 202811 (Linzess (linaclotide))_DGIEP (IBS-C)_Kovacs_Finalized in DARRTS 02/09/2016 (DARRTS Reference ID: 3884859).
- AT 2014-157_sNDA 202811 (Linzess (linaclotide))_DGIEP (IBS-C)_Kovacs_Finalized in DARRTS 02/23/2015 (DARRTS Reference ID: 3705799).

Disease Background

Irritable bowel syndrome (IBS) is a common, chronic disorder characterized by abdominal pain with associated alterations in bowel function. These changes in bowel patterns may manifest as diarrhea, constipation, or a mix between the two. IBS is considered a functional GI disorder and the diagnosis of IBS has been described by the Rome III criteria as summarized in Table 1-1 from the Integrated Summary of Efficacy (provided below).

Table 1–1 Rome III Criteria for the Diagnosis of IBS

Diagnostic Criteria[a]
Recurrent abdominal pain or discomfort[b] at least 3 days per month in the last 3 months associated with 2 or more of the following:
1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

IBS=irritable bowel syndrome

[a] Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

[b] Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 days a week during screening evaluation for subject eligibility.

Investigational Product

Tenapanor is a gastrointestinally restricted, locally acting inhibitor of NHE3, an antiporter expressed on the apical surface of the small intestine and colon primarily responsible for the absorption of dietary sodium. By actively reducing the dietary uptake of sodium from the small intestine and colon, tenapanor increases water secretion into the intestinal lumen, which accelerates intestinal transit time and results in a softer stool consistency in both animals and humans.

Other Materials Reviewed

- Ardelyx submission (SDN #0020(20)) received 03/13/2019, containing the IR response to request for qualitative data

- Ardelyx submission (SDN #0018(18)) received February 02/19/2019, containing the IR response with data tables and empirical cumulative distribution function (eCDF) and probability density function (PDF) curves.
- Internal Team Meeting Discussions held [redacted] (b) (5)
- DGIEP Clinical Outcome Assessments Consult Request dated 09/20/2018, entered into DARRTS 09/21/2018 (DARRTS Reference ID: 4324407).
- Ardelyx submission (SDN #0001 (1)) received 09/12/2018, containing the following:
  - Study 301 Protocol and Statistical Analysis Plan (SAP)
  - Study 303 Protocol and SAP
  - ISE Report, Tables, Figures, and Listings, and SAP
  - Draft label
- IND 108732. Meeting Minutes for the pre-NDA meeting held on 05/01/2018. Finalized in DARRTS 05/10/2018 (DARRTS Reference ID: 4261209).
- Linzess (linaclotide) [Labeling – package insert}. Irvine, CA: Allergan USA, Inc.; 2017.
- FDA Guidance for Industry: Irritable Bowel Syndrome – Clinical Evaluation of Products for Treatment. May 2012.

2 FIT-FOR-PURPOSE SUMMARY

Table 2. Fit-for-purpose assessment (based on available evidence)

COA Name(s)	Attribute sufficiently established[2]	Supported by:	Location of Supporting Materials
IBS Symptom eDiary/ IVRS	☐ Yes ☒ Potentially - insufficient evidence available; additional information is needed ☐ No	☒ Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) ☐ Evidence of content validity ☒ Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) ☐ COA well-defined and concept is able to be accurately communicated ☐ COA is sensitive to detect change ☐ COA is culturally adapted and adequately translated, if appropriate	FDA Guidance for Industry: Irritable Bowel Syndrome – Clinical Evaluation of Products for Treatment. May 2012.

Reviewer's comment(s):
The IBS Symptom eDiary/IVRS developed by the applicant is fit-for-purpose to assess complete spontaneous bowel movements (CSBMs) and abdominal pain, as described in the

[2] See Sections 5 and 6 of this COA review for more detailed information.

FDA Guidance for Industry for Products to treat Irritable Bowel Syndrome. However, while the assessment of multiple different abdominal symptoms has face validity, there is insufficient evidence to determine whether it is fit for regulatory purposes in terms of patients being able to differentiate among the concepts of abdominal fullness, abdominal bloating, abdominal cramping, and abdominal discomfort; and whether these concepts are considered meaningfully different from abdominal pain. Refer to the Reviewer's comment(s) in "Section 7: Content Validity" of this review.

3 CONTEXT OF USE

3.1 Clinical Trial Population

The pooled population for studies TEN-01-301, TEN-01-302, and D5612C0001 included 714 adult subjects aged 18 to 75 years. Subjects were ambulatory and met the definition of IBS-C using Rome III Criteria for the diagnosis of IBS.

A complete list of the inclusion and exclusion criteria is summarized in each respective study protocol and in the Integrated Summary of Efficacy.

Reviewer's comment(s):
Subjects randomized into the studies were from approximately 100 to 120 U.S. clinical centers across the Northeast, East, Southeast, Midwest, Midsouth, and West geographic regions.

3.2 Clinical Trial Design

Tables 3 and 4 describe the clinical trial design of Studies 301 and 302, respectively.

Table 3. Clinical Trial Design for Study 301

Trial Phase	Trial Design	Trial Duration*	Registration Intent
Phase 3	☐ Single arm ☐ Open label ☒ Double-blind ☒ Randomized ☒ Placebo-/Vehicle-controlled ☐ Active comparator-controlled ☐ Cross-over ☐ Multinational ☐ Non-inferiority	12 weeks	Yes

*Length of the treatment period

Table 4. Clinical Trial Design for Study 302

Trial Phase	Trial Design	Trial Duration*	Registration Intent
Phase 3	☐ Single arm ☐ Open label ☒ Double-blind	26 weeks	Yes

Trial Phase	Trial Design	Trial Duration*	Registration Intent
	☒ Randomized ☒ Placebo-/Vehicle-controlled ☐ Active comparator-controlled ☐ Cross-over ☐ Multinational ☐ Non-inferiority		

*Length of the treatment period

Reviewer's comment(s):
Refer to the ISE Report for more details on the clinical trial design for each study.

3.3 Endpoint Position, Definition, and Assessment Schedule

Table 5 describes the efficacy analysis per the ISE Documentation of Statistical Methods.

Table 5. Endpoint Position, Definition, and Assessment Schedule for the Efficacy Analyses

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Primary	IBS Symptom eDiary/IVRS; daily patient-reported outcome (PRO)	6/12 week overall combined weekly responder rate (abdominal pain and CSBM responder)	Subject who had at least 6 weeks during the 12-week treatment period where the subject was considered an overall combined weekly responder (abdominal pain and CSBM responder)	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	6/12-week CSBM responder rate	Subject who had at least 6 weeks during the 12-week treatment period where the subject was considered a CSBM weekly responder	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	6/12-week abdominal pain responder rate	Subject who had at least 6 weeks during the 12-week treatment period where the subject was considered an abdominal pain weekly responder	☒ Weekly score (based on daily eDiary)

COA Tracking ID: C2018288
NDA Number/Referenced IND: NDA 211801 // Referenced IND 108732

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	9/12-week overall responder rate	Subject who had at least 9 weeks during the 12-week treatment period where the subject was considered an overall weekly responder and the average weekly CSBMs were ≥3 for the same weeks	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	9/12-week CSBM responder rate	Subject who had at least 9 weeks during the 12-week treatment period where the subject was considered a CSBM weekly responder and the average weekly CSBMs were ≥3 for the same week	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	9/12-week abdominal pain responder rate	Subject who had at least 9 weeks during the 12-week treatment period where the subject was considered an abdominal pain weekly responder	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Durable overall responder rate	A subject was considered a durable overall responder if the subject was a 9/12 week overall responder for the first 12 weeks of treatment and, additionally, the subject's last 3/4 weeks of the first 12 weeks of the treatment period also met response criteria	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Durable CSBM responder rate	A subject was considered a durable overall CSBM responder if the subject was a 9/12-week overall CSBM responder for the first 12 weeks of treatment and, additionally, the subject's last 3/4 weeks of the first 12 weeks of the treatment period also met response criteria	☒ Weekly score (based on daily eDiary)

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Durable abdominal pain responder rate	A subject was considered a durable overall abdominal pain responder if the subject was a 9/12 week overall abdominal pain responder for the first 12 weeks of treatment and, additionally, the subject's last 3/4 weeks of the first 12 weeks of the treatment period also met response criteria	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Weekly overall responder rate	Combined weekly responder: Subject who was both a CSBM weekly responder and an abdominal pain weekly responder for the same week.	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Weekly CSBM responder	Subjects who met the CSBM response criterion (the sum of the number of CSBMs reported during each day of the defined weekly period divided by the number of days CSBMs were reported multiplied by 7) for that week	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Weekly abdominal pain responder rate	Subjects who met the abdominal pain response criterion (a decrease of 30% or more of percent change in average weekly worst abdominal pain from baseline) for that week	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Weekly proportion of subjects with ≥3 CSBMs		☒ Weekly score (based on daily eDiary)

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Average weekly CSBMs	The sum of the number of CSBMs reported during each day of the defined weekly period divided by the number of days the phone diary was completed multiplied by 7	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Average weekly SBMs	The sum of the number of SBMs reported during each day of the defined weekly period divided by the number of days the phone diary was completed multiplied by 7	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Average weekly stool consistency	Calculated as the average score (using the BSFS scale) for all valid SBMs during the week. For purposes of calculating an average, days with no stools were scored a 0	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Average weekly straining score	Straining was scored for each SBM using the scale 1=not at all, 2=a little bit, 3=a moderate amount, 4=a great deal, 5=an extreme amount. Average weekly straining score was calculated as the average score for all valid SBMs during the week	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	6/12 & 9/12-week abdominal symptom[1] responder rate	Subject who had at least 6 weeks and 9 weeks during the 12-week treatment period where the subject was considered a weekly responder for each abdominal symptom	☒ Weekly score (based on daily eDiary)
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Weekly abdominal symptoms responder rate	Subjects who met the response criterion for that week, for each abdominal symptom	☒ Weekly score (based on daily eDiary)

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Secondary ☒ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Average weekly abdominal symptoms responder rate	Average scores for all days during a given week	☒ Weekly score (based on daily eDiary)
Secondary ☐ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Weekly IBS severity score	IBS severity rated on a weekly basis using the scale: 1=none, 2=mild, 3=moderate, 4=severe, 5=very severe. Baseline for the severity ratings was the average of the 2 ratings during the screening period	☒ Weekly score (based on daily eDiary)
Secondary ☐ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Weekly constipation severity score	Constipation severity rated on a weekly basis using the scale: 1=none, 2=mild, 3=moderate, 4=severe, 5=very severe. Baseline for the severity ratings was the average of the 2 ratings during the screening period	☒ Weekly score (based on daily eDiary)
Secondary ☐ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Weekly adequate relief of IBS symptoms	Adequate relief of IBS symptoms (1=yes, 2=no) asked on a weekly basis	☒ Weekly score (based on daily eDiary)
Secondary ☐ Multiplicity adjusted	IBS Symptom eDiary/IVRS; daily PRO	Weekly degree of relief of IBS symptoms score	Degree of relief of IBS symptoms (1-7 scale: 1=completely relieved, 2=considerably relieved, 3=somewhat relieved, 4=unchanged, 5=somewhat worse, 6=considerably worse, 7=as worse as I can imagine) scored on a weekly basis	☒ Weekly score (based on daily eDiary)

[1] "Abdominal symptoms" includes 5 items: abdominal pain, abdominal discomfort, abdominal bloating, abdominal fullness, and abdominal cramping.

Reviewer's comment(s):
Per the ISE report, should a subject not have data reported for a given week (due to a gap in reporting, less than 4 response days in a given week, or due to discontinuation), the subject

was considered to be a non-responder for that week. This reviewer defers to Office of Biostatistics (OB) statistical reviewer on the appropriateness of this method and any impacts it may have on interpretation of the clinical trial data.

Per the ISE, the key secondary efficacy endpoints for each study were tested using a sequential testing procedure at level α=0.05, following a sequential order. Following discussion at the internal labeling meeting on December 18, 2018, this approach appears appropriate.

3.4 Labeling or promotional claim(s) based on the COA

The applicant has proposed the following specific targeted COA-related labeling claims in section 14 of the draft labeling.

14 CLINICAL STUDIES

The efficacy of IBSRELA for the treatment of IBS-C was established in two double-blind, placebo-controlled, randomized, multicenter trials in adult patients (TEN-01-301 and TEN-01-302). (b) (4)

(b) (4)

To enter the (b) (4) all patients met Rome III criteria for IBS-C and were required to meet the following clinical criteria during the 2-week baseline run-in period:

- a mean abdominal pain score of at least 3 on a 0-to-10-point numeric rating scale where a score of 0 indicates no pain and 10 indicates very severe pain
- less than 3 complete spontaneous bowel movements (CSBMs) per week, where a CSBM is defined as a spontaneous bowel movement (SBM) that is associated with a sense of complete evacuation (an SBM is a bowel movement occurring in the absence of laxative use)
- less than or equal to 5 SBMs per week

(b) (4)

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's comment(s):

The following tables from the ISE Tables, Figures and Listings document show the analysis of the pooled study data for the following:

- ***Secondary endpoints: Average weekly spontaneous bowel movement (SBM), Average weekly stool consistency, and Average weekly straining***

Table 4.3.9
Analysis of Average Weekly Spontaneous Bowel Movement (SBM)
(Intent-to-Treat Analysis Set)

Study Week	D5612C00001		TEN-01-301		TEN-01-302		Pooled	
	Placebo (N=89)	50 MG BID (N=84)	Placebo (N=299)	50 MG BID (N=307)	Placebo (N=300)	50 MG BID (N=293)	Placebo (N=688)	50 MG BID (N=684)
Week 12								
n	74	73	232	226	246	227	552	526
Mean	3.82	5.19	3.69	5.35	3.77	6.36	3.75	5.76
Standard deviation	3.321	4.273	3.270	5.260	2.973	5.350	3.143	5.192
Median	3.00	4.67	3.00	4.20	3.50	5.00	3.00	4.67
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	16.3	24.0	19.0	41.0	15.8	28.0	19.0	41.0
Change from baseline to Week 12								
n	74	73	232	226	246	227	552	526
Mean	1.90	3.14	1.86	3.55	2.06	4.66	1.95	3.97
Standard deviation	3.243	4.054	3.227	5.117	3.059	5.320	3.151	5.103
Median	1.22	2.33	0.92	2.29	1.33	3.50	1.03	2.92
Minimum	-3.8	-2.2	-5.3	-3.8	-4.3	-4.3	-5.3	-4.3
Maximum	15.2	18.7	17.8	40.5	14.6	24.0	17.8	40.5
LS Mean(SE)[2]	1.77 (0.48)	3.11 (0.47)	2.01 (0.30)	3.72 (0.31)	2.26 (0.29)	4.86 (0.30)	2.02 (0.21)	4.06 (0.21)
95% CI LS Mean	(0.83, 2.71)	(2.17, 4.04)	(1.42, 2.60)	(3.12, 4.33)	(1.69, 2.83)	(4.27, 5.46)	(1.62, 2.42)	(3.65, 4.48)
LS Mean Diff(SE)(vs placebo)[2]		1.34 (0.61)		1.71 (0.40)		2.60 (0.39)		2.04 (0.25)
95% CI LS Mean Diff(vs placebo)		(0.13, 2.54)		(0.93, 2.50)		(1.84, 3.37)		(1.55, 2.54)
p-value(vs placebo)[2]		0.030		<0.001		<0.001		<0.001

Note: The treatment period for Studies D5612C0001 and TEN-01-301 is 12 weeks. The treatment period for Study TEN-01-302 is 26 weeks.
The first 12 weeks of treatment are pooled for these three studies.
[1] Baseline is defined as the average of Week -1 and Week -2.
[2] Least Squares (LS) means, Standard error (SE), 95% Confidence intervals (CIs), and p-values are from an analysis of covariance (ANCOVA) model with study, treatment and geographic region as factors and baseline value as a covariate for pooled data. For each study, the ANCOVA model has treatment and geographic region as factors and baseline value as a covariate.

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Table 4.3.10
Analysis of Average Weekly Stool Consistency
(Intent-to-Treat Analysis Set)

Study Week	D5612C00001		TEN-01-301		TEN-01-302		Pooled	
	Placebo (N=89)	50 MG BID (N=84)	Placebo (N=299)	50 MG BID (N=307)	Placebo (N=300)	50 MG BID (N=293)	Placebo (N=688)	50 MG BID (N=684)
Week 12								
n	74	73	232	225	246	227	552	525
Mean	1.43	2.66	1.39	2.23	1.48	2.72	1.44	2.50
Standard deviation	1.077	1.846	1.300	1.829	1.285	1.909	1.264	1.878
Median	1.18	2.75	0.86	2.00	1.17	2.47	1.00	2.25
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	4.4	7.0	5.4	7.0	6.1	7.0	6.1	7.0
Change from baseline to Week 12								
n	74	73	232	225	246	227	552	525
Mean	0.89	2.07	0.92	1.77	1.02	2.28	0.96	2.04
Standard deviation	1.122	1.715	1.249	1.739	1.299	1.867	1.255	1.805
Median	0.62	2.09	0.43	1.50	0.61	2.00	0.57	1.80
Minimum	-1.0	-0.6	-1.5	-1.4	-1.2	-1.0	-1.5	-1.4
Maximum	4.2	6.1	4.9	6.4	5.8	6.9	5.8	6.9
LS Mean(SE)[2]	0.74 (0.19)	1.95 (0.19)	1.00 (0.11)	1.87 (0.11)	1.10 (0.11)	2.36 (0.11)	1.02 (0.08)	2.10 (0.08)
95% CI LS Mean	(0.37, 1.11)	(1.59, 2.32)	(0.79, 1.21)	(1.65, 2.08)	(0.89, 1.32)	(2.14, 2.59)	(0.87, 1.16)	(1.94, 2.25)
LS Mean Diff(SE)(vs placebo)[2]		1.22 (0.24)		0.87 (0.14)		1.26 (0.15)		1.08 (0.09)
95% CI LS Mean Diff(vs placebo)		(0.74, 1.69)		(0.59, 1.14)		(0.97, 1.55)		(0.90, 1.26)
p-value(vs placebo)[2]		<0.001		<0.001		<0.001		<0.001

Note: The treatment period for Studies D5612C0001 and TEN-01-301 is 12 weeks. The treatment period for Study TEN-01-302 is 26 weeks.
The first 12 weeks of treatment are pooled for these three studies.
[1] Baseline is defined as the average of Week -1 and Week -2.
[2] Least Squares (LS) means, Standard error (SE), 95% Confidence intervals (CIs), and p-values are from an analysis of covariance (ANCOVA) model with study, treatment and geographic region as factors and baseline value as a covariate for pooled data. For each study, the ANCOVA model has treatment and geographic region as factors and baseline value as a covariate.

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Table 4.3.11
Analysis of Average Weekly Straining Score
(Intent-to-Treat Analysis Set)

Study Week	D5612C00001		TEN-01-301		TEN-01-302		Pooled	
	Placebo (N=89)	50 MG BID (N=84)	Placebo (N=299)	50 MG BID (N=307)	Placebo (N=300)	50 MG BID (N=293)	Placebo (N=688)	50 MG BID (N=684)
Week 12								
n	74	73	232	225	246	227	552	525
Mean	1.24	1.20	1.10	1.13	1.12	1.21	1.13	1.18
Standard deviation	0.947	0.749	0.876	0.763	0.762	0.739	0.837	0.750
Median	1.00	1.14	1.00	1.00	1.00	1.08	1.00	1.00
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	4.0	3.4	3.6	3.6	3.5	4.0	4.0	4.0
Change from baseline to Week 12								
n	74	73	232	225	246	227	552	525
Mean	0.34	0.20	0.21	0.25	0.24	0.38	0.24	0.30
Standard deviation	0.987	0.864	0.881	0.818	0.818	0.816	0.868	0.825
Median	0.29	0.03	0.02	0.17	0.22	0.29	0.12	0.19
Minimum	-2.0	-1.6	-1.8	-2.4	-2.5	-2.2	-2.5	-2.4
Maximum	3.8	3.0	3.3	3.0	3.2	3.6	3.8	3.6
LS Mean(SE)[2]	0.35 (0.11)	0.26 (0.11)	0.22 (0.06)	0.26 (0.06)	0.27 (0.05)	0.38 (0.05)	0.27 (0.04)	0.32 (0.04)
95% CI LS Mean	(0.13, 0.56)	(0.05, 0.48)	(0.11, 0.32)	(0.14, 0.37)	(0.17, 0.37)	(0.28, 0.48)	(0.20, 0.34)	(0.25, 0.40)
LS Mean Diff(SE)(vs placebo)[2]		-0.08 (0.14)		0.04 (0.07)		0.11 (0.07)		0.05 (0.05)
95% CI LS Mean Diff(vs placebo)		(-0.36, 0.19)		(-0.10, 0.18)		(-0.02, 0.24)		(-0.04, 0.14)
p-value(vs placebo)[2]		0.548		0.580		0.101		0.254

Note: The treatment period for Studies D5612C0001 and TEN-01-301 is 12 weeks. The treatment period for Study TEN-01-302 is 26 weeks.
The first 12 weeks of treatment are pooled for these three studies.
[1] Baseline is defined as the average of Week -1 and Week -2.
[2] Least Squares (LS) means, Standard error (SE), 95% Confidence intervals (CIs), and p-values are from an analysis of covariance (ANCOVA) model with study, treatment and geographic region as factors and baseline value as a covariate for pooled data. For each study, the ANCOVA model has treatment and geographic region as factors and baseline value as a covariate.

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Based on these data, efficacy of the investigational drug is supported by the analysis of the primary efficacy endpoint. The applicant did not win on the first key secondary endpoint of 6/12 week CSBM responder rate in study 301. However, per discussion with the review team, interest remained on whether a nominal treatment effect was observed on the other secondary endpoints. Refer to the Reviewer's comments in sections 7 through 9 of this review for additional information. It is important to note that the applicant did not show a statistically significant treatment difference for the straining endpoint in the phase 3 clinical trials.

4 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the IBS Symptom eDiary/IVRS are summarized in Table 6.

Table 6. Concepts of Interest for the IBS eDiary/IVRS

COA name	Concept(s)
IBS Symptom eDiary/IVRS	Bowel movement (BM) Frequency, spontaneous bowel movement (SBM) frequency, CSBM frequency, stool consistency, straining, abdominal pain, abdominal discomfort, abdominal bloating, abdominal fullness,

	abdominal cramping, use of rescue medications, global IBS severity, global Constipation severity, adequate relief of IBS symptoms, degree of relief of IBS symptoms

The conceptual framework for the IBS Symptom eDiary/IVRS is shown in Table 7.

Table 7. Conceptual Framework for the IBS Symptom eDiary/IVRS

Item	Domain (if applicable)	General Concept
Item 1. BM Frequency	Bowel Movement Symptoms	IBS Symptoms
Item 2: CSBM		
Item 3: Stool consistency		
Item 4: Straining		
Item 5: Abdominal Pain	Abdominal symptoms	
Item 6: Abdominal discomfort		
Item 7: Abdominal bloating		
Item 8: Abdominal fullness		
Item 9: Abdominal cramping		
Item 10: Use of rescue medications	Use of rescue medications to treat IBS symptoms	
Item 11: Global IBS Severity (Weekly)	Severity of IBS	
Item 12: Global Constipation Severity (Weekly)	Severity of constipation	
Item 13: Adequate relief of IBS Symptoms (Weekly)	IBS Symptom relief	
Item 14: Degree of relief of IBS symptoms (Weekly)		

5 CLINICAL OUTCOME ASSESSMENT(S)

IBS Symptom eDiary/IVRS

IBS symptoms were captured using a telephone diary (Interactive Voice Response System (IVRS) diary) administered utilizing a touch-tone phone. Subjects were asked 9 items daily and 4 items weekly. The recall period was "the past 24 hours" for the daily items and was "the past week" for the weekly items. The IBS IVRS script can be found in Appendix 1.

6 SCORING ALGORITHM

IBS Symptom eDiary/IVRS

Symptom severity based on the IBS Symptom eDiary/IVRS was assessed daily. The following table shows the scoring algorithm for daily and weekly scores.

Table 8. Daily and Weekly Scoring Algorithm for the IBS Symptom eDiary/IVRS

Item	Daily Score	Weekly Score
Item 1. BM Frequency	Score: Raw # of bowel movements	

Item 2. Completeness of bowel emptying (for each bowel movement)	Score not generated; used to differentiate Spontaneous Bowel Movements (SBMs) from CSBMs, based on data from item 1	
Item 3. Stool consistency using BSFS[1] (for each bowel movement)	Refer to Appendix 2 for a copy of the BSFS. Scores ranged from 1-7, with higher scores indicating more liquid bowel movement	
Item 4. Straining (for each bowel movement)	Score range of 1-5, with higher scores representing more severe straining	
Item 5. Abdominal Pain Item 6. Abdominal Discomfort Item 7. Abdominal Bloating Item 8. Abdominal Fullness Item 9. Abdominal Cramping	Score range of 0-10, with higher scores representing greater abdominal symptom severity	
Item 10. Use of rescue medication	Scored as dichotomous variable – "Yes" or "No"	
Item 11. Global IBS Severity (weekly) Item 12. Global Constipation Severity (weekly)		Score range 1-5, with higher scores representing greater severity
Item 13. Adequate relief of IBS Symptoms		Scored as dichotomous variable – "Yes" or "No"

[1] Bristol Stool Form Scale

7 CONTENT VALIDITY

The applicant did not submit a PRO evidence dossier.

To date, the following information has been submitted (check all that apply):

- ☐ Literature review and/or publications
- ☐ Documentation of expert input
- ☐ Qualitative study protocols and interview guides for focus group or patient interviews
- ☐ Chronology of events for item generation, modification, and finalization (item tracking matrix)
- ☐ Synopsis of qualitative findings
- ☐ Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
- ☐ Quantitative summary report with evidence to support item retention and scoring
- ☐ Transcripts (if available)

Table 9 documents the adequacy of the content of the IBS Symptom eDiary/IVRS.

Table 9. Review of Content Validity for the IBS Symptom eDiary/IVRS.

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☒ Yes ☐ No	☒ Literature ☒ Clinical input e.g. discussion with clinical reviewer	FDA Guidance for Industry on the Clinical Evaluation of Drugs for Treatment of Irritable Bowel syndrome
Content validity	☐ Yes ☒ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☒ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☐ Target sample for qualitative research is appropriate. ☐ Studied sample for qualitative research adequately represents the target patient population ☐ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☐ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☐ COA is culturally adapted and adequately translated ☐ Descriptive statistics (if available) support content relevance ☐ Other (see Reviewer's comments)	Supporting material based on patient input not submitted by applicant.

Testing other measurement properties (reliability, construct validity, and ability to detect change), while important, will not replace or rectify problems with content validity.

Reviewer's comment(s):
Despite not submitting a full PRO evidence dossier to support the PRO items, based on the all available evidence submitted this reviewer concludes that the PRO items used to assess bowel frequency and abdominal pain are fit-for-purpose to support the respective pre-specified primary and secondary endpoints intended for inclusion in labeling claims in the target patient population. Although some of the remaining concepts have face validity based on the

literature and discussion with clinician experts, (b) (4) [redacted]

The following IR was sent by the Agency to the applicant on March 8, 2019.

(b) (4) [redacted]

This reviewer agrees that abdominal pain does not require further qualitative data given that this concept is described as an acceptable endpoint in FDA's Guidance for Industry on the Clinical Evaluation of Drugs for Treatment of Irritable Bowel Syndrome.

8 OTHER MEASUREMENT PROPERTIES

Other measurement properties (reliability, construct validity and ability to detect change) are not reviewed until the COA's content validity has been established. The applicant did not submit evidence to support the measurement properties of the IBS Symptom eDiary/IVRS.

9 INTERPRETATION OF SCORES

To date, the following information has been submitted (check all that apply):

- ☒ Anchor-based analyses
- ☒ Anchor-based empirical cumulative distribution function (eCDF) curves
- ☒ eCDF study arm curves (Treatment vs. Placebo/Active Comparator)
- ☒ Anchor-based probability density function (PDF) curves
- ☒ PDF study arm curves (Treatment vs. Placebo/Active Comparator)

☐ Qualitative support for meaningful change (e.g., patient input)

Table 9 documents the adequacy of the score interpretability of the IBS Symptom eDiary/IVRS.

Table 9. Review of Score Interpretability for the IBS Symptom eDiary/IVRS

COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Score Interpretability	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Appropriate global anchor scales were included for anchor-based analyses ☐ Threshold(s) for within-patient meaningful change identified (anchor-based methods) ☐ Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) ☐ Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) ☐ Other (see Reviewer's comments)	Applicant's IR responses received 02/19/2019 and 03/13/2019

Reviewer's comment(s):
The applicant did not administer anchor scales to support an anchor-based analysis of clinically meaningful within-patient change. However, the Division agreed with the COA Staff recommendation to use the weekly items asking about IBS Severity and Constipation Severity as anchors.

An Information Request sent on February 4, 2019 is shown below.

1. Request for patient global scale tables

For studies 301 and 302, please create and submit the following tables (Tables 1 through 10) corresponding to the data used for the primary and pre-specified secondary endpoints (CSBMs, abdominal pain, SBMs, BSFS stool consistency, straining, abdominal discomfort, abdominal bloating, abdominal cramping, and abdominal fullness). Please use the following endpoint scores when populating the table shells, depending on the endpoint definition:

- For abdominal pain, use percent and raw change in abdominal pain score separately when populating the table shells.
- For all other endpoint scores, use the raw change in scores.

Please use the following table shells for Tables 1 through 10 as a template:

1. For patients who achieved a 1-point improvement from baseline in IBS Severity:

		Baseline IBS Severity anchor scale category			
		Mild	Moderate	Severe	Very Severe
Endpoint score (i.e., change from baseline in score)	N				
	10th Percentile				
	25th Percentile				
	Median (50th percentile)				
	75th Percentile				
	90th Percentile				

2. For patients who achieved a 2-point improvement from baseline in IBS Severity:

		Baseline IBS Severity anchor scale category		
		Moderate	Severe	Very Severe
Endpoint score (i.e., change from baseline in score)	N			
	10th Percentile			
	25th Percentile			
	Median (50th percentile)			
	75th Percentile			
	90th Percentile			

3. For patients who achieved no change from baseline in IBS Severity:

		Baseline IBS Severity anchor scale category				
		None	Mild	Moderate	Severe	Very Severe
Endpoint score (i.e., change from baseline in score)	N					
	10th Percentile					
	25th Percentile					
	Median (50th percentile)					
	75th Percentile					
	90th Percentile					

4. For patients who achieved a 1-point worsening from baseline in IBS Severity:

		Baseline IBS Severity anchor scale category			
		None	Mild	Moderate	Severe
Endpoint score (i.e., change from baseline in score)	N				
	10th Percentile				
	25th Percentile				
	Median (50th percentile)				
	75th Percentile				
	90th Percentile				

5. For patients who achieved a 2-point worsening from baseline in IBS Severity:

		Baseline IBS Severity anchor scale category		
		None	Mild	Moderate
Endpoint score (i.e., change from baseline in score)	N			
	10th Percentile			
	25th Percentile			
	Median (50th percentile)			
	75th Percentile			
	90th Percentile			

For the weekly item assessing Constipation Severity

6. For patients who achieved a 1-point improvement from baseline in Constipation Severity:

		Baseline Constipation Severity anchor scale category			
		Mild	Moderate	Severe	Very Severe
Endpoint score (i.e., change from baseline in score)	N				
	10th Percentile				
	25th Percentile				
	Median (50th percentile)				
	75th Percentile				
	90th Percentile				

7. For patients who achieved a 2-point improvement from baseline in Constipation Severity:

		Baseline Constipation Severity anchor scale category		
		Moderate	Severe	Very Severe
Endpoint score (i.e., change from baseline in score)	N			
	10th Percentile			
	25th Percentile			
	Median (50th percentile)			
	75th Percentile			
	90th Percentile			

2

8. For patients who achieved no change from baseline in Constipation Severity:

		Baseline Constipation Severity anchor scale category				
		None	Mild	Moderate	Severe	Very Severe
Endpoint score (i.e., change from baseline in score)	N					
	10th Percentile					
	25th Percentile					
	Median (50th percentile)					
	75th Percentile					
	90th Percentile					

9. For patients who achieved a 1-point worsening from baseline in Constipation Severity:

		Baseline Constipation Severity anchor scale category			
		None	Mild	Moderate	Severe
Endpoint score (i.e., change from baseline in score)	N				
	10th Percentile				
	25th Percentile				
	Median (50th percentile)				
	75th Percentile				
	90th Percentile				

10. For patients who achieved a 2-point worsening from baseline in Constipation Severity:

		Baseline Constipation Severity anchor scale category		
		None	Mild	Moderate
Endpoint score (i.e., change from baseline in score)	N			
	10th Percentile			
	25th Percentile			
	Median (50th percentile)			
	75th Percentile			
	90th Percentile			

2. Request for empirical cumulative distribution function (eCDF) and probability distribution (PDF) figures

To estimate clinically meaningful within-patient change, we recommend the use of an anchor-based approach. This approach is supplemented with both anchor-based empirical cumulative distribution function (eCDF) and probability density function (PDF; often estimated using kernel density estimation) curves to determine a range of clinically meaningful within-patient improvement thresholds.

We recommend that the weekly items asking about IBS Severity and Constipation Severity be used as your anchor scales. Please submit anchor-based eCDF and PDF curves of the severity change scores from baseline to week 12 for the primary and pre-specified secondary endpoints assessed by IVRS in studies 301 and 302 (CSBMs, abdominal pain, SBMs, BSFS stool consistency, straining, abdominal discomfort, abdominal bloating, abdominal cramping, and abdominal fullness) for all patients by the IBS Severity change score from baseline to week 12 (e.g., +4 points change, +3 points change, +2 points change, +1 point change, 0 point change, –1 point change, –2 points change, –3 points change, and -4 points change) and another separate set of eCDF figures by Constipation Severity change score from baseline to week 12. Please see our note under Request #1 above regarding using percent versus raw score change.

Please include the sample size and median score for each eCDF and PDF anchor curve in each figure's legend. In addition, provide and justify which anchor response category represents clinically meaningful within-patient change. These analyses should be performed separately for each phase 3 study using blinded pooled study arm data (i.e., establishing meaningful improvement thresholds for each phase 3 trial separately). If any of these figures are included in a previous submission, please indicate where they are located.

The applicant submitted the IR response on February 19, 2019. Refer to section 7 of this review for a second IR asking the applicant to provide evidence of content validity for the

(b) (4)

(b) (4)

If a pre-defined responder threshold for an endpoint was not available, the eCDF curves were used to estimate the range for a given endpoint where 50% of patients reported a meaningful improvement based on the IBS Disease Severity anchor and Constipation Severity anchor response categories. If a pre-defined responder threshold for an endpoint was available, the eCDF curves were used to assess the corresponding improvement in the anchor scales. The y-axes for these figures represent the cumulative percentage of patients with a change in the endpoint and the x-axes show the change in the endpoint from baseline to week 12. The range of thresholds representing improvement for a given endpoint was estimated by determining whether there was clear separation between the curves representing the meaningful anchor scale response categories (e.g., separation from the no change and worsening categories) and, if so, what values on the x-axis corresponded to the change in anchor scale categories reported by 50% of subjects in the pooled study arm data.

The completed anchor-based table shells were submitted by the applicant in response to the February 4, 2019 IR. Based on those data, it does not appear that the meaningfulness of the anchor-based thresholds was influenced by baseline severity ratings that patients reported using the IBS Disease Severity and Constipation Severity anchor scales. The eCDF curves for the CSBM, abdominal pain, SBM, stool consistency, and straining endpoints can be found in their respective sections below.

<u>CSBMs</u>
Refer to Figures 1-6 below for the eCDF curves for average weekly CSBMs. A CSBM weekly responder was defined as an increase of ≥ 1 in average weekly CSBMs from baseline.

For studies 301 and 302, it appears that there is clear separation between the curves representing different levels of improvement in the IBS Severity anchor scale (Figure 1 and Figure 3, respectively) and Constipation Severity anchor scale (Figure 2 and Figure 4, respectively) at the pre-defined responder threshold of CSBM weekly responder. The corresponding change for both the anchor scales met by the median for the pooled study arms is approximately a 2-point improvement.

Figure 5 shows the eCDF curves by Treatment Group for Study 301 and Figure 6 shows the eCDF curves by Treatment Group for Study 302. For both studies there is separation between the placebo and Tenapanor 50mg BID study arms at the median line for the pre-defined responder threshold for CSBM weekly responder. Note that in Study 301 the curves for each study arm appear to come together, but do not cross.

Figure 1. Study 301 – Change in CSBM Rate from Baseline to Week 12 Average Weekly CSBMs by IBS Disease Severity Anchor Scale (Pooled Study Arm Data)

Figure S1.1.cdf.ibs.1
TEN-01-301: eCDF of Raw Change from Baseline to Week 12 in Average Weekly CSBMs by IBS Severity Anchor Response Category
Intent-to-Treat Analysis Set

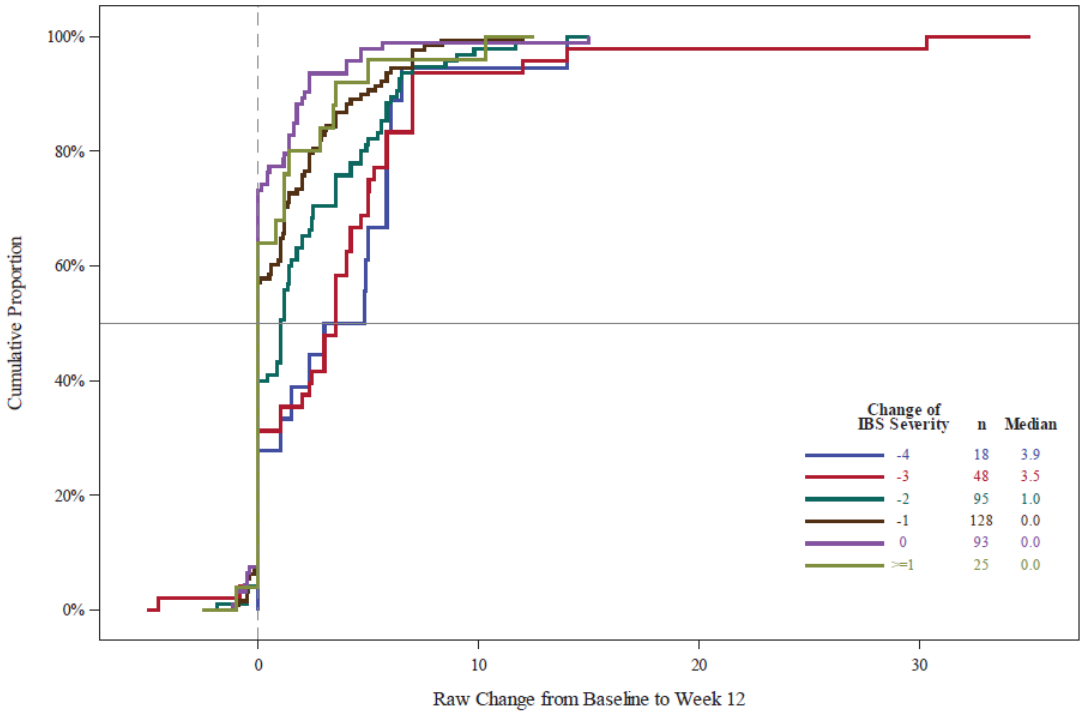


Figure 2. Study 302 – Change in CSBM Rate from Baseline to Week 12 Average Weekly CSBMs by IBS Disease Severity Anchor Scale (Pooled Study Arm Data)

Figure S2.1.cdf.ibs.1
TEN-01-302: eCDF of Raw Change from Baseline to Week 12 in Average Weekly CSBMs by IBS Severity Anchor Response Category
Intent-to-Treat Analysis Set

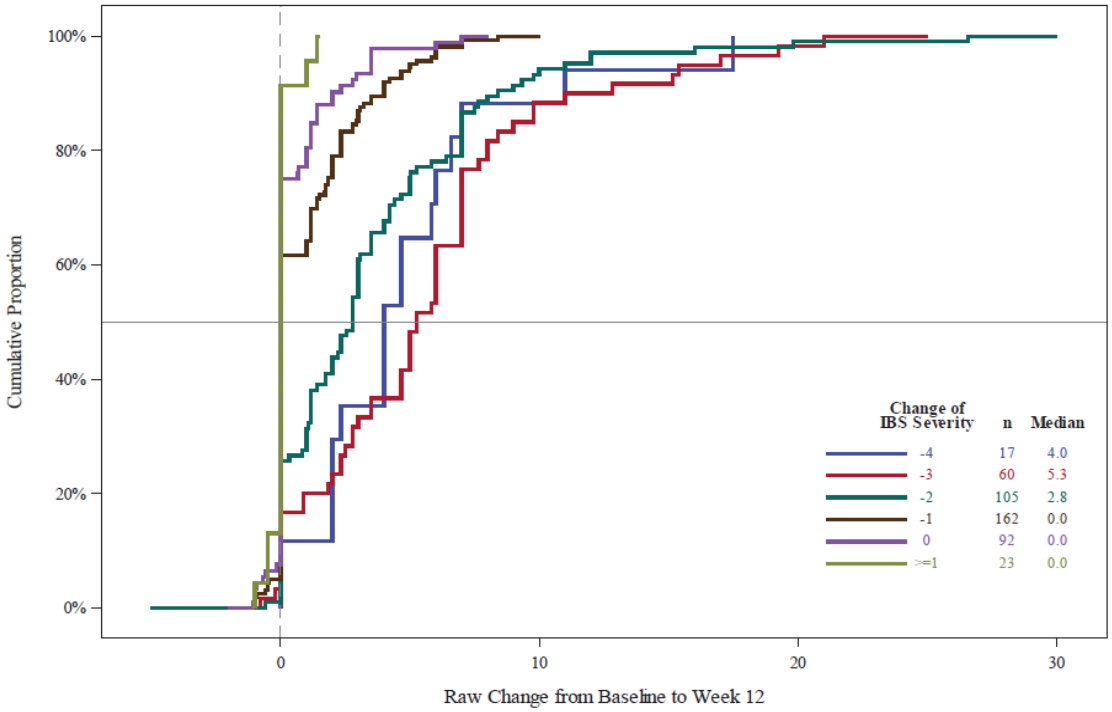


Figure 3. Study 301 – Change in CSBM Rate from Baseline to Week 12 Average Weekly CSBMs by Constipation Severity Anchor Scale (Pooled Study Arm Data)

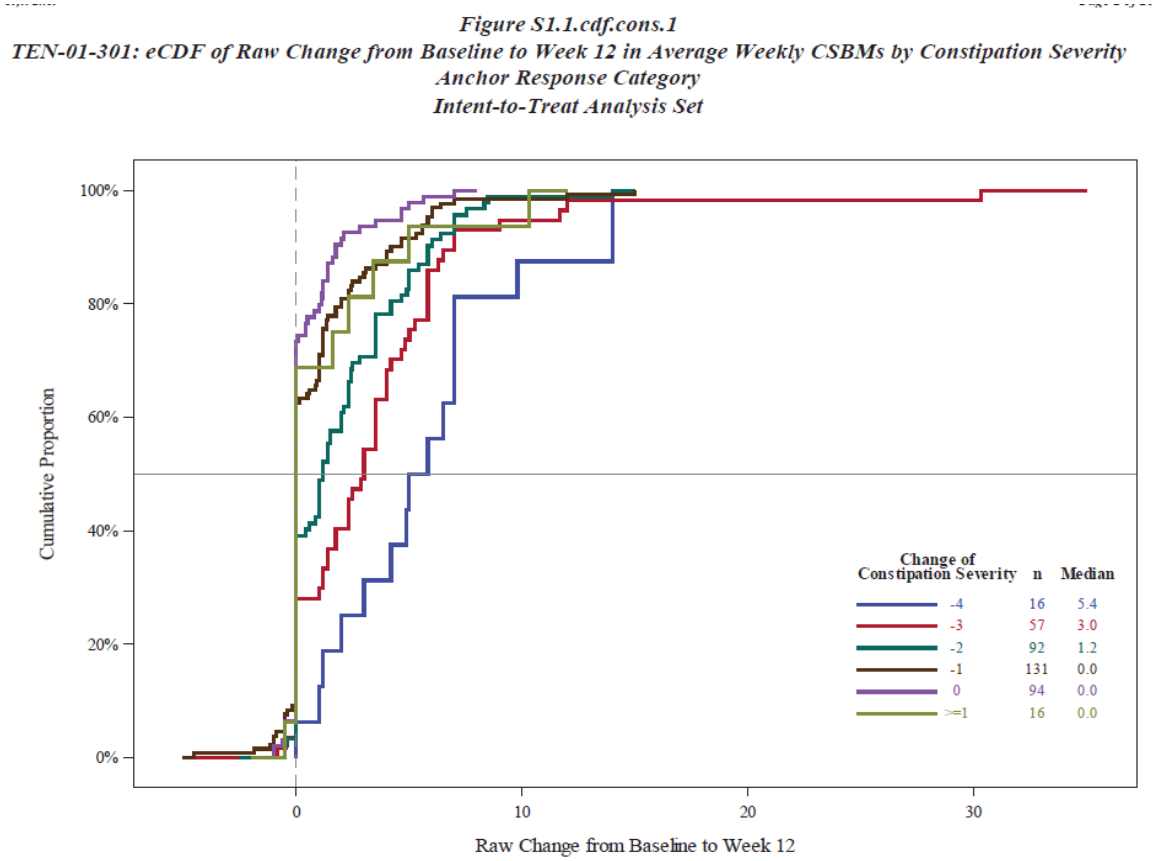


Figure 4. Study 302 – Change in CSBM Rate from Baseline to Week 12 Average Weekly CSBMs by Constipation Severity Anchor Scale (Pooled Study Arm Data)

Figure S2.1.cdf.cons.1
TEN-01-302: eCDF of Raw Change from Baseline to Week 12 in Average Weekly CSBMs by Constipation Severity Anchor Response Category
Intent-to-Treat Analysis Set

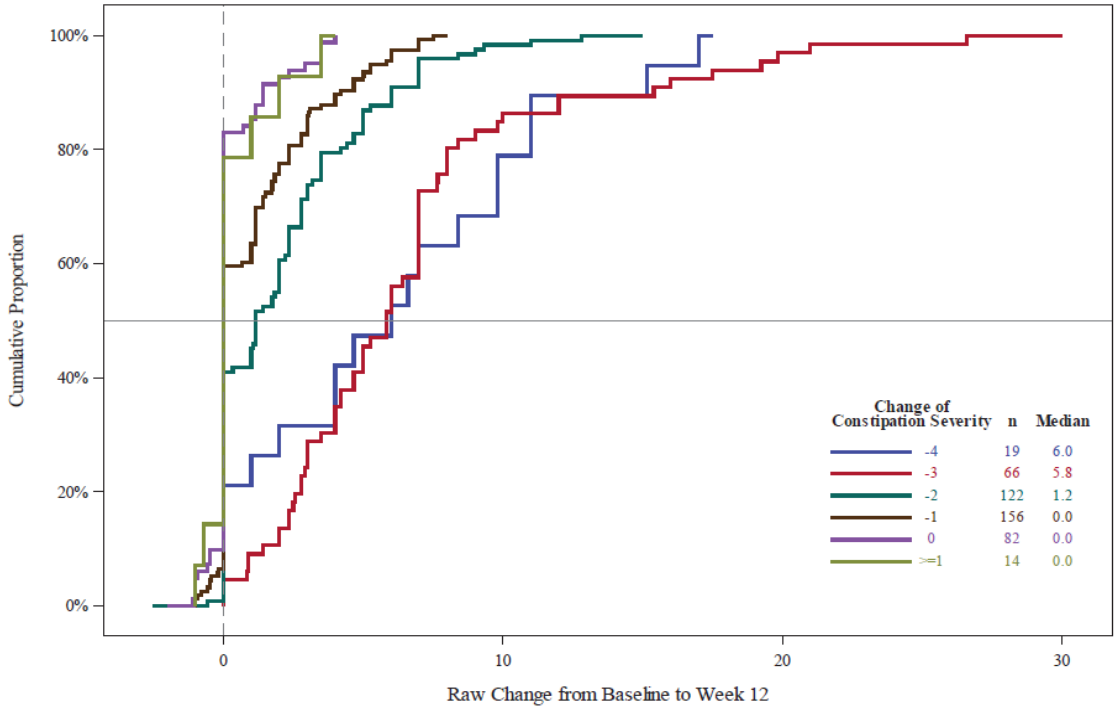


Figure 5. Study 301 - Average Weekly CSBMs by Study Arm

Figure S1.2.cdf.trt.1
TEN-01-301: eCDF of Raw Change from Baseline to Week 12 in Average Weekly CSBMs by Planned Treatment Group
Intent-to-Treat Analysis Set

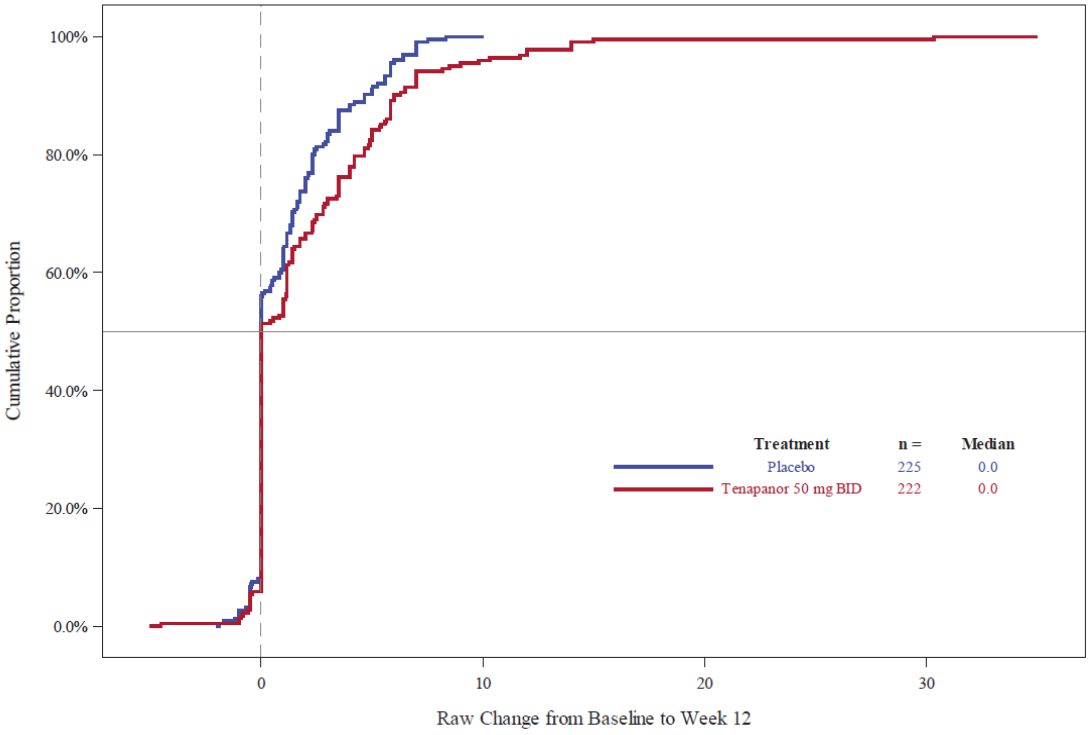
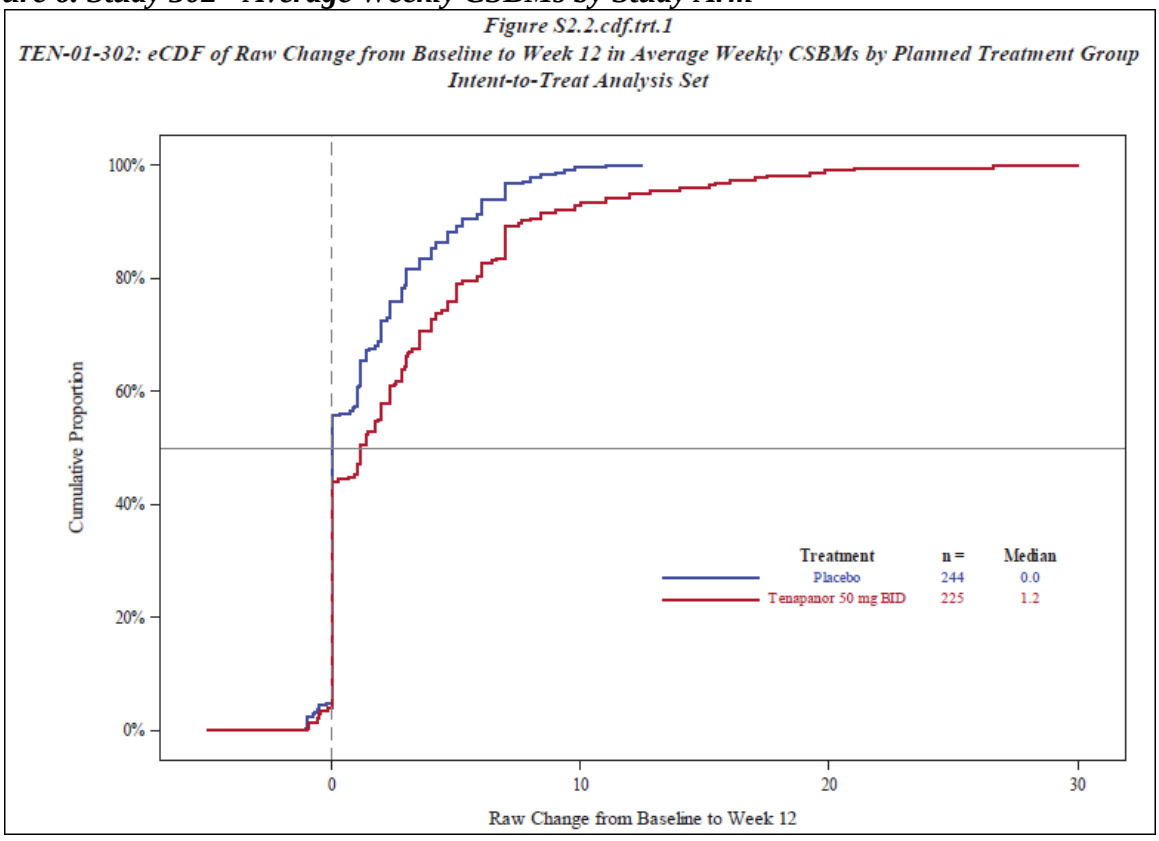


Figure 6. Study 302 - Average Weekly CSBMs by Study Arm



<u>Abdominal Pain</u>

Refer to Figures 7-12 below for the eCDF curves for average weekly abdominal pain from baseline to week 12. An abdominal pain weekly responder was defined as a decrease of 30% in average weekly worst abdominal pain from baseline.

For studies 301 and 302, it appears that there is clear separation between the curves representing different levels of improvement in the IBS Severity Anchor Scale (Figure 7 and Figure 9, respectively) and Constipation Severity Anchor Scale (Figure 8 and Figure 10, respectively) at the pre-defined responder threshold for the abdominal pain weekly responder. The corresponding meaningful threshold for both the anchor scales is approximately a one-category improvement.

Figure 11 shows the eCDF curves by Study Arm for Study 301 and Figure 12 shows the eCDF curves by study arm for Study 302. For both studies there is separation between the placebo and Tenapanor 50mg BID treatment groups at the median line for the pre-defined responder threshold for average weekly abdominal pain.

Figure 7. Study 301 – Percentage Change in Average Weekly Abdominal Pain from Baseline to Week 12 by IBS Disease Severity Anchor Scale (Pooled Study Arm Data)

Figure S1.1.cdf.ibs.3
TEN-01-301: eCDF of Percentage Change from Baseline to Week 12 in Average Weekly Abdominal Pain Score by IBS Severity Anchor Response Category
Intent-to-Treat Analysis Set

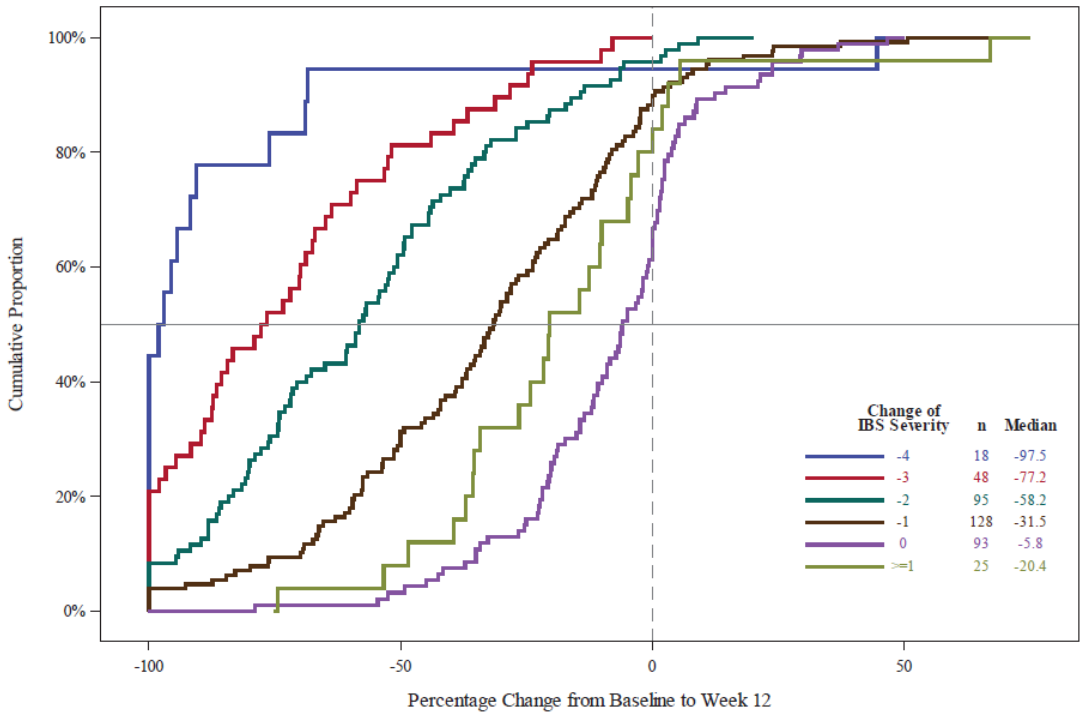


Figure 8. Study 302 – Percentage Change in Average Weekly Abdominal Pain from Baseline to Week 12 by IBS Disease Severity Anchor Scale (Pooled Study Arm Data)

Figure S2.1.cdf.ibs.3
TEN-01-302: eCDF of Percentage Change from Baseline to Week 12 in Average Weekly Abdominal Pain Score by IBS Severity Anchor Response Category
Intent-to-Treat Analysis Set

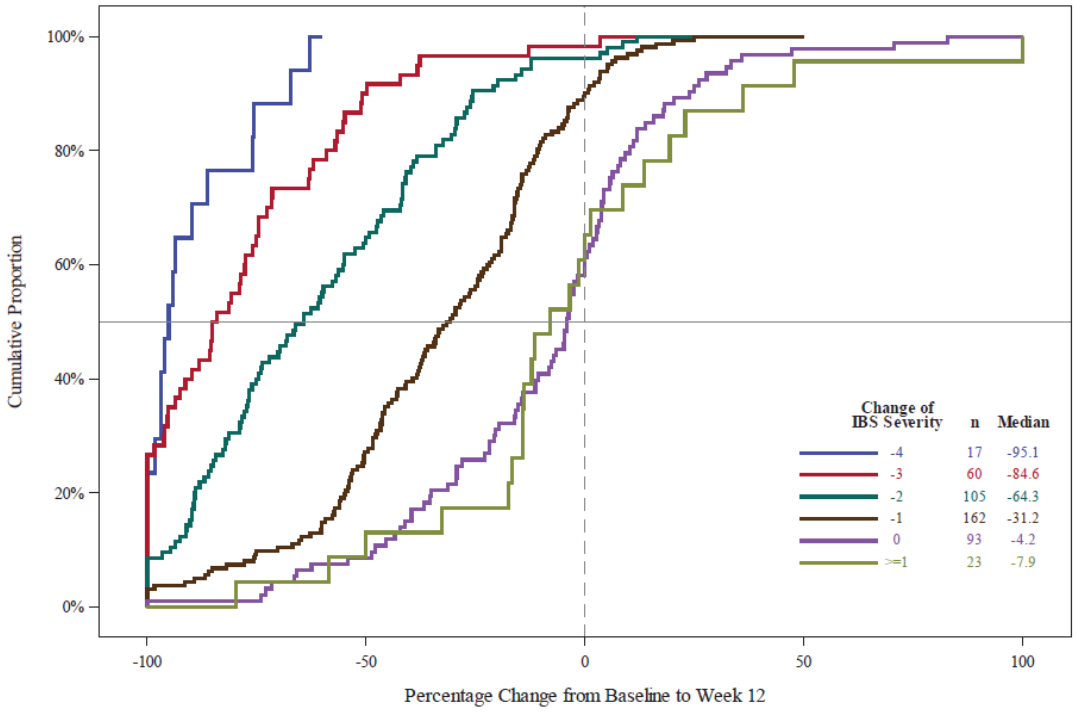


Figure 9. Study 301 – Percentage Change in Average Weekly Abdominal Pain from Baseline to Week 12 by Constipation Severity Anchor Scale (Pooled Study Arm Data)

Figure S1.1.cdf.cons.3
TEN-01-301: eCDF of Percentage Change from Baseline to Week 12 in Average Weekly Abdominal Pain Score by Constipation Severity Anchor Response Category
Intent-to-Treat Analysis Set

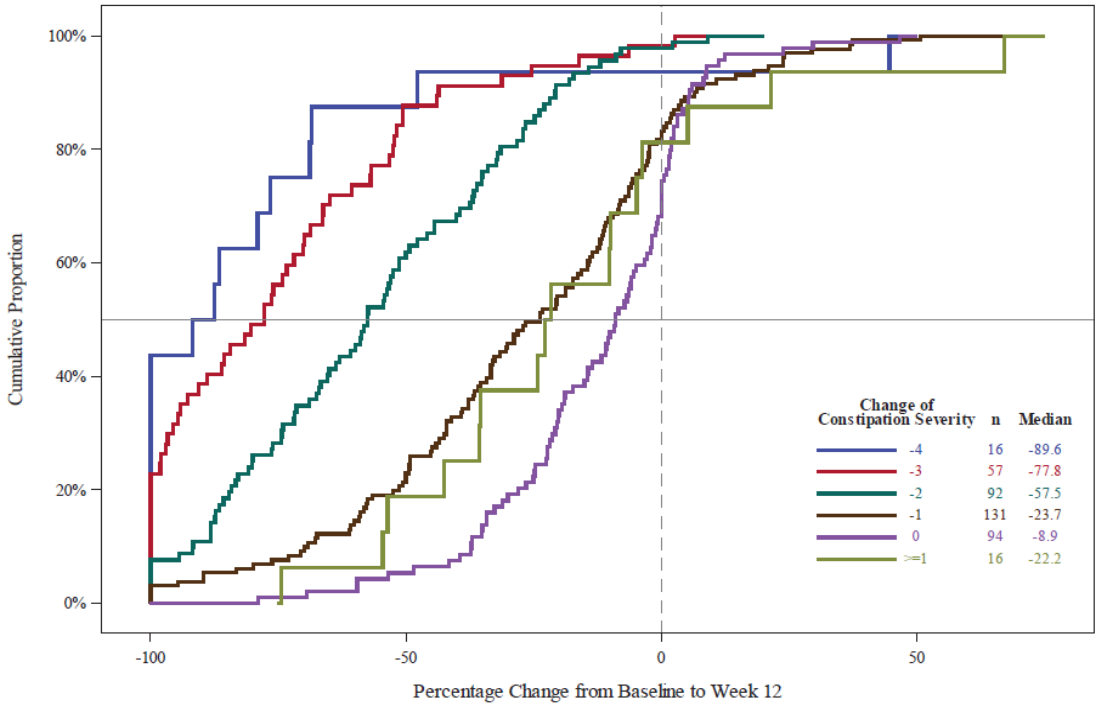


Figure 10. Study 302 – Percentage Change in Average Weekly Abdominal Pain from Baseline to Week 12 by Constipation Severity Anchor Scale (Pooled Study Arm Data)

Figure S2.1.cdf.cons.3
TEN-01-302: eCDF of Percentage Change from Baseline to Week 12 in Average Weekly Abdominal Pain Score by Constipation Severity Anchor Response Category
Intent-to-Treat Analysis Set

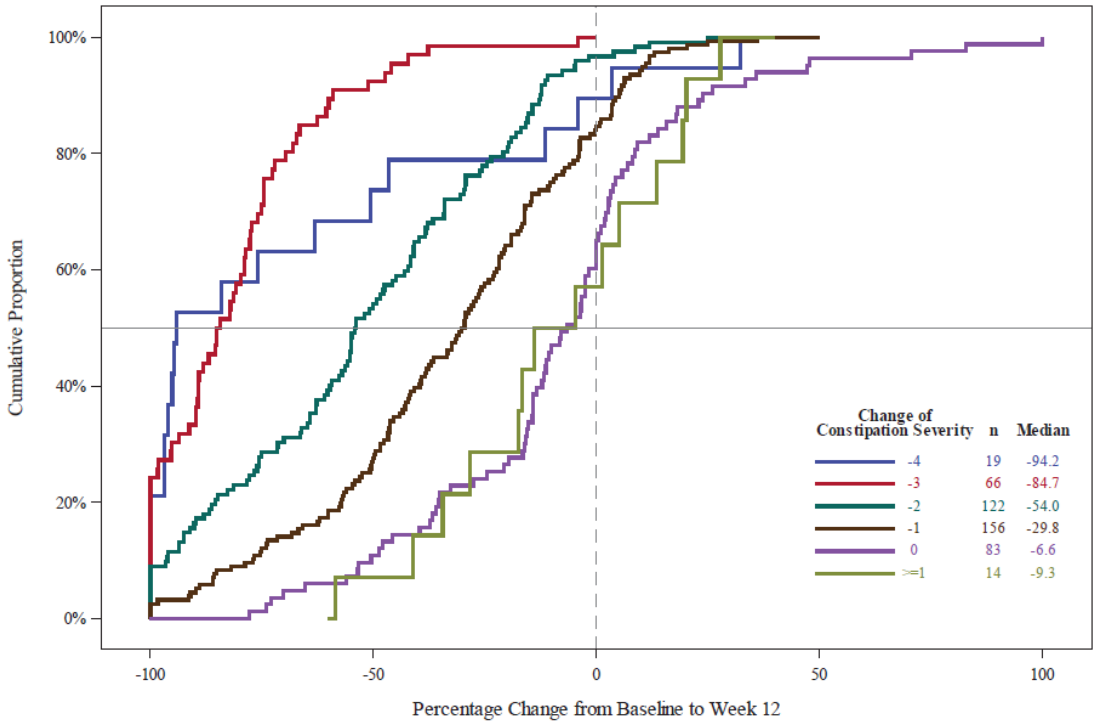


Figure 11. Study 301 – Percentage Change from Baseline to Week 12 in Average Weekly Abdominal Pain Score by Study Arm

Figure S1.2.cdf.trt.3
TEN-01-301: eCDF of Percentage Change from Baseline to Week 12 in Average Weekly Abdominal Pain Score by Planned Treatment Group
Intent-to-Treat Analysis Set

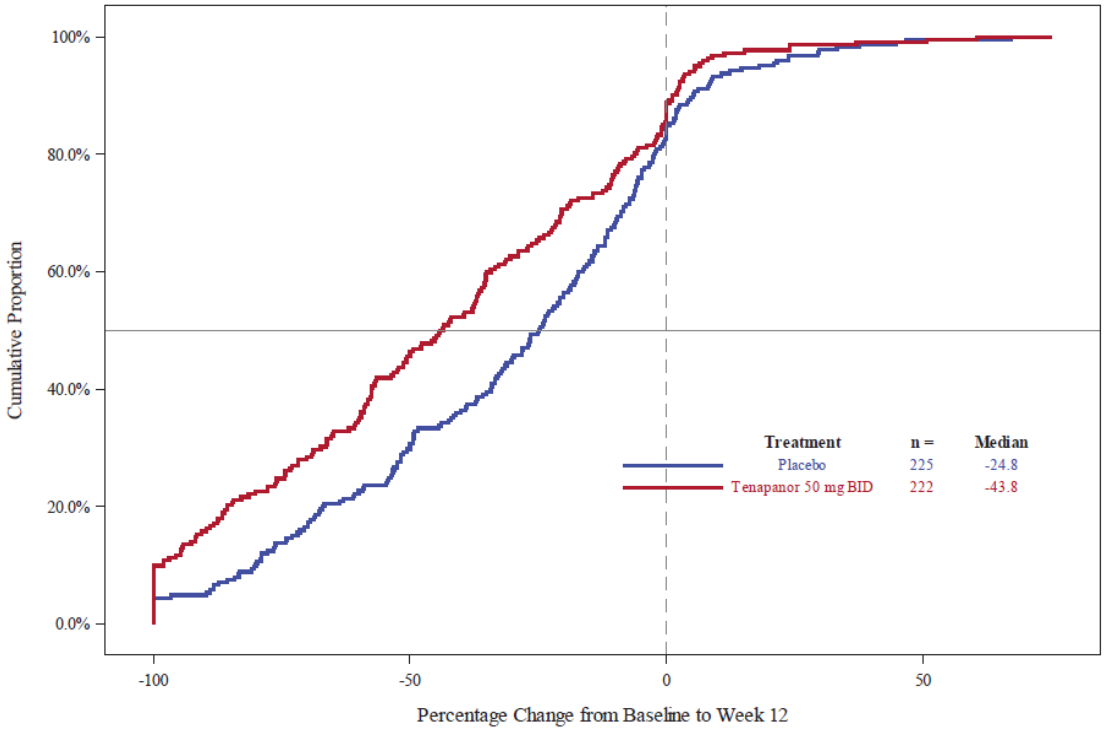
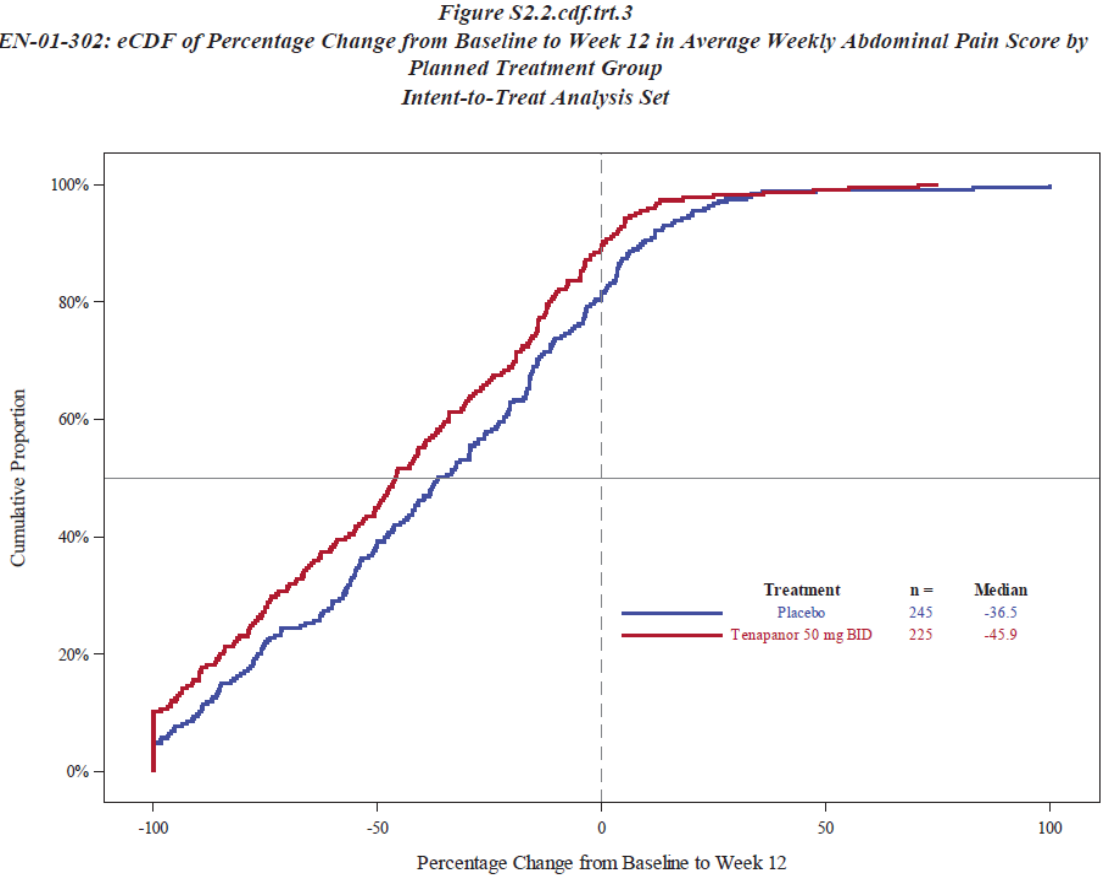


Figure 12. Study 302 - Percentage Change from Baseline to Week 12 in Average Weekly Abdominal Pain Score by Study Arm



SBMs

Refer to Figures 13-18 below for the eCDF curves for average weekly SBMs from baseline to week 12. A pre-defined responder threshold for SBMs was not included in the ISE.

For studies 301 and 302, the curves representing different levels of improvement in the anchor scale categories (Figures 13 through 16) did not always appear clearly separated, thus, a range to define an improvement threshold for average weekly SBMs based on the applicant's administered anchor scales could not clearly be estimated. However, it appears that the improvement threshold may be between a one- and two-category improvement in the anchor scales. The eCDF curves by study arm for study 301 (Figure 17) show a separation between study arm curves and a similar observation was made for study 302 (Figure 18).

Figure 13. Study 301 – Change in Average Weekly SBMs from Baseline to Week 12 by IBS Disease Severity Anchor Scale (Pooled Study Arm Data)

Figure S1.1.cdf.ibs.4
TEN-01-301: eCDF of Raw Change from Baseline to Week 12 in Average Weekly SBMs by IBS Severity Anchor Response Category
Intent-to-Treat Analysis Set

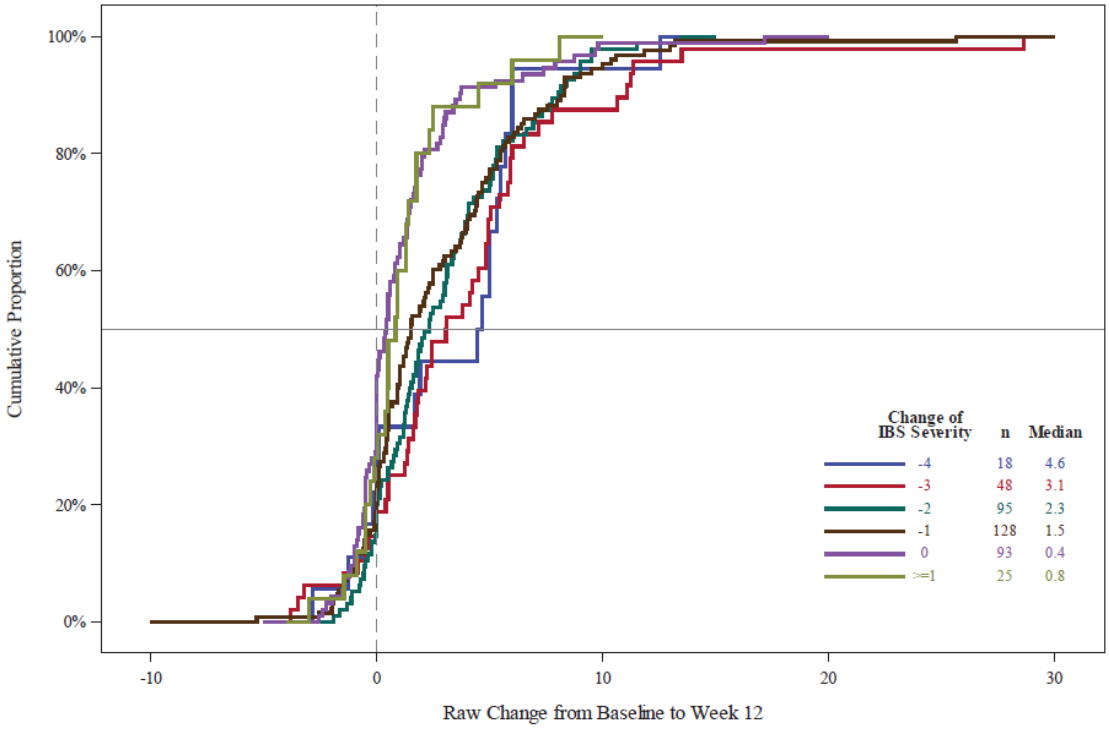


Figure 14. Study 302 – Change in Average Weekly SBMs from Baseline to Week 12 by IBS Disease Severity Anchor Scale (Pooled Study Arm Data)

Figure S2.1.cdf.ibs.4
TEN-01-302: eCDF of Raw Change from Baseline to Week 12 in Average Weekly SBMs by IBS Severity Anchor Response Category
Intent-to-Treat Analysis Set

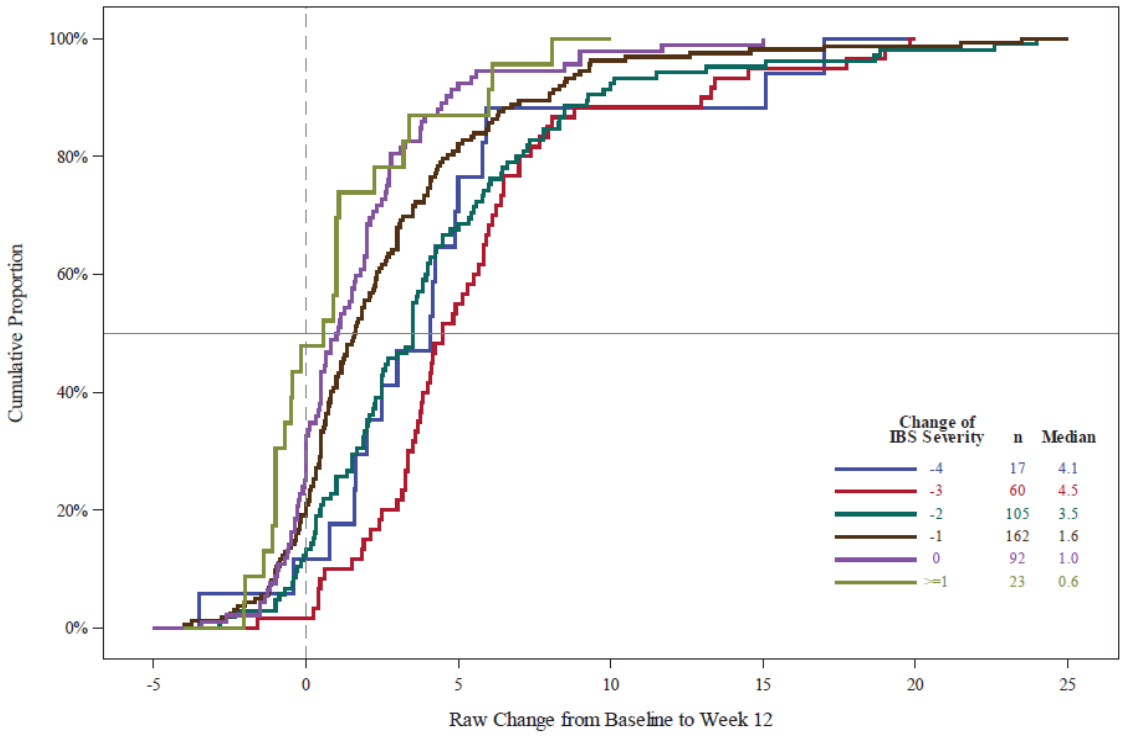


Figure 15. Study 301 – Change in Average Weekly SBMs from Baseline to Week 12 by Constipation Severity Anchor Scale (Pooled Study Arm Data)

Figure S1.1.cdf.cons.4
TEN-01-301: eCDF of Raw Change from Baseline to Week 12 in Average Weekly SBMs by Constipation Severity Anchor Response Category
Intent-to-Treat Analysis Set

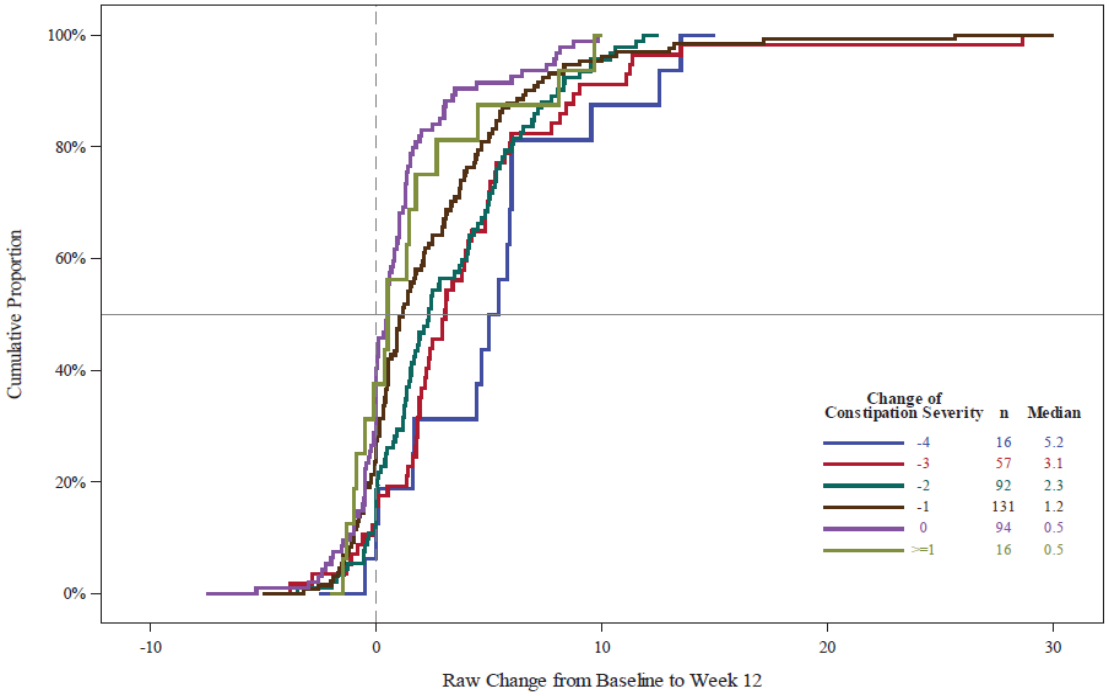


Figure 16. Study 302 – Change in Average Weekly SBMs from Baseline to Week 12 by Constipation Severity Anchor Scale (Pooled Study Arm Data)

Figure S2.1.cdf.cons.4
TEN-01-302: eCDF of Raw Change from Baseline to Week 12 in Average Weekly SBMs by Constipation Severity Anchor Response Category
Intent-to-Treat Analysis Set

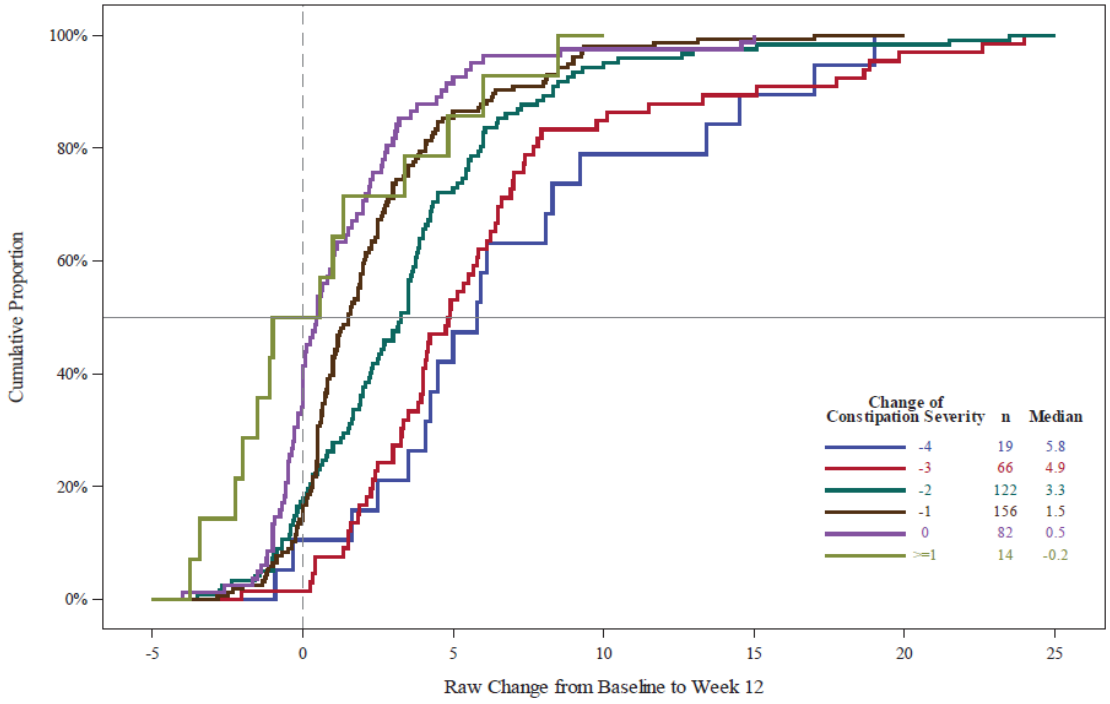


Figure 17. Study 301 - Average Weekly SBMs by Study Arm

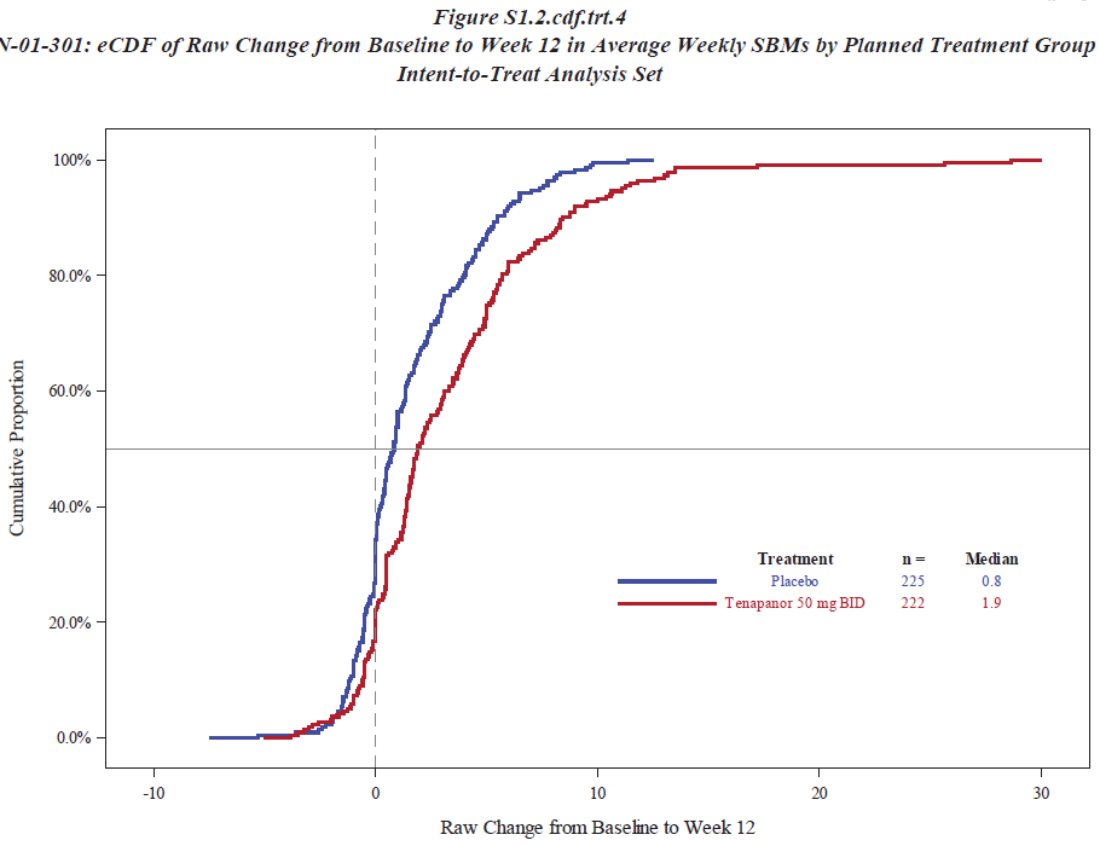
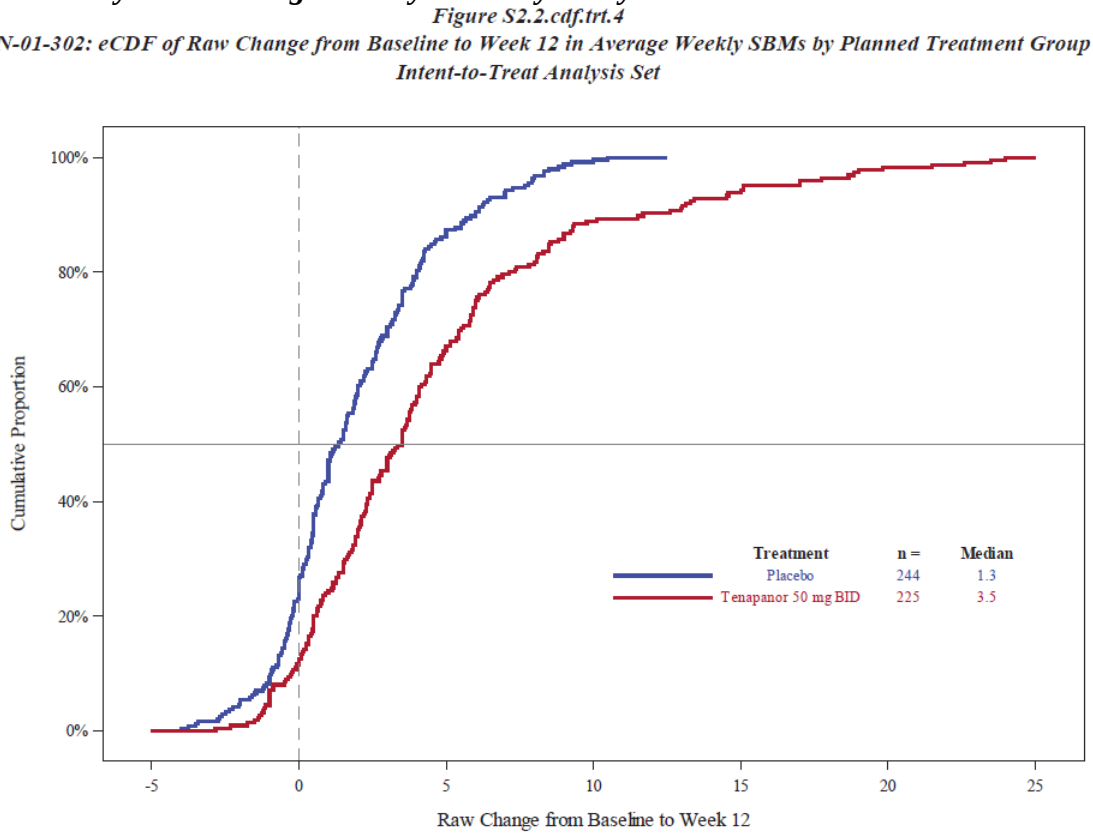


Figure 18. Study 302 - Average Weekly SBMs by Study Arm



<u>Stool Consistency</u>
Refer to Figures 19-24 below for the eCDF curves for average weekly stool consistency from baseline to week 12.

For studies 301 and 302, the curves representing different levels of improvement in the anchor scale categories (Figures 19 through 22) appear to support a meaningful improvement threshold corresponding with a two-category improvement in the anchor scales. The eCDF curves by study arms for study 301 (Figure 23) show some separation between curves and a similar observation was made for study 302 (Figure 24).

Figure 19. Study 301 – Change in Average Weekly Stool Consistency from Baseline to Week 12 by IBS Disease Severity Anchor Scale (Pooled Study Arm Data)

Figure S1.1.cdf.ibs.5
TEN-01-301: eCDF of Raw Change from Baseline to Week 12 in Average Weekly Stool Consistency by IBS Severity Anchor Response Category
Intent-to-Treat Analysis Set

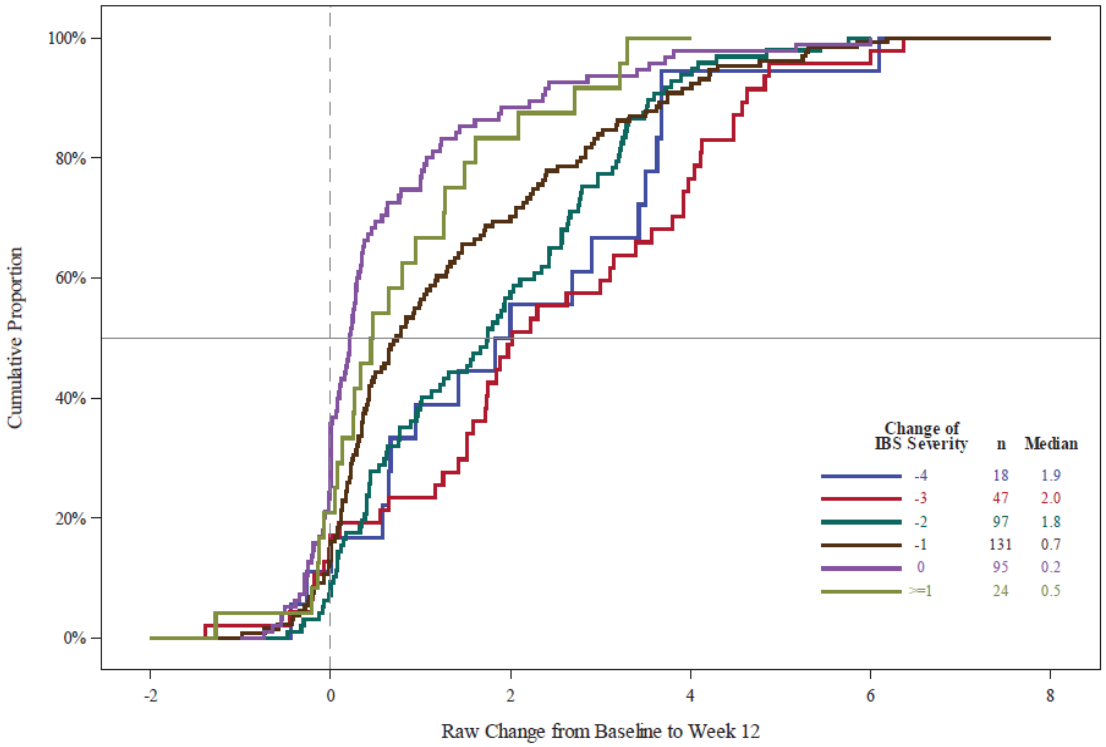


Figure 20. Study 302 – Change in Average Weekly Stool Consistency from Baseline to Week 12 by IBS Disease Severity Anchor Scale (Pooled Study Arm Data)

Figure S2.1.cdf.ibs.5
TEN-01-302: eCDF of Raw Change from Baseline to Week 12 in Average Weekly Stool Consistency by IBS Severity Anchor Response Category
Intent-to-Treat Analysis Set

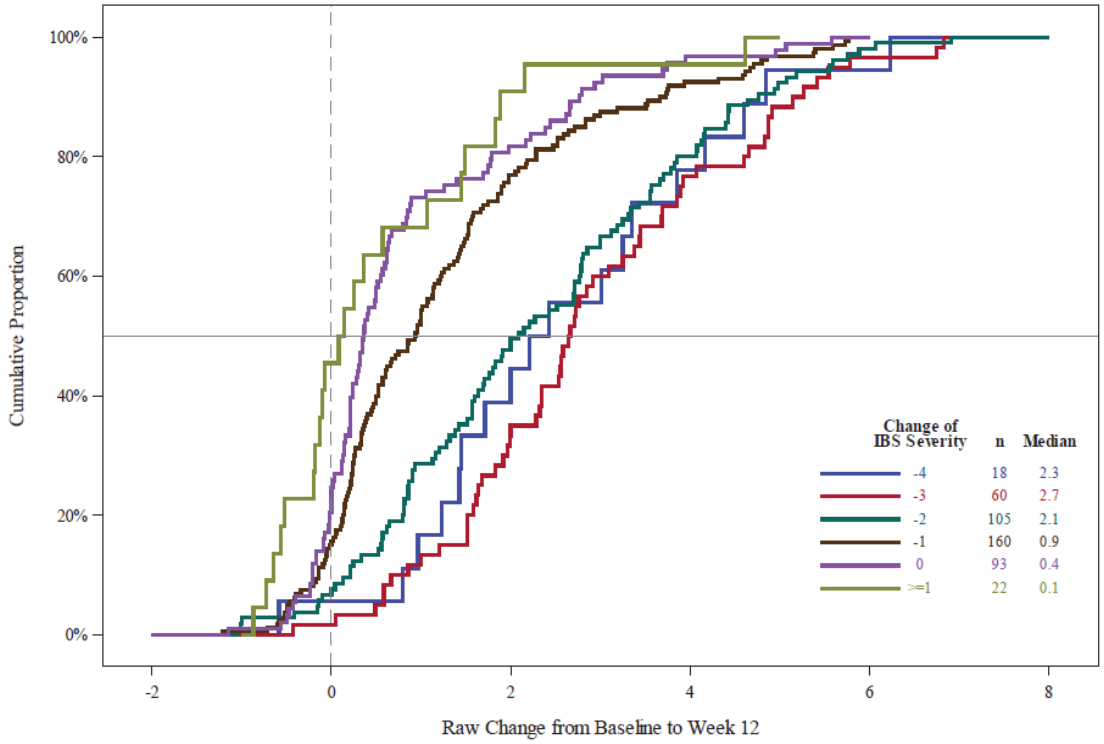


Figure 21. Study 301 – Change in Average Weekly Stool Consistency from Baseline to Week 12 by Constipation Severity Anchor Scale (Pooled Study Arm Data)

Figure S1.1.cdf.cons.5
TEN-01-301: eCDF of Raw Change from Baseline to Week 12 in Average Weekly Stool Consistency by Constipation Severity Anchor Response Category
Intent-to-Treat Analysis Set

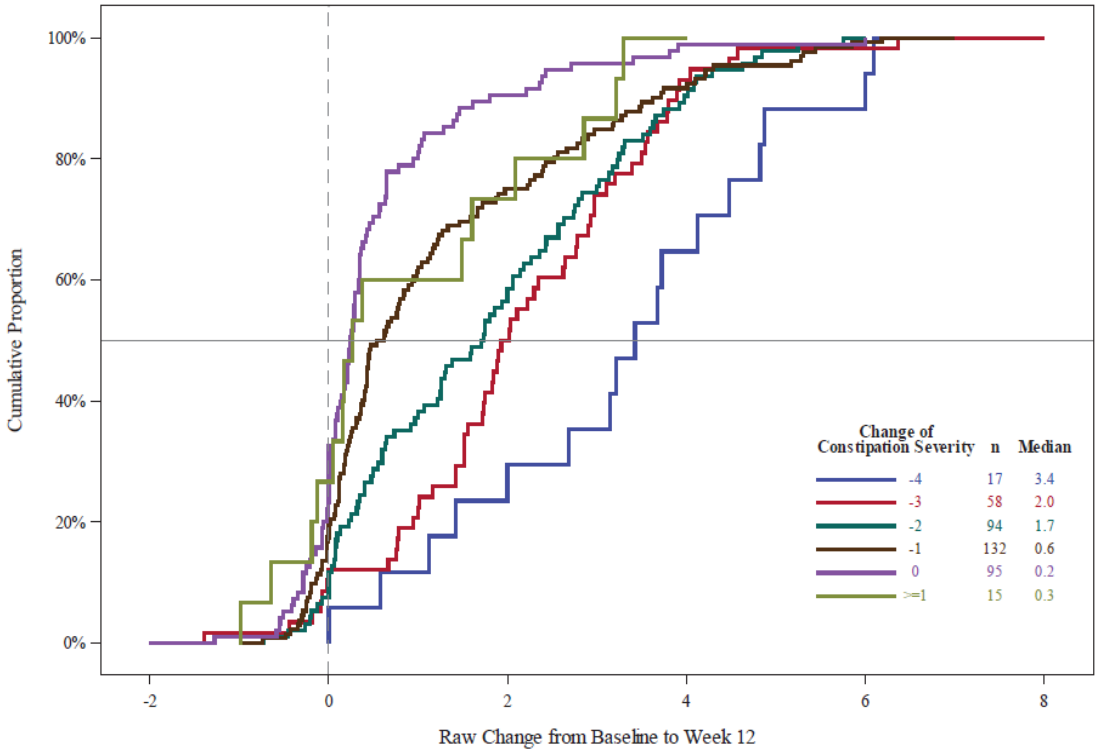


Figure 22. Study 302 – Change in Average Weekly Stool Consistency from Baseline to Week 12 by Constipation Severity Anchor Scale (Pooled Study Arm Data)

Figure S2.1.cdf.cons.5
TEN-01-302: eCDF of Raw Change from Baseline to Week 12 in Average Weekly Stool Consistency by Constipation Severity Anchor Response Category
Intent-to-Treat Analysis Set

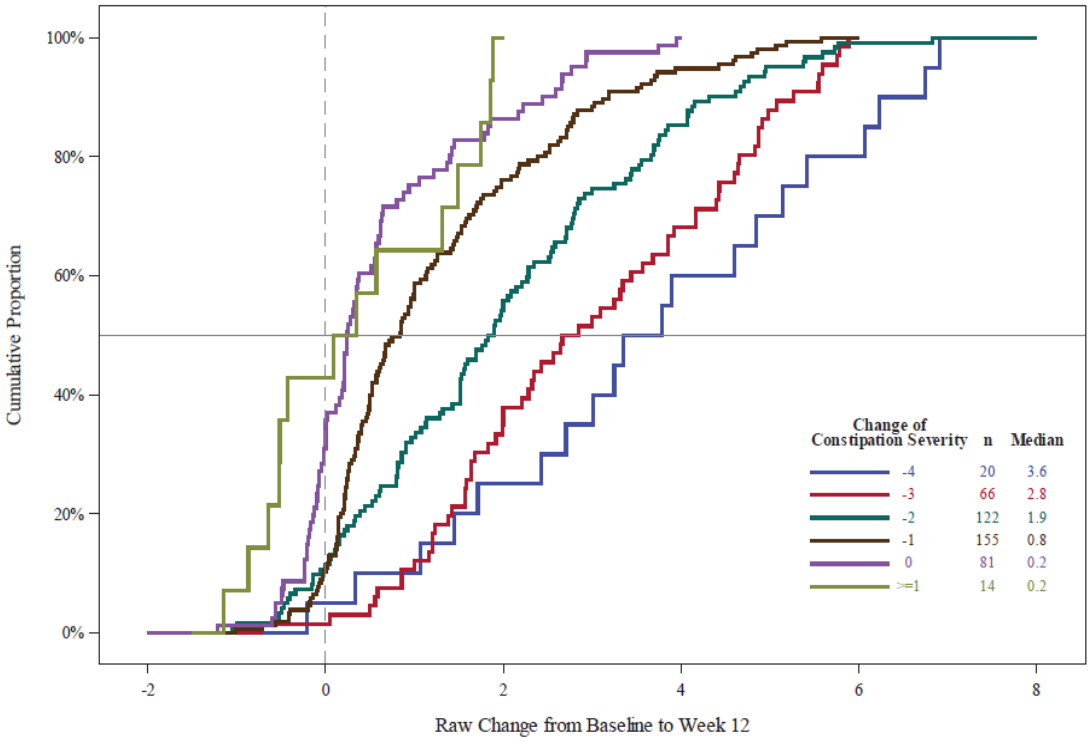


Figure 23. Study 301 - Average Weekly Stool Consistency by Study Arm

Figure S1.2.cdf.trt.5
TEN-01-301: eCDF of Raw Change from Baseline to Week 12 in Average Weekly Stool Consistency by Planned Treatment Group
Intent-to-Treat Analysis Set

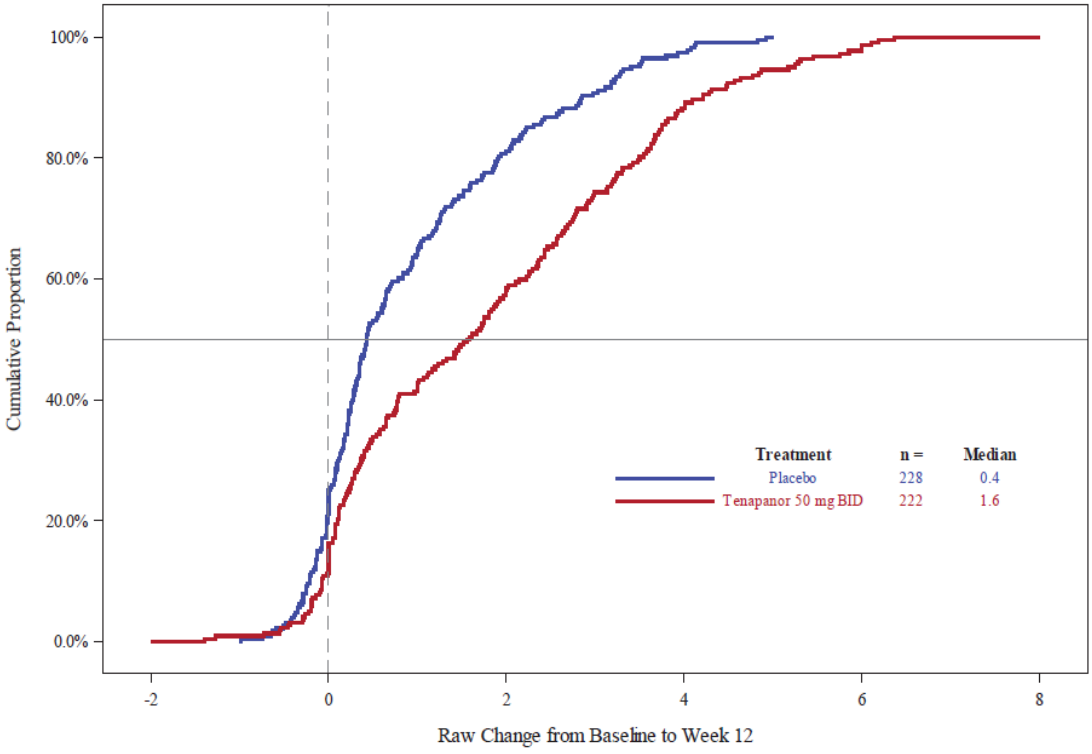
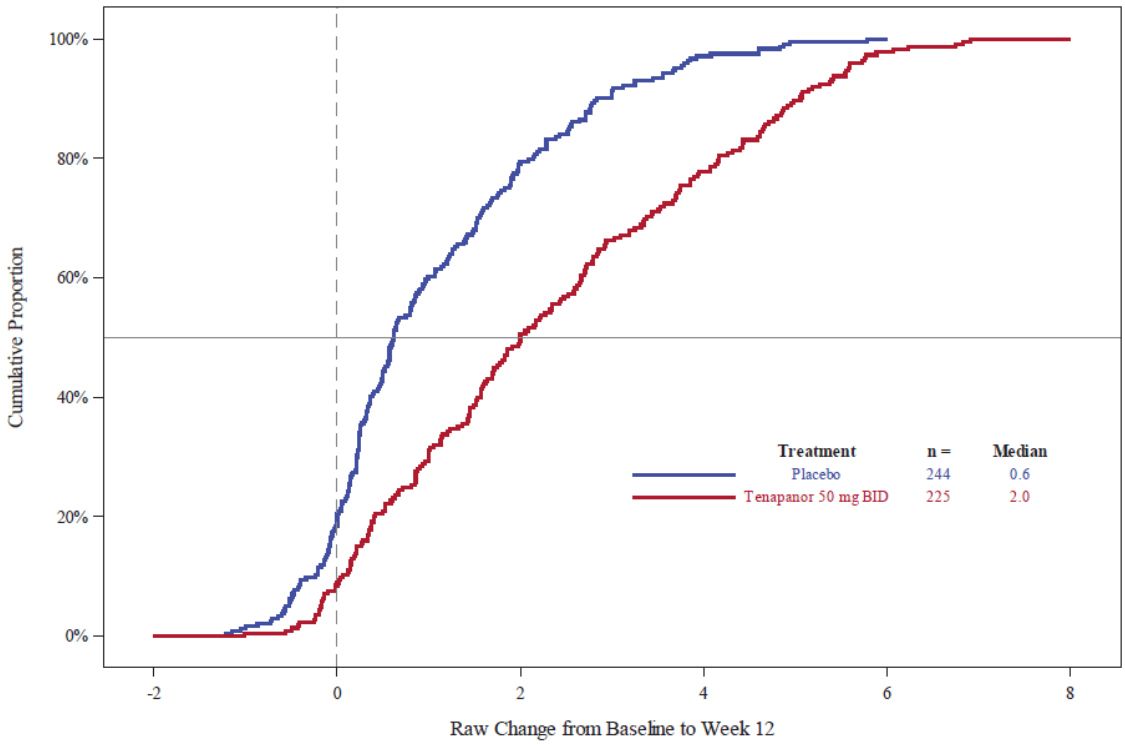


Figure 24. Study 302 - Average Weekly Stool Consistency by Study Arm

Figure S2.2.cdf.trt.5
TEN-01-302: eCDF of Raw Change from Baseline to Week 12 in Average Weekly Stool Consistency by Planned Treatment Group
Intent-to-Treat Analysis Set



Straining

Refer to Figures 25-30 below for the eCDF curves for change in average weekly straining score from Baseline to Week 12. A pre-defined responder threshold for the change in average weekly straining score was not submitted by the applicant.

The eCDF curves for straining based on improvement in the anchors and study arms are not clearly separated.

Figure 25. Study 301 – Change in Average Weekly Straining Score from Baseline to Week 12 by IBS Disease Severity Anchor Scale (Pooled Study Arm Data)

Figure S1.1.cdf.ibs.6
TEN-01-301: eCDF of Raw Change from Baseline to Week 12 in Average Weekly Straining Score by IBS Severity Anchor Response Category
Intent-to-Treat Analysis Set

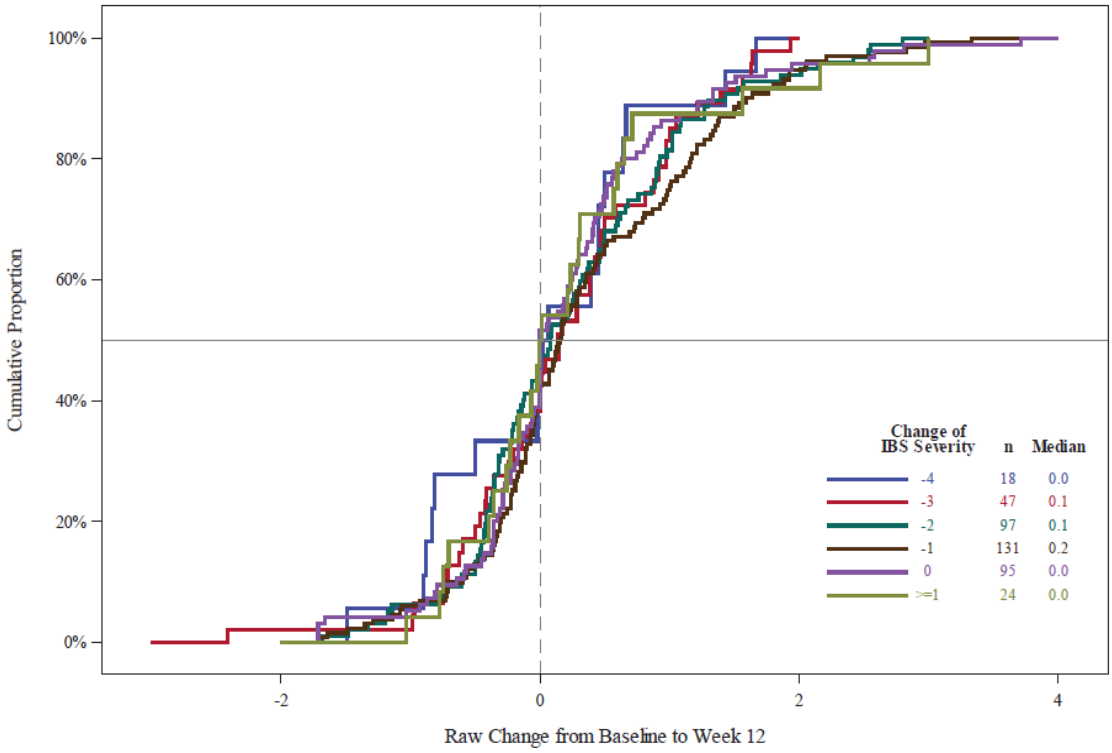


Figure 26. Study 302 – Change in Average Weekly Straining Score from Baseline to Week 12 by IBS Disease Severity Anchor Scale (Pooled Study Arm Data)

Figure S2.1.cdf.ibs.6
TEN-01-302: eCDF of Raw Change from Baseline to Week 12 in Average Weekly Straining Score by IBS Severity Anchor Response Category
Intent-to-Treat Analysis Set

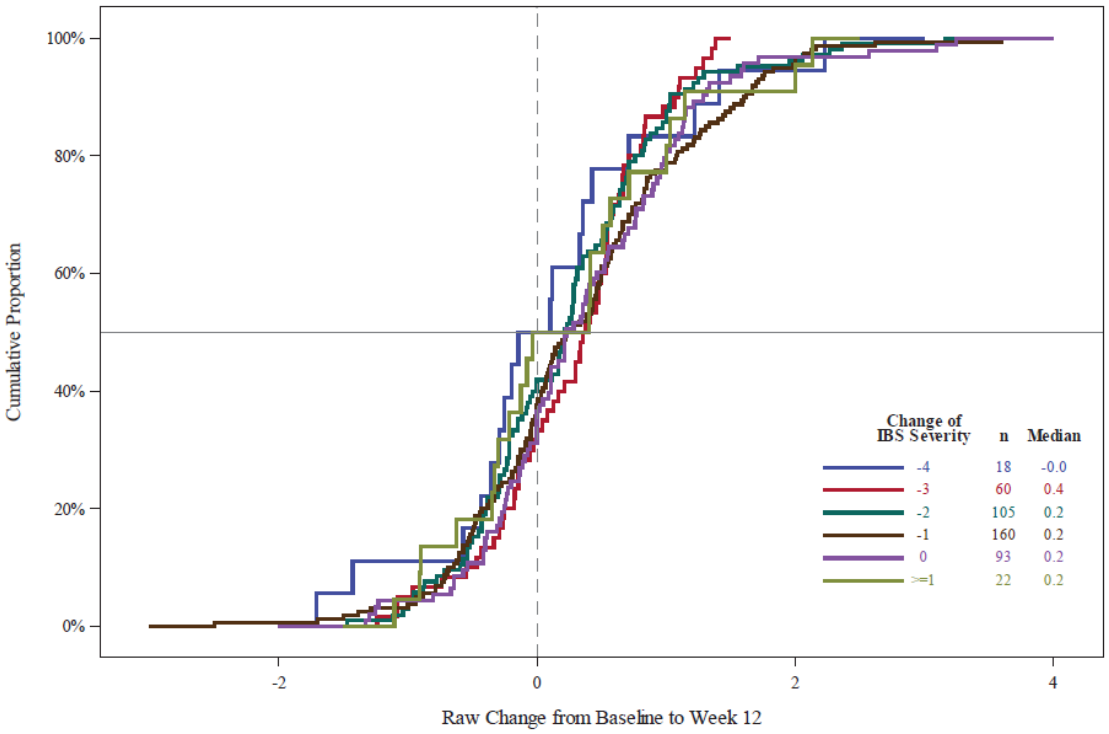


Figure 27. Study 301 – Change in Average Weekly Straining Score from Baseline to Week 12 by Constipation Severity Anchor Scale (Pooled Study Arm Data)

Figure S2.1.cdf.cons.6
TEN-01-302: eCDF of Raw Change from Baseline to Week 12 in Average Weekly Straining Score by Constipation Severity Anchor Response Category
Intent-to-Treat Analysis Set

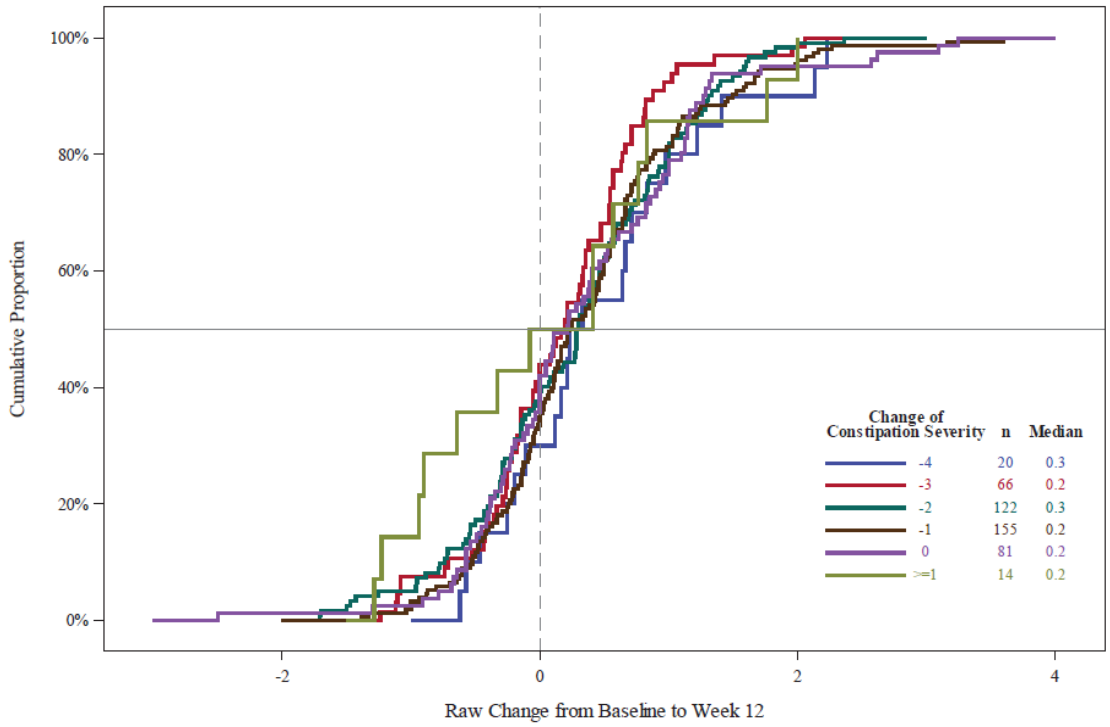


Figure 28. Study 302 – Change in Average Weekly Straining Score from Baseline to Week 12 by Constipation Severity Anchor Scale (Pooled Study Arm Data)

Figure S1.1.cdf.cons.6
TEN-01-301: eCDF of Raw Change from Baseline to Week 12 in Average Weekly Straining Score by Constipation Severity Anchor Response Category
Intent-to-Treat Analysis Set

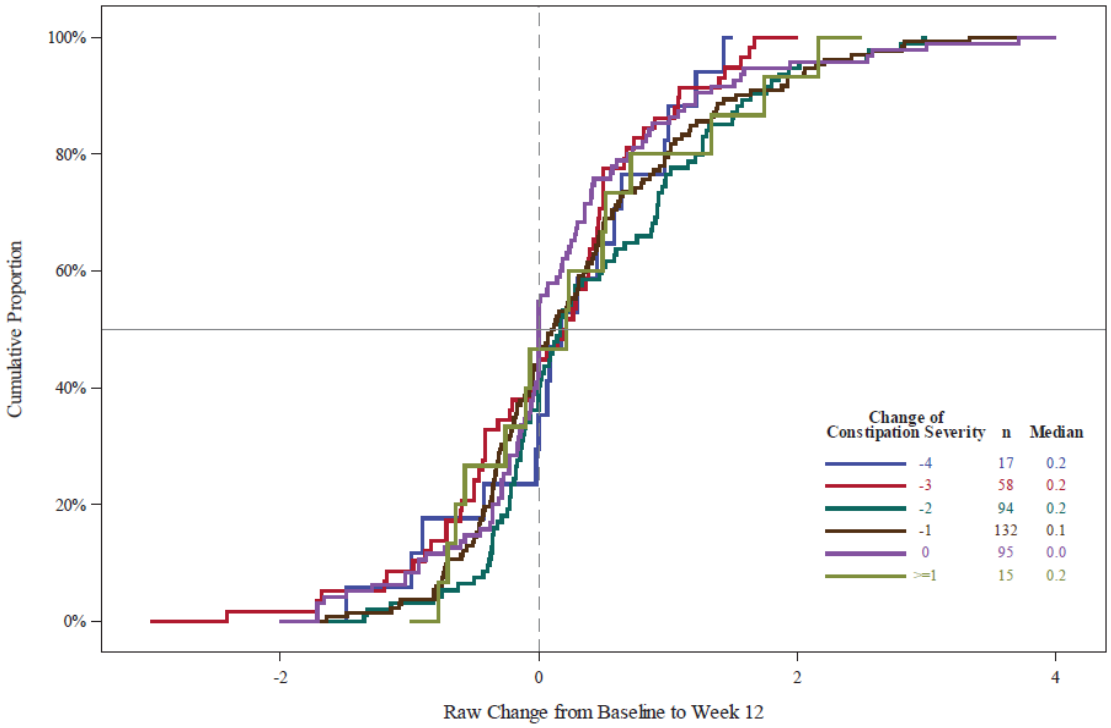


Figure 29. Study 301 - Change in Average Weekly Straining Score from Baseline to Week 12 by Study Arm

Figure S1.2.cdf.trt.6
TEN-01-301: eCDF of Raw Change from Baseline to Week 12 in Average Weekly Straining Score by Planned Treatment Group
Intent-to-Treat Analysis Set

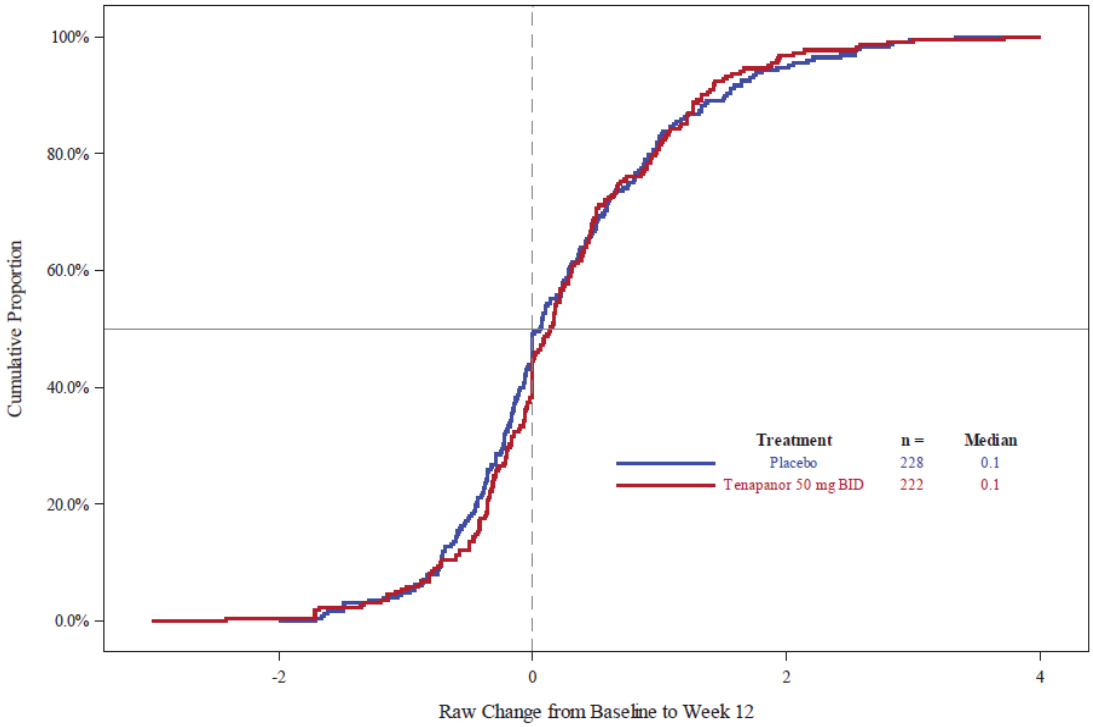
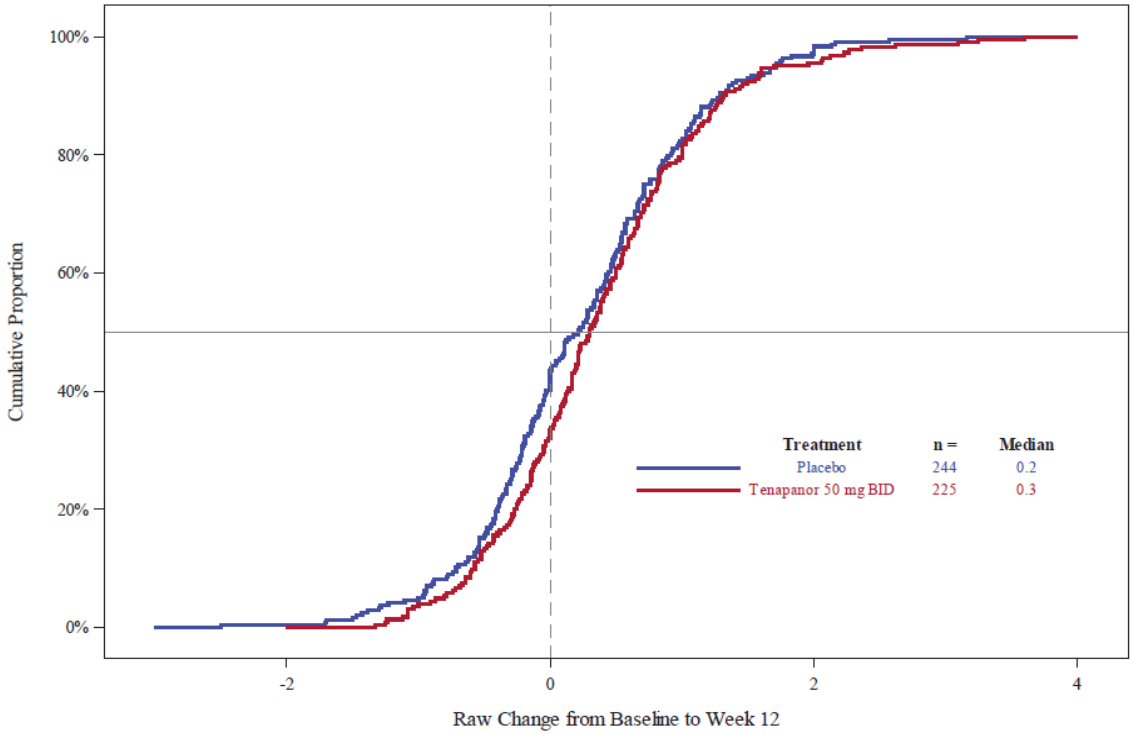


Figure 30. Study 302 - Change in Average Weekly Straining Score from Baseline to Week 12 by Study Arm

Figure S2.2.cdf.trt.6
TEN-01-302: eCDF of Raw Change from Baseline to Week 12 in Average Weekly Straining Score by Planned Treatment Group
Intent-to-Treat Analysis Set



D. APPENDICES

Appendix 1: IBS Symptom eDiary/Interactive Voice Response System (IVRS)
Appendix 2: Bristol Stool Form Scale (BSFS)

Appendix 1. IBS Symptom eDiary/IVRS Script

BM frequency

"How many bowel movements have you had in the past 24 hours?"
"Please enter the time of bowel movement <number> using the 12 hour AM/PM format. For AM press 1, for PM press 2."

Completeness of bowel emptying (for each bowel movement)

"Did you feel like you completely emptied your bowels? For yes press 1 for no press 2."

Stool consistency using BSFS (for each bowel movement)

"Refer to the Bristol Stool Form Scale given to you. Please enter the number that best describes the consistency of bowel movement <number> following the scale:
Press 1 for separate hard lumps, like nuts (hard to pass)
Press 2 for sausage shaped but lumpy
Press 3 for like a sausage but with cracks on its surface
Press 4 for like a sausage or a snake, smooth and soft
Press 5 for soft blobs with clear cut edges (passed easily)
Press 6 for fluffy pieces with ragged edges, a mushy stool
Press 7 for watery, no solid pieces (entirely liquid)"

Straining (for each bowel movement)

"How much did you strain during the bowel movement? Please use the following scale. Press 1 for not at all. Press 2 for a little bit. Press 3 for a moderate amount. Press 4 for a great deal. Press 5 for an extreme amount."

Abdominal Pain

"How would you rate your worst abdominal pain over the past 24 hours? Please use the scale where 0 represents no abdominal pain and 10 represents very severe abdominal pain. Please enter a value between 0 and 10 followed by pound or hash sign."

Abdominal discomfort

How would you rate your abdominal discomfort over the past 24 hours? Please use the scale where 0 represents no abdominal discomfort and 10 represents very severe abdominal discomfort. Please enter value between 0 and 10 followed by pound or
hash sign

Abdominal bloating

"How would you rate your abdominal bloating over the past 24 hours? Please use the scale where 0 represents no abdominal bloating and 10 represents very severe abdominal bloating. Please enter a value between 0 and 10 followed by pound or hash
sign."

Abdominal fullness

"How would you rate your abdominal fullness over the past 24 hours? Please use the
scale where 0 represents no abdominal fullness and 10 represents very severe abdominal fullness. Please enter a value between 0 and 10 followed by pound or hash
sign."

Abdominal cramping

"How would you rate your abdominal cramping over the past 24 hours? Please use the scale where 0 represents no abdominal cramping and 10 represents very severe abdominal cramping. Please enter a value between 0 and 10 followed by pound or hash sign."

Use of rescue medications

If diary was completed the previous day "Have you taken any rescue medication over the past 24 hours? For yes press 1, for no press 2."
If diary was NOT completed the previous day "Have you taken any rescue medication over the past 48 hours? For yes press 1, for no press 2."
If yes. "Please enter the date you took the rescue medication, using the 8-digit format;
2 digits for the month, 2 digits for the day and 4 digits for the year."
"Please enter the time you took rescue medication, using a 12 hour AM/PM format. "

"For AM press 1, for PM press 2"

Weekly: IBS Severity

"How would you rate the severity of your IBS over the past week? Please use the following scale. Press 1 for None. Press 2 for Mild. Press 3 for Moderate. Press 4 for
Severe. Press 5 for Very Severe."

Weekly: Constipation Severity

"How would you rate the severity of your constipation over the past week? Please use the following scale. Press 1 for None. Press 2 for Mild. Press 3 for Moderate.
Press 4 for Severe. Press 5 for Very Severe."

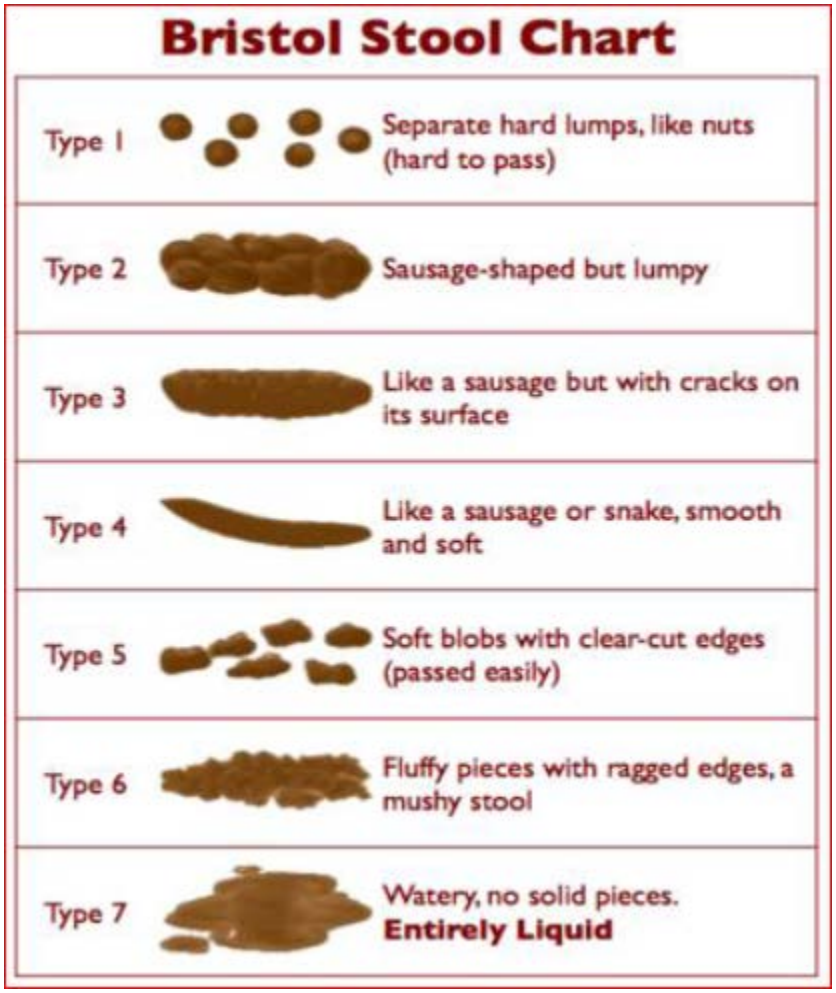
Weekly: Adequate Relief of IBS Symptoms

"Have you had adequate relief of your IBS symptoms over the past week? Press 1 for
Yes. Press 2 for No."

Weekly: Degree of Relief of IBS Symptoms (weekly)

"How would you rate the degree of relief of your IBS symptoms over the past week?
Please use the following scale. Press 1 for Completely relieved. Press 2 for Considerably relieved. Press 3 for Somewhat relieved. Press 4 for Unchanged. Press 5
for Somewhat worse. Press 6 for Considerably worse. Press 7 for as bad as I can imagine."

Appendix 2. Bristol Stool Form Scale (BSFS)



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/s/

SUSAN M PRETKO
07/17/2019 08:59:19 AM

SARRIT M KOVACS
07/18/2019 03:43:44 PM

ELEKTRA J PAPADOPOULOS
07/23/2019 10:00:18 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 3, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 211801
Product Name and Strength:	Ibsrela (tenapanor) tablet, 50 mg
Applicant/Sponsor Name:	Ardelyx, Inc.
FDA Received Date:	June 25, 2019
OSE RCM #:	2018-1994-1
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on June 25, 2019 for Ibsrela. Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised container labels for Ibsrela (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Abraham, S. and Labeling Review for Ibsrela (NDA 211801). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 24. RCM No.: .2018-1994

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 25, 2019

Container labels

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/s/

SHERLY ABRAHAM
07/03/2019 11:50:51 AM

IDALIA E RYCHLIK
07/03/2019 12:28:29 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Telephone: 301-796-2200
FAX: 301-796-9744

Maternal Health Labeling Review

Date: May 23 2019 **Date consulted:** October 12, 2018

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Division Director, DPMH

To: Division of Gastroenterology and Inborn Errors Products (DGEIP)

Drug: Tenapanor HCl

Class: Irritable Bowel Syndrome Drugs (IBS-C)

NDA: 211801

Applicant: Ardelyx, Inc

Subject: Pregnancy and Lactation Labeling Rule (PLLR)

Indication: For treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

Materials Reviewed:

- September 12, 2018 submission for Tenapanor hydrochloride, an original application under 505-(b)(1) pathway
- October 12, 2018, DGEIP's consult request to DPMH for tenapanor labeling review, DARRTS Reference ID: 4334234.

- May 9, 2019 Applicant's response to Information request of May 7, 2019 regarding pregnancy Birth Outcomes during the drug development cycle.

Consult Question: Assist with Pregnancy and Lactation Labeling Rule (PLLR).

INTRODUCTION

On September 12, 2018, the applicant, Ardelyx, Inc, submitted an original NDA 211801, proposing a labeling in PLLR format. The Division of Gastroenterology and Inborn Errors Products (DGEIP) consulted the Division of Pediatric and Maternal Health (DPMH) on October 12, 2018, to provide input for appropriate labeling of the *Pregnancy* and *Lactation* subsections of tenapanor labeling to comply with the PLLR.

BACKGROUND

Tenapanor Drug Characteristics[1]

- Tenapanor is a locally acting sodium/hydrogen exchanger 3 (NHE3) inhibitor
- Following single and repeated oral dosing of IBSRELA 50 mg twice daily, a small amount is absorbed, with plasma concentrations of tenapanor below the limit of quantitation (< 0.5 ng/mL) in the majority of healthy subjects.
- Plasma protein binding of tenapanor and its major metabolite, M1, is approximately 99% and 97%, respectively
- Molecular weight of 1218 D.
- Half-life (t1/2) could not be determined

REVIEW

PREGNANCY

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day was not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss; however, the doses were toxic to the maternal animals. No adverse fetal effects were observed in rats at 0.1 times the maximum recommended human dose and in rabbits at doses up to 8.8 times the maximum recommended human dose (based on body surface area).

Review of Literature

Applicant's Review

The applicant did not identify any publications regarding tenapanor use in pregnancy.

DPMH Review

This reviewer did not identify any publications on tenapanor use in pregnancy. There were no entries in TERIS, ReproTox, or GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation.

[1] Tenapanor proposed labeling as of September 12, 2018

Pharmacovigilance Review

The applicant reports 4 pregnant patients in the clinical trials.

- The first patient received tenapanor for 12-weeks followed by placebo for 4 weeks. She was found to be pregnant while on placebo (one month after stopping study drug). She was told to continue taking placebo (unknown if investigator who told her this was unblinded). There is only one follow up piece of information saying that a prenatal test showed no evidence of birth defects.
- The second patient received tenapanor for 4 weeks and had unprotected sex. She asked the PI for a Plan B prescription. She had a positive pregnancy test (HCG) and a repeat one a week later that showed showed declining values that the PI interpreted as compatible with pregnancy loss.
- The two other patients received placebo. They discontinued the placebo and continued their pregnancies to term. One delivered vaginally a live female infant at 38 weeks with elevated bilirubin. No other abnormalities with the pregnancy, birth, or newborn were reported. The other patient delivered a live male infant. No further information was available.

No information on pregnancy outcomes in patients who became pregnant while receiving study drug exist.

Reviewer comment

There are very few pregnancies during tenapanor treatment. The fact that the applicant did not have a complete record of these pregnancies is unacceptable.

Summary

Case reports on tenapanor exposure in pregnant women have not identified any drug associated risk.

LACTATION

Animal Data

No lactation studies in animals have been conducted.

Review of Literature

Applicant's Review

The applicant did not identify any publications regarding the presence of tenapanor in human milk, its effects on milk production or any effects on the breastfed infant.

DPMH Review

In addition to the search of published literature performed by the applicant, DPMH also conducted a literature search in PubMed, Embase and the databases Toxnet/LactMed for tenapanor and use in pregnancy. No iformation could be identified. GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation and Thomas Hale in Medications and Mother's Milk did not have any entries.

Pharmacovigilance Review

The applicant did not identify any cases in their pharmacovigilance database.

Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor provides minimal systemic availability with plasma concentrations below the limit of quantification (<0.5 ng/mL) in the majority of healthy subjects following oral administration. It is unlikely that the minimal systemic absorption of tenapanor will result in a clinically relevant exposure to breastfed infants.

However, concern has been raised over the findings following tenapanor exposure in the animal juvenile toxicity studies. This similar concern has lead to two other FDA-approved products on the market for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults to have an agreed upon postmarketing clinical lactation study. DPMH continues to discuss the need for a milk-only clinical lactation study for tenapanor with the Division (clinical team and ADL).

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Animal Data

Tenapanor was not tumorigenic in male and female rats at oral doses up to 5 mg/kg/day (approximately 0.5 times the maximum recommended human dose, based the body surface area). Tenapanor was not genotoxic in the in vitro bacterial reverse mutation (Ames) assays, an in vitro chromosomal aberration assay in cultured human peripheral blood lymphocytes or the in vivo micronucleus assays in mice and rats. Tenapanor had no effect on fertility or reproductive function in male rats at oral doses up to 10 mg/kg/day (approximately 0.97 times the maximum recommended human dose, based on the body surface area) and in female mice at oral doses up to 50 mg/kg/day (approximately 2.4 times the maximum recommended human dose, based on the body surface area).

Applicant's and DPMH Review of Literature

The applicant did not identify any published data on the effects of tenapanor use on fertility. DPMH was unable to locate any published literature. GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation, does not report anything on Females and Males of Reproductive Potential.

Pharmacovigilance Review

The applicant did not identify any cases in their pharmacovigilance database. No specific reports exist.

Summary

There are no human data on the effects of tenapanor on fertility and no evidence of infertility in animal studies. There are no recommendations for pregnancy testing nor contraception. Therefore, subsection 8.3, *Females and Males of Reproductive Potential* will not be included in tenapanor labeling.

CONCLUSIONS

Tenapanor labeling has been revised to comply with the PLLR. There are no published data on safety issues with tenapanor use in pregnant or lactating women, and no data on tenapanor effects on fertility. DPMH has the following recommendations for the tenapanor labeling.

- Pregnancy, Subsection 8.1

The *Pregnancy* subsection of tenapanor labeling was formatted in the PLLR format to include the *Risk Summary*, and *Data* headings.

- Lactation, Subsection 8.2

  The *Lactation* subsection of tenapanor labeling was formatted in the PLLR format to include the *Risk Summary* heading.

RECOMMENDATIONS

DPMH presented the following recommendations for the tenapanor labeling to the Division on March 8, 2019 for compliance with the PLLR. DPMH refers to the final NDA approval letter for final labeling.

PRESCRIBING INFORMATION

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available data on IBSRELA exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (<0.5 ng/mL) following oral administration *[see Clinical Pharmacology (12.3)]* Therefore, maternal use is not expected to result in fetal exposure to the drug. In reproduction studies with tenapanor in rats and rabbits, no adverse fetal effects were observed in rats at 0.1 times the maximum recommended human dose and in rabbits at doses up to 8.8 times the maximum recommended human dose (based on body surface area).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.1 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 8.8 times the maximum recommended human dose, based on body surface area).

In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 9.7 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (<0.5 ng/mL) following oral administration *[see Clinical Pharmacology (12.3)]*. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IBSRELA and any potential adverse effects on the breastfed infant from IBSRELA or from the underlying maternal condition.

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/s/

CHRISTOS MASTROYANNIS
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TAMARA N JOHNSON
05/23/2019 03:13:12 PM

LYNNE P YAO
05/24/2019 02:27:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone: 301-796-2200
FAX: 301-796-9855

PEDIATRIC LABELING REVIEW

From:	Carolyn L. Yancey, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Hari Cheryl Sachs, MD, Pediatric Team Leader, DPMH John J. Alexander, MD, MPH, Deputy Director, DPMH
NDA Number:	211801
Sponsor:	Ardelyx, Incorporated
Drug:	Ibsrela (tenapanor) Tablets
Drug Class:	Sodium/hydrogen exchanger 3 (NHE3) inhibitor
Dosage Form and Route of Administration:	Tablets, for oral use
Dosing Regimen:	50 mg tablet taken orally twice daily
Proposed Indication:	For the treatment of irritable bowel syndrome (IBS) with constipation (IBS-C) in adults
Consult Request:	The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests the DPMH Pediatric Team review of pediatric labeling for the 505(b)(1) new drug application (NDA) 211801 Ibsrela (tenapanor) manufactured by (b) (4) DGIEP also requests DPMH assistance to prepare for the Pediatric Review Committee (PeRC) Meeting discussion to include postmarketing requirements (PMRs) addressing the pediatric IBS-C clinical development program for tenapanor. The consult is due on May 10, 2019 (consult is dated October 12, 2018).

Background

The labeling under review is for Ibsrela (tenapanor), NDA 211801 submitted on September 12, 2018, a new molecular entity (NME) proposed for the treatment of IBS-C in adults. Tenapanor is a locally acting, selective small molecule NHE3 inhibitor that is minimally absorbed.[1] In vitro and animal studies indicate

[1] NDA 211801 IBSRELA (tenapanor) Tablets, Module 2.5 Clinical Overview, subsection 2.5.1 Product Development Rationale, pages 8 - 13.

that tenapanor's major metabolite, M1, is not active against NHE3. NHE3 has a central role in the sodium re-uptake process in the gastrointestinal (GI) tract and is considered a contributor in maintaining intestinal water/sodium homeostasis. In constipation disorders, such as IBS-C, the proposed mechanism of action of tenapanor is to reduce sodium re-uptake and increase water secretion in the small intestine and colon, accelerating intestinal transit time and resulting in softer stool consistency.[1] The proposed to-be-marketed drug product is an immediate-release tablet in a 50 mg strength (equivalent to 53.2 mg of tenapanor hydrochloride) with an adult dosing regimen of 50 mg, orally, twice daily.

Non-clinical Information

Per the applicant, nonclinical data demonstrates an increase in GI motility and decrease in visceral pain.[2] In published literature, nonclinical studies suggest that tenapanor also decreases visceral hypersensitivity.[3] In a rat model of IBS-like colonic hypersensitivity, tenapanor is reported to have normalized visceral motor reflex response to colorectal distension and normalized colonic sensory neuronal excitability.[4] Per the applicant, (b) (4) [5] In a 21-day oral dose range-finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats [post-natal day (PND) 5] at doses of 5 and 10 mg/kg/day and was not tolerated in male and female pups. The study was terminated on study day 11 (PND 16) due to mortalities and decreased body weight (24% to 29% reduction compared with control pups). Per the Pharmacology Toxicology reviewer, study data does not describe stool volume/consistency and there were no internal target organs of toxicity.

Reviewer Comments: The existing non-clinical data, including juvenile animal (neonatal rats), does not provide data to support the pediatric population 6 years to less than 12 years of age. Similar juvenile toxicology findings are reported for plecanatide and linaclotide. Therefore, a non-clinical study in older juvenile animals through PND (b) (4) will be required under the Pediatric Research Equity Act (PREA) as a postmarketing requirement (PMR) before clinical studies in patients 6 years to less than 12 years may be initiated. See summary of PREA PMRs later in this review.

Armamentarium of Approved Treatment

Currently, FDA-approved products for treatment of IBS-C in adults include Amitiza (lubiprostone), Linzess (linaclotide), and Trulance (plecanatide). The mechanism of action (MOA) for Amitiza is to loosen stools as a chloride channel activator and for Trulance and Linzess is to loosen stools as a guanylate cyclase-C agonist. By contrast, the MOA for tenapanor is to loosen stools by blocking sodium absorption in the GI tract (see above **Background**). Linzess and Trulance labeling include a Contraindication for patients less than 6 years of age due to the risk of serous dehydration. There are no products approved for treatment of IBS-C in pediatric patients. PREA requirements are ongoing for IBS-C for Trulance and Linzess. At this time, Amitiza does not have PREA PMRs for the indication of IBS-C. Amitiza pediatric studies as postmarketing study commitments (PMCs) were originally deferred (dated January 31, 2006) for pediatric patients from birth to 17 years) for the treatment of chronic idiopathic constipation (CIC). The sponsor fulfilled the pediatric study requirement for pediatric ages 6 years to less than 18 years of age (PMR Study 572-4) for Pediatric Functional Constipation (PFC) though the study failed to demonstrate effectiveness for the treatment of PFC in a 12 week, randomized, double-blind, placebo controlled trial conducted in 606 patients 6 years to 17 years of age with PFC comparing Amitiza to placebo. Adverse reactions to Amitiza were similar to those reported in adults. The pediatric study requirement for patients from birth to 5 years of

[2] NDA 211801 IBSRELA (tenapanor) Tablets, Module 2.5 Clinical Overview, subsection 2.5.1 Product Development Rationale, page 8.
[3] Eutamene H et al. Visceral antinociceptive effects of RDX5791, a first-in-class minimally systemic NHE3 inhibitor on stress-induced colorectal hypersensitivity to distension in rats. Gastroenterology 2011; 140: S-57-58 (abstract).
[4] Wouters et al. Histamine receptor H1-mediated sensitization of TRPV1 mediates visceral hypersensitivity and symptoms in patients with irritable bowel syndrome. Gastroenterology. 2016 Apr 1;150(4):875-87.
[5] NDA 211801 IBSRELA (tenapanor) Tablets, proposed labeling, Section 8.4 Juvenile Animal Toxicity Data (dated 26March2019)

age is waived because necessary studies are impossible or highly impracticable. This is because IBS-C does not occur in this age group or the population is too small.[6]

Clinical Development Program for Tenapanor in Adults with IBS-C

The clinical development program for tenapanor in IBS-C is under investigational new drug (IND) 108732.[7] NDA 211801 is supported by two pivotal Phase 3 studies in adults, TEN-01-301 and TEN-01-302, a supportive Phase 2b study, D562C00001, and the ongoing long-term, open label (OL) safety study, TEN-01-303 with 52 weeks exposure. All enrolled patients with IBS-C met the ROME III criteria.[8] Per the sponsor, the adult data show statistically significant improvements in responder rates based on complete spontaneous bowel movements (CSBM) and abdominal pain. Supportive efficacy and safety data include completed studies in patients with chronic kidney disease (CKD)/end-stage renal disease (ESRD) under IND (b) (4) in the Division of Cardiovascular and Renal Products (DCaRP). The primary efficacy endpoint was based on a patient being a weekly responder for at least 6 of the first 12 weeks of treatment (designated "6/12 weeks").[9, 10] The combined CSBM and abdominal pain responder rate for 6/12 weeks with tenapanor 50 mg BID demonstrates a statistically significant difference from PBO in favor of tenapanor ($p \leq 0.021$) in the intent-to-treat (ITT) population. The 9/12-week data demonstrates a durable and sustained response for constipation, abdominal pain, and normalization of BM frequency in the efficacy studies shown in **Table 1**.

Table 1. Overview of Efficacy Studies for Tenapanor in Adult IBS-C

Study ID, Phase	Study Design	Tenapanor Treatment	Key Results
TEN-01-301 Phase 3 United States (US)	12-week randomized (R), double-blind (DB), placebo-controlled (PBO-C) study followed by a 4-week randomized withdrawal (RW) period. [2-week screening, 12-week treatment, 4-week RW] Efficacy and safety	Tenapanor 50 mg BID (n=307); PBO (n=299)	CSBM and abdominal pain combined responder rate for 6/12 weeks was statistically significantly higher, tenapanor vs PBO (p=0.021).* No secondary endpoint achieved statistically significant response for tenapanor vs PBO (only shows positive trends).
TEN-01-302 Phase 3 US	26-week R, DB, PBO-C study [2-week screening, 26-week treatment] Efficacy and safety	Tenapanor 50 mg BID (n=293), PBO (n=299)	CSBM and abdominal pain combined responder rate for 6/12 weeks was statistically significantly higher w/tenapanor vs PBO ($p < 0.001$). Secondary endpoints were statistically significantly improved w/tenapanor vs PBO.
D5612C00001 Phase 2b US	12-week, R, DB, study [2-week screening, 12-week treatment, 4-week follow-up] Efficacy and safety	Tenapanor 5 mg BID 20 mg BID 50 mg BID PBO BID	Statistically significant increases in CSBM responder rate and overall combined responder rate (secondary endpoint) at 50 BID. Abdominal pain responder rate was 48% w/PBO and 66% w/tenapanor 50 mg BID.
Source: Revised from NDA 211801 IBSRELA (tenapanor), Module 2.7.3 Summary of Clinical Efficacy, Table 1-1, pp 19 - 20. Note: Patients receiving tenapanor during the 12-week treatment period were re-randomized to continue tenapanor or switch to			

[6] NDA 021908/Supplement 005 Amitiza (lubiprostone), per the Approval letter for Amitiza for the treatment of IBS-C in women greater than or equal to 18 years old (dated April 29, 2008).
[7] Tenapanor is also being developed for control of serum phosphorus in chronic kidney disease patients on dialysis under the Division of Cardiovascular and Renal Products (DCaRP), IND (b) (4)
[8] ROME III Criteria, ROME Endpoints and Outcomes Conference 2009: http://www.romecriteria.org/meetings_events/endout_conf_program.cfm#
[9] NDA 211801 IBSRELA (tenapanor) tablet, Module 2.5.4.1.1 Clinical Overview Section, pages 37 to 38
[10] *Guidance for Industry, Irritable Bowel Syndrome - Clinical Evaluation of Products for Treatment* (dated May 2012).

PBO (patients on PBO were switched to tenapanor). This treatment arm was not part of the primary analysis. Per DGIEP clinical and statistics review teams, the RW information is not included in labeling.

Exposure and Safety

A total of 2,085 patients with IBS-C received tenapanor across the completed clinical studies (as of June 12, 2018) including over 500 patient-years of exposure. Of the total patients, 1073 of 2085 patients received tenapanor, 50 mg BID. The most common treatment emergent adverse events (TEAEs) in greater than or equal to 2%, tenapanor 100 mg treatment groups and more frequent than PBO are: diarrhea (14.82% compared with 2.30% PBO), nausea (2.52% compared with 2.44% PBO) and flatulence (2.24% compared with 1.63% PBO). In addition, rectal bleeding, possibly representing colitis, is reported in 7 of 1230 patients in the two Phase 3 studies and one case of colitis is reported in the CKD study (D5610C00001) in patients treated with tenapanor. Isolated case reports of hyperkalemia were reported more frequently in IBS-C patients treated with tenapanor than with PBO.

Reviewer Comments: DPMH recommends that a PMR be considered for pharmacovigilance monitoring and reporting on the risk of colitis as well as hyperkalemia potentially associated with the use of tenapanor in patients with IBS-C. These two risks should also be monitored in the pediatric clinical development program for IBS-C.

Pediatric Research Equity Act Requirements

Under PREA, (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. All requirements under PREA apply to tenapanor as an NME.

Agreed initial Pediatric Study Plan

An Agreed initial Pediatric Study Plan (iPSP), dated September 26, 2017, includes plans to request a partial waiver in pediatric patients from birth to less than 6 years of age because necessary studies are impossible or highly impracticable in the very young and a deferral of pediatric studies in patients 6 years to less than 18 years of age with IBS-C. Non-clinical study plans include a juvenile animal toxicology single-dose study in 4-day old mice and an 8-week, repeat dose study in rats up to PND 21 to support treatment in humans 2 years to less than 12 years.

Bridging adult efficacy/exposure-response (E-R) data in IBS-C to pediatric patients with IBS-C will include conduct of a Phase 2 dose ranging, efficacy, and safety study in patients 6 years to less than 12 years along with a Phase 3 efficacy and safety study in adolescent patients, 12 years to less than 18 years of age, to be followed by a Phase 3 efficacy and safety in patients 6 years to less than 12 years old. Clinical responders to the primary efficacy endpoint (CSBMs and abdominal pain) will be eligible to enroll in a long term, OL safety extension study to be conducted in patients 6 years to less than 18 years of age. (b) (4) The timeline for submission of the Phase 2 pediatric dose-ranging study is December 2020.

Proposed PREA PMRs

3581: A 60-day, repeat dose, GLP juvenile animal toxicology study in rats in which the dosing of the animal should be initiated on post-natal day (PND) 21.

3581-2: A phase 2, randomized, double blind, placebo controlled, dose ranging study to assess safety and efficacy of tenapanor in pediatric patients with IBS-C ages 6 years to less than 12 years of age. The study will include at least 2 doses and treatment duration will be 4 weeks.

3581-3: A 12-week, randomized, double blind, placebo-controlled phase 3 study to assess the safety and efficacy of tenapanor for the treatment of constipation predominant irritable bowel syndrome (IBS-C) in patients 12 to less than 18 years of age.

3581-4: A randomized, double blind, placebo-controlled Phase 3 study to assess the safety and efficacy of tenapanor for the treatment of constipation predominant irritable bowel syndrome (IBS-C) in pediatric patients 6 to less than 12 years of age.

3581-5: An open-label, long term extension study to assess the safety of ongoing treatment with tenapanor for constipation predominant irritable bowel syndrome (IBS-C) in pediatric patients aged 6 years to <18 years of age, who participated in a prior tenapanor clinical study.

Reviewer Comment: DPMH recommends that PREA PMR 3581-5 address long-term tolerability and safety in pediatric patients (6 years to less than 18 years of age) (b) (4) *We recommend adding the specific duration* (b) (4) *to PREA PMR 3581-5. DPMH recommends including monitoring for* (b) (4) *among other reported gastrointestinal risks associated with use of tenapanor.*

DPMH Pediatric Labeling Recommendations

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population compared with the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric population. Ibsrela (tenapanor) has no indication in pediatric patients. Proposed labeling, submitted in PLR and PLLR format, includes a Boxed Warning on the risk of serious dehydration in pediatric patients and the indication is limited to adults with IBS-C.[10] DPMH supports addition of nonclinical juvenile animal study information to Warnings and Precautions (5.1) on the risk of serious dehydration in pediatric patients and addition of Warnings and Precautions (5.3) on hyperkalemia based on reports of increased potassium in patients receiving tenapanor who have predisposing conditions to hyperkalemia (e.g., renal impairment as well as elderly patients). Subsection 8.4 Pediatric Use is updated to inform prescribers that Ibsrela is contraindicated in patients less than 6 years of age and that safety and effectiveness of Ibsrela is patients less than 18 years of age have not been established.

This review focuses on labeling sections and revisions that directly address pediatric use. These recommendations are based on the DGIEP substantially complete proposed IBSRELA labeling (dated May 7, 2019). DPMH's recommended information to be added to the labeling is underlined. Information to be deleted has a ~~strikethrough~~. Comments and rationale for DPMH's recommendations to the labeling are in *italics*.

HIGHLIGHTS OF PRESCRIBING INFORMATION

IBSRELA (tenapanor) tablets, for oral use
Initial U.S. Approval: 2019

BOXED WARNING

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

See full prescribing information for complete boxed warning.

- IBSRELA is contraindicated in patients less than 6 (b) (4) years of age; in young juvenile rats, tenapanor caused death presumed to be due to dehydration. (4, 8.4)
- Avoid use of IBSRELA in patients 6 (b) (4) years to less than 12 (b) (4) years of age (5.1, 8.4)
- The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age (8.4)

INDICATIONS AND USAGE

IBSRELA is (b) (4) indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

CONTRAINDICATIONS

(b) (4)

Reviewer Comments: PREA PMR's are planned for pediatric patients 6 years and older with IBS-C; however, initiation of pediatric trials in patients less than 12 years should be delayed until juvenile toxicology data is available. DPMH recommends that the indication statement reflect approval in adults only and that the Contraindications retain the lower age limit of 6 years rather than (b) (4) years for the risk of serious dehydration because pediatric patients in this age group, unlike patients in the younger cohort, are more likely to report thirst and be capable of seeking fluids. DPMH also recommends that tenapanor include a contraindication in patients less than 6 years for consistency with linaclotide as well as plecanatide labeling. In the Boxed Warning, DPMH supports including the "avoid use" statement for pediatric patients 6 years to less than 12 years to discourage off-label use, given the risks of hyperkalemia, lack of juvenile animal data to support use in pediatric patients 6 years and older, as well as the lack of safety and efficacy data in any pediatric population. DPMH recommends adding Warnings and Precautions (b) (4)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IBSRELA is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

4 CONTRAINDICATIONS

IBSRELA is contraindicated in:

- Patients below 6 years of age due to the risk of serious dehydration *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*.
- Patients with known or suspected mechanical gastrointestinal obstruction.

Reviewer Comments: See above DPMH comments to Highlights of Prescribing Information sections that apply to the Full Prescribing Information, BOXED WARNING, Section 1 Indications and Usage, as well as Section 4 Contraindications.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Dehydration in Pediatric Patients

IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in

patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age) (b) (4) (b) (4) decreased body weight and deaths occurred -presumed to be due to dehydration, following oral administration of (b) (4) tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).

Avoid the use of IBSRELA in patients 6 years to less than (b) (4) years of age. ~~Although there is no data in older juvenile~~ (b) (4) ~~rats,~~ Ggiven the deaths in younger (b) (4) rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 (b) (4) years of age *[see Contraindications (4), Use in Specific Populations (8.4)]*.

Reviewer Comments: DPMH recommends revisions in Warnings and Precautions (5.1) Risk of Serious Dehydration in Pediatric Patients to align with risk information in the Boxed Warning and in Contraindications. DPMH supports the Contraindication for patients below 6 years of age due to the risk of serious dehydration, for reasons stated above.

5.3 Hyperkalemia

(b) (4) Eelevations in potassium have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Patients at increased risk of developing hyperkalemia include those with conditions predisposing to hyperkalemia (e.g., renal impairment), use of drugs that increase the risk of hyperkalemia, or increased susceptibility to hyperkalemia (e.g., elderly patients) *[see Drug Interactions (7.1), Use in Specific Populations (8.5)]*. Consider monitoring serum potassium concentrations in high risk patients during treatment with ISBRELA.

Reviewer Comments: DPMH supports the addition of hyperkalemia to the Warnings and Precautions (5.3) to inform prescribers about hyperkalemia, particularly in patients at risk for this specific electrolyte imbalance (e.g., renal impairment as well as the elderly).

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

IBSRELA is contraindicated in patients less than (b) (4) 6 years of age. Avoid IBSRELA in patients (b) (4) 6 years to less than (b) (4) years of age *[see Contraindications (4), Warnings and Precautions (5.1)]*.

The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established.

In ~~a~~ nonclinical (b) (4) studies (b) (4) deaths occurred in young juvenile rats (less than 1 (b) (4) -week-old-rats (b) (4) approximate~~ly~~ (b) (4) human age equivalent of (b) (4) -less than 2 years of age) following oral administration of (b) (4) -tenapanor, as described below in Juvenile Animal Toxicity Data.

Juvenile Animal Toxicity Data

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats (post-natal day (PND) 5) at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on study day 11 (PND 16) due mortalities and decreased body weight (24% to 29% reduction, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from postnatal day 5 through postnatal day 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. Mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at all doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5 and 5 mg/kg/day dose groups. (b) (4) (b) (4) (b) (4) *[see Contraindications (4), Warnings and Precautions (5.1)].*

Reviewer Comments: DPMH recommends 1) revising the contraindications to apply to patients less than 6 years rather than less than (b) (4) *years of age due to the risk of serious dehydration for additional reasons stated above and 2) adding juvenile animal data in neonatal rats to inform prescribers on reported deaths and decreased body weight compared to controls. DPMH recommends retaining cross-reference to Contraindications (4) and Warnings and Precautions (5.1).*

17 PATIENT COUNSELING

Accidental Ingestion

Accidental ingestion of IBSRELA in children, especially children less than (b) (4) 6 years of age, may result in severe diarrhea and dehydration. Instruct patients to store IBSRELA securely and out of reach of children *[see Contraindications (4), Warnings and Precautions (5.1)]*.

Reviewer Comment: DPMH recommends revising the pediatric age for risks with accidental ingestion from 6 years of age for consistency with the Boxed Warning, Contraindications (4), Warnings and Precautions (5.1), and Pediatric Use (8.4).

DPMH Actions and Labeling Recommendations

DPMH reviewed Ardelyx, Incorporated proposed labeling for Ibsrela (tenapanor) tablets and participated in meetings with the DGIEP Clinical Team from November 2018 to May 7, 2019. The most recent proposed labeling revisions per DPMH are dated May 7, 2019. DPMH labeling recommendations were provided in track changes for DGIEP consideration to revise the Ibsrela labeling to conform to the *Draft Guidance for Industry and Review Staff* on Pediatric Labeling.[11] DPMH's input will be reflected in the final labeling and the action letter from the DGIEP. Should this product be approved, final labeling will be negotiated with the applicant, and may differ from recommendations in this DPMH labeling review.

[11] *Draft Guidance for Industry and Review Staff* - Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling, February 2013

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CAROLYN L YANCEY
05/08/2019 10:38:59 AM
NDA 211801 IBSRELA (tenapanor) in IBS-C in Adult Patients, DPMH Labeling Review

JOHN J ALEXANDER
05/08/2019 03:30:08 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 24, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 211801
Product Name and Strength:	Ibsrela (tenapanor) tablet, 50 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Ardelyx, Inc.
FDA Received Dates:	September 12, 2018 December 14, 2018
OSE RCM #:	2018-1994
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader (Acting):	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

As part of the approval process for Ibsrela, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the proposed Ibsrela prescribing information (PI) and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI) and container labels, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The National Drug Code (NDC) number is denoted by a placeholder (XXXXX-XXXX-XX).	Per 21 CFR 207.33, drug products subject to listing with the FDA must have a unique NDC to identify its labeler, product, and package size and type.	Request the Applicant to submit the actual NDC number instead of the placeholder.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION

Table 3. Identified Issues and Recommendations for Ardelyx, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	As depicted, the product's proprietary name lacks readability. The use (b) (4) product's tradename.	(b) (4) This presentation may lead to medication dispensing errors.	Remove the (b) (4) and ensure the proprietary name is readable and legible taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with Draft Guidance: Container and Carton, April 2013 (line 140-146, 188, 194-196, 219-222) and 21 CFR 201.10 (a), 21 CFR 202.1(a)(1) are considered.
2.	The National Drug Code (NDC) number is denoted by a placeholder (XXXXX-XXXX-XX).	Per 21 CFR 207.33, drug products subject to listing with the FDA must have a unique NDC to identify its labeler, product, and package size and type.	Submit the actual NDC number on all label and labeling. Ensure that NDC numbers have different NDC package codes (last 2 digits of the NDC) for the trade container and sample container.
3.	Medication guide statement is missing from Principal Display panel.	21 CFR 208.24(d)	Unbold and revise the bolded statement, "ATTENTION PHARMACIST: (b) (4) to read "ATTENTION PHARMACIST:

Table 3. Identified Issues and Recommendations for Ardelyx, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			Dispense the accompanying medication guide to each patient."
4.	As stated, the intended meaning of the storage statement, (b) (4) is unclear.	It is unclear if the storage statement directs the pharmacist (b) (4)	Revise the statement, (b) (4) to read "Attention Pharmacist: Dispense the TRADENAME in original container to patient."
5.	The format for expiration date is defined incorrectly.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	Change the expiration date to the correct format. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

4 CONCLUSION

Our evaluation of the proposed Ibsrela prescribing information and container labels identified areas of vulnerability that may lead to medication errors. Above, we have provided Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Ardelyx, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Ibsrela that Ardelyx, Inc. submitted on December 14, 2018.

Table 3. Relevant Product Information for Ibsrela	
Initial Approval Date	N/A
Active Ingredient	Tenapanor
Indication	Treatment of irritable bowel syndrome with constipation (IBS-C) in adults
Route of Administration	Oral
Dosage Form	Tablet
Strength	50 mg
Dose and Frequency	• 50 mg twice daily • immediately prior to breakfast or the first meal of the day and immediately prior to dinner
How Supplied	Bottle of 60
Storage	• Store at (b) (4) • Keep in original container • Protect from moisture

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Ibsrela labels and labeling submitted by Ardelyx, Inc.

- Container labels received on September 12, 2018
- Prescribing information (not imaged) received on December 14, 2018

F.2 Label and Labeling Images

Prescribing information (not imaged)

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Container label:

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Sample container label:

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
04/24/2019 02:06:39 PM

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04/24/2019 02:18:10 PM

Clinical Inspection Summary

Date	April 4, 2019
From	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Elizabeth Mannick, M.D., Medical Officer, DGIEP
NDA #	211801
Applicant	Ardelyx, Inc.
Drug	Tenapanor
NME	Yes
Division Classification	Irritable Bowel Syndrome
Proposed Indication	Treatment of Irritable Bowel Syndrome with Constipation (IBS-C) in adults
Consultation Request Date	November 5, 2018
Summary Goal Date	Originally February 15, extended to April 15, 2019
Action Goal Date	September 12, 2019
PDUFA Date	September 12, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspections for this NDA were conducted at five clinical investigator (CI) sites and the sponsor. Four of the clinical sites and the sponsor have the final classification of No Action Indicated (NAI). One clinical site has the final classification of Voluntary Action Indicated (VAI). No significant regulatory findings or data integrity issues were noted. The data generated by these sites and the sponsor are acceptable in support of the application.

II. BACKGROUND

The sponsor submitted this NDA for a new molecular entity (NME) tenapanor for the indication of treatment of irritable bowel syndrome with constipation (IBS-C) in adults. Tenapanor is a locally acting inhibitor of the Sodium/Hydrogen Exchanger 3 (NHE3). The proposed mechanism of action of tenapanor is to reduce Na+ re-uptake. This decrease in Na+ uptake increases the net fluid volume in the GI tract. The sponsor claims that restoration of normal luminal fluid content facilitates intestinal transit and stimulates motility.

Drug: tenapanor

Studies– Protocol numbers and titles for all studies that were inspected

1. Protocol TEN-01-301 entitled "A 12-Week, Randomized, Double-Blind, Placebo-Controlled Study with a 4-Week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Tenapanor for the Treatment of Constipation Predominant Irritable Bowel Syndrome (IBS-C)"

Number of subjects: 629 subjects
Number of sites: 122 sites
Number of countries where subjects were enrolled: USA only
Dates that study was conducted: November 2015 to March 2017
Efficacy endpoints: 6 out of 12 week overall combined responder rate (CSBM and abdominal pain)

- CSBM is a Complete Spontaneous Bowel Movement for which the subject responded yes to the question, "Did you feel like you completely emptied your bowels?" and had not taken rescue medication within the previous 24 hours.
- An abdominal pain weekly responder was defined as a decrease of ≥30% of percent change from baseline in average weekly worst abdominal pain. Abdominal pain was scored daily using the scale 0 = no pain to 10 = very severe pain.

Sites were chosen based on enrollment, inspectional history, and number of INDs in the OSI database

2. Protocol TEN-01-302 entitled "A 26-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Tenapanor for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C)"

Number of subjects: 620 subjects
Number of sites: 92 sites
Number of countries where subjects were enrolled: USA only
Dates that study was conducted: December 2015 to August 2017
Efficacy endpoints: 6 out of 12 week overall combined responder rate (CSBM and abdominal pain)

- CSBM is a Complete Spontaneous Bowel Movement for which the subject responded yes to the question, "Did you feel like you completely emptied your bowels?" and had not taken rescue medication within the previous 24 hours.
- An abdominal pain weekly responder was defined as a decrease of ≥30% of percent change from baseline in average weekly worst abdominal pain. Abdominal pain was scored daily using the scale 0 = no pain to 10 = very severe pain.

Sites were chosen based on enrollment, inspectional history, and number of INDs in the OSI database

III. RESULTS (by site):

Name and Type of Inspected Entity/Address	Site #/Protocol #/ # of Subjects randomized	Inspection Dates	Classification
CI: Manuel Lam, M.D. 14221 SW 137 Avenue Miami, FL 33186	Site 106 TEN-01-301/15 subjects TEN-01-302/11 subjects	December 7 to 13, 2018	NAI
CI: Yaneicy Gonzalez-Rojas, M.D. 18951 Southwest 106th Ave Room 202 Cutler Bay, FL 33157	Site 178 TEN-01-301/23 subjects TEN-01-302/20 subjects	February 4 to 8, 2019	NAI
CI: Michael Feldman, M.D. 830 N. Krome Ave Homestead, FL 33030	Site 287 TEN-01-301/17 subjects	January 28 to February 1, 2019	NAI
Julian Gonzalez, M.D. 15035 East Freeway Suite C Channelview, TX 77530	Site 180 TEN-01-302/19 subjects	January 3 to 16, 2019	VAI
Francisco Velazquez, M.D. 10700 Stancliff Road Houston, TX 77099	Site 286 TEN-01-302/11 subjects	November 26 to 29, 2019	*NAI
Sponsor: Ardelyx, Inc. 34175 Ardenwood Blvd Suite 100 Fremont, CA 94555	TEN-01-301/629 subjects TEN-01-302/620 subjects	March 7 to 12, 2019	*NAI

Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data may be unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Manuel Lam, M.D.
   14221 SW 137 Avenue, Miami, FL 33186

At this site, for Protocol TEN-01-301, there were 23 subjects screened, 15 subjects were randomized, and 14 subjects completed the study. A total of 15 subject records were reviewed. At this site, for Protocol TEN-01-302, there were 12 subjects screened, 11 subjects were randomized, and completed the study. A total of 11 subject records were reviewed for informed consent process, staff training, test article accountability, efficacy parameters, protocol deviations, concomitant medications, eligibility criteria, and adverse events. Source documents for protocol adherence and data verification

were compared to line listings from the NDA. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events.

The studies appear to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

2. Yaneicy Gonzalez-Rojas, M.D.
   18951 Southwest 106th Ave Room 202, Cutler Bay, FL 33157

At this site, for Protocol TEN-01-301, there were 40 subjects screened, 23 subjects were randomized, and 22 subjects completed the study. One subject withdrew because they moved out of the area. The records for all 23 randomized subjects were reviewed. At this site, for Protocol TEN-01-302, there were 30 subjects screened, 20 subjects were randomized, and 18 subjects completed the study. Two subjects withdrew because they moved out of the area. The records for all 20 randomized subjects were reviewed. The records were reviewed for informed consent process, staff training, test article accountability, efficacy parameters, protocol deviations, concomitant medications, eligibility criteria, and adverse events. Source documents for protocol adherence and data verification were compared to line listings from the NDA. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events.

The studies appear to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

3. Michael Feldman, M.D.
   830 N. Krome Ave, Homestead, FL 33030

At this site, for Protocol TEN-01-301, there were 40 subjects screened, 17 subjects were randomized and completed the study. Most of the screen failures were due to dietary noncompliance. The records of all 17 randomized subject records were reviewed. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

4. Julian Gonzalez, M.D.
   15035 East Freeway Suite C, Channelview, TX 77530

At this site, for Protocol TEN-01-302, there were 30 subjects screened, 19 subjects were randomized, and 16 subjects completed the study. A total of 19 subject records were reviewed. The data in the line listings was compared with the source documents. No significant deviations or discrepancies were noted. Although there was a Form FDA 483 observation for not reporting adverse events, on review, these consisted mostly of clinically insignificant laboratory values, except for Subject (b) (6) with a serum glucose of 46 mg/dL and Subject (b) (6) with a serum glucose of 450 mg/dL.

A Form FDA 483, Inspectional Observations, was issued at the close of the inspection. Key findings are that an investigation was not conducted in accordance with the signed statement of investigator and investigational plan because the following protocol violations were noted:

a. The protocol required study drug to be dispensed on Visits 2, 4, 5, 6, 7, and 8. Subject (b) (6) was not dispensed drug on Visit 7 and Subject (b) (6) was not dispensed study drug on Visit 8.

Reviewer note: This is reflected in the line listings for these subjects.

b. Numerous adverse events (AEs) were not recorded on the eCRF.

Reviewer note: The AEs listed on the Form FDA 483 were slightly out of range urinalysis results and bloodwork as well as out of range bloodwork apparently due to hemolysis of samples. Except for the values noted in the previous paragraph, they are not clinically significant to this reviewer.

c. A subject screening log was not provided to the ORA investigator during the inspection.

Reviewer note: During the inspection, the CI stated that they would check with the study monitor who may have taken the screening log. In their response, the site provided the print out from the (b) (4) system that was used at this site. The site stated that they placed a printed copy in the regulatory binder.

In addition to the above:

- There was inadequate informed consent for two subjects because the informed consent document was not dated by Subjects (b) (6) and (b) (6).
- There was inadequate drug accountability because Subject (b) (6) returned pills in a baggie and not a bottle and the absence of a returned bottle was not documented.

Dr. Gonzalez adequately responded to the inspection findings in a letter dated January 30, 2019. This inspection is classified as VAI because, while regulatory violations exist, these do not have a significant impact on data reliability or on the rights, safety, or welfare of subjects.

The study appears to have been conducted adequately at this site, and the data generated by this site may be used in support of the respective indication.

5. Francisco Velazquez, M.D.
   10700 Stancliff Road, Houston, TX 77099

At this site, for Protocol TEN-01-302, there were 22 subjects screened, 11 subjects were randomized, and 10 subjects completed the study. One subject was lost to follow-up. A total of 22 subject records were reviewed. The data in the line listings was compared with the source documents. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

6. Ardelyx, Inc.
   34175 Ardenwood Blvd Suite 100, Fremont, CA 94555

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of Protocols TEN-01-301 and TEN-01-302, including selection and oversight of contract research organizations (CROs), monitoring, financial disclosure, FDA Form 1572s, quality assurance (QA), and handling of data. The inspection included review of general correspondence and contracts, site monitoring for the clinical sites above, and other sponsor/monitor related activities. The sponsor maintained adequate oversight of the clinical trials. One site that participated in both clinical trials was closed because of non-compliance and the site closure was reported to FDA.

These studies appear to have been conducted adequately by the sponsor and the data generated may be used in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Susan Thompson, M.D.
Team Leader
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CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

cc:
Central Doc. Rm.
Review Division /Acting Division Director/Dragos Roman
Review Division /Medical Team Leader/Tara Altepeter
Review Division /Project Manager/Mary Chung
Review Division/Medical Officer/Elizabeth Mannick
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Susan D. Thompson
OSI/DCCE/GCP Reviewer/ Susan Leibenhaut
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

SUSAN LEIBENHAUT
04/04/2019 04:31:33 PM

SUSAN D THOMPSON
04/04/2019 05:02:04 PM

KASSA AYALEW
04/05/2019 07:42:31 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 27, 2019

From: Stephen M. Grant, M.D.
Clinical Reviewer
Division of Cardiovascular and Renal Products

Through: Norman Stockbridge, Ph.D., M.D.
Director
Division of Cardiovascular and Renal Products

To: Mary H Chung, Pharm.D.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

Subject: DCaRP consult to opine on a potential signal that a NME, tenapanor, increases the risk of adverse cardiac events

On September 12, 2018, Ardelyx Inc submitted NDA 211801 to DGIEP to market tenapanor, an inhibitor of the Sodium/ Hydrogen Exchanger 3 (NHE3) in the gastrointestinal tract, for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults. Under IND (b) (4) Ardelyx Inc is also developing tenapanor for the treatment of hyperphosphatemia in ESRD patients. We were asked to assist in the assessment of a potential cardiac safety signal you identified during your review of the NDA 211801

We reviewed the following materials:

- Your consult dated 24 December 2018
- Analyses performed by the DGIEP clinical reviewer of NDA 211801
- A consult completed 13 March by Dr. Xiao, who is the clinical reviewer of IND (b) (4), concerning the occurrence of thrombotic events in studies of patients with renal failure in studies being conducted under IND (b) (4)

Background

The primary support for the safety and efficacy of tenapanor for the treatment of IBS-C comes three clinical studies:

- TEN-01-301, in which 629 subjects were randomized to double-blind administration of either 50 mg of tenapanor or placebo for 12 weeks followed by a 4-week randomized withdrawal
- TEN-01-302, in which 620 subjects were randomized to double-blind administration of either 50 mg of tenapanor or placebo for 26 weeks
- TEN-01-303, a 52-week extension safety study in which subjects who completed either study TEN-01-301 or study TEN-01-301

Additionally, Ardelyx submitted safety data from three short-term phase 2 and phase 3 clinical studies of various doses of tenapanor in patients with end-stage renal disease (ESRD) conducted under IND (b) (4) (D5611C00001, D5613C00001, and TEN-02-201) as supportive studies. These studies have been separately reviewed by Dr. Xiao.

We understand from our discussions with you that:

- Tenapanor is minimally absorbed so that there is little systemic exposure.
- Neither the safety pharmacology studies nor the clinical studies suggest that tenapanor has a significant effect on blood pressure or heart rate.

In our initial interactions with you, we indicated that a drug with minimal exposure and no effects on hemodynamics was unlikely to increase serious cardiac events after a brief period of exposure without a plausible mechanism for injury. Hence, we advised that your analyses of cardiovascular risk should include only adverse events with permanent sequelae. We advised that the following serious cardiac adverse events be grouped based on pathophysiology as follows:

- CV death, MI, ischemic stroke
- Heart failure, new onset or requiring hospitalization
- Serious ventricular arrhythmias (defined as ventricular tachycardia or fibrillation associated with symptoms or lasting at least 30 seconds)
- New onset sustained atrial arrhythmias, such as atrial fibrillation or atrial flutter
- Miscellaneous CV events that result in hospitalization

We also advised that events related to stent/ graft clots in fistulae or shunts being used for dialysis and venous thromboembolic events that occurred in studies of patients with ESRD be reviewed by Dr. Xiao as these are not cardiac events. They were separately reviewed by Dr. Xiao and he did not identify any definite concerns or any signal of a hypercoagulable state.

Using the categories we suggested, you identified very few serious cardiac events occurring in the studies of patients of patients with IBS-C and certainly no signal of harm. In ESRD you developed the following table (modified to include the events relevant to this consult):

Number of Patients with Cardiovascular AEs (without hypertension) by SOC, PT: ESRD Safety Set by Treatment Groups

Diagnosis	Tenapanor N=400 (47.3PY)	Placebo N=151 (11.1PY)	Demo	Study Days	Other AEs (Study Days)	Comments
CV death, MI, stroke						
Death (cardiac failure)	1		66WM	42	Critical left leg ischemia (20) Arteriovenous fistula thrombosis (8)	Patient died
Acute myocardial infarction	2	1	56WF	17-19	Vomiting (4-7) Pneumonia (11-23)	Recovered
			59BM	16	Emphysema (25-30)	Required procedure
			56BF	58-61	Hypokalemia (60-62)	Required procedure
Ischemic stroke	1		68HF	30-33		Resolved
Cerebrovascular accident	1		40BM	37-42	Enterococcus fecalis septicemia (35-84), abdominal tenderness (15), cerebral calcification (35-42), encephalopathy (35-42), acute respiratory failure (54-57), Enterococcus fecalis urinary tract infection (35-84), pulmonary edema (54-57), fluid overload (54-57),	Drug interrupted

					endocarditis (35-84)	
Total	**5/400 (1.1%) 0.13/PY**	**1/151 (0.66%) 0.09/PY**				
Congestive Heart Failure (requiring hospitalization)						
Congestive heart failure	3		47BF 65BM 55WM	44-49 80-83 48-50	Fluid overload (80-83), hypertension (80-83) Chest pain (48-50, 68) Pleural effusion (48-50) Hypertension (48-50) Blood urea increased (57-85) Fungal skin infection (85-ET)	Drug interrupted
Total	**3/400 (0.75%) 0.063/PY**	**0/151 (0%) 0/PY**				
New-onset Atrial Arrhythmias						
Atrial fibrillation	2		65BM 49WM	42-ET 6	Hypotension (42-49) Bradycardia (32-ET) Hypermagnesemia (84-ET) Coded as non-cardiac chest pain, required hospitalization	
Total	**2/400 (0.50%) 0.042/PY**	**0/151 (0%) 0/PY**				

Miscellaneous CV Events Requiring Hospitalization						
Artery dissection	1		47WM	7	Arteriosclerosis AV block, 1st degree Cardiac bifurcation stenosis	
Total	**1/400 (0.25%) 0.021/PY**	**0/151 0% 0/PY**				

DCaRP Assessment

There is an adverse trend toward greater CV events in the patients with ESRD exposed to tenapanor, but, even not considering that most of the events were confounded by the co-occurrence of other serious conditions, there are too few events for reliable inference about the risk of each of type of CV risks to be made. Our initial assessment was that the lack of appreciable systemic exposure and the lack of plausible mechanism for cardiovascular injury made it unlikely that administration of tenapanor would increase the risk of serious cardiac injury. In that context, we do not find the data from the clinical studies particularly worrisome. We also note that the adverse trend was observed only in patients with ESRD, who are at high risk for adverse CV events, and not in the population proposed for marketing. We are further reassured because the IBS-C population does not appear to be at high risk for serious adverse CV events and so are not be particularly susceptible.

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/s/

STEPHEN M GRANT
03/28/2019 11:28:02 AM

MARTIN ROSE
03/28/2019 01:02:36 PM

NORMAN L STOCKBRIDGE
03/28/2019 01:04:13 PM

Division of Cardiovascular and Renal Products
Consultation for Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Shen Xiao, M.D., Ph.D. Medical Officer
Division of Cardiovascular and Renal Products

Through: Aliza Thompson, M.D., Medical Team Leader/Deputy Division Director
Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D. Division Director
Division of Cardiovascular and Renal Products

To: Mary Chung, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

Application: NDA 211-801
Name of Drug: Tenapanor
Proposed Indication: Irritable bowel syndrome with constipation (IBS-C)
Sponsor: Ardelyx, Inc.

Date of Consult: January 29, 2019

Background
Ardelyx Inc is developing tenapanor, a minimally absorbed inhibitor of the Sodium/ Hydrogen Exchanger 3 (NHE3), for the treatment of irritable bowel syndrome with constipation (IBS-C) and for the treatment of hyperphosphatemia in ESRD patients (INDs 108732 and (b) (4) in DGIEP and DCRP, respectively). On September 12, 2018, Ardelyx submitted an NDA to DGIEP to support an indication for the treatment of IBS-C in adults.

On January 24, 2019, DGIEP placed a consult with DCRP for cardiology input to assist with "interpreting a potential signal noted based on ECG changes from baseline" and "increased risk of thrombotic events." DGIEP subsequently placed a second consult requesting input from a nephrology reviewer on DGIEP's safety analyses of studies in patients with ESRD that were conducted under DCRP's IND for hyperphosphatemia. Specifically, DGIEP had identified "higher rates of thromboembolic events and of cardiovascular AEs on treatment than placebo" and wanted nephrology input on this issue.

Initial findings that raised concern
The clinical team became concerned about a potential signal when they noted a disproportionate number of AV graft thromboses in patients on tenapanor as compared to placebo in the ESRD safety data set provided by the applicant. In order to understand whether the signal was limited to vascular access or reflected a more general hypercoagulable state, the team pooled events they thought might be reflective of such a state. The table below shows the results of their analysis. According to this analysis, 18/400 (4.7%) of subjects experienced "venous thromboembolism" events in the tenapanor arm as compared to 0/151 on placebo and 32/400 (8%) of subjects experienced "significant cardiovascular AEs" in the tenapanor arm as compared to 1/151 (~0.7%) on placebo.

DGIEP Table/Analysis

Diagnosis	Tenapanor (T) N=400 47.3PY	Placebo (P) N=151 11.1PY	Demo	USubjID and Study	Study Days	Other AEs (Study Days)	Comments
CV death, MI, stroke							
Death (cardiac failure)	1		66WM	(b) (6)	42	Critical left leg ischemia (20) Arteriovenous fistula thrombosis (8)	Patient died
Acute myocardial infarction	2	1	56WF		17-19	Vomiting (4-7) Pneumonia (11-23)	Recovered
			59BM		16	Emphysema (25-30)	Required procedure
			56BF		58-61	Hypokalemia (60-62)	Required procedure
Lacunar infarct	1		65WM		38-41	Medical device complication (right upper extremity access clotting) (38-44), dizziness (37-44), device (pacemaker) failure (40-43), nausea (37-44), vomiting (37-44)	Resolved with sequelae
Ischemic stroke	1		68HF		30-33		Resolved
Cerebrovascular accident	1		40BM		37-42	Enterococcus fecalis septicemia (35-84), abdominal tenderness (15), cerebral calcification (35-42), encephalopathy (35-42), acute respiratory failure (54-57), Enterococcus fecalis urinary tract infection (35-84), pulmonary edema	Drug interrupted

						(54-57), fluid overload (54-57), endocarditis (35-84)	
Total CV Deaths, MI and Stroke	6/400 (1.5%) 0.13/PY	1/151 (0.66%) 0.09/PY					
Congestive Heart Failure (requiring hospitalization)							
Congestive heart failure	3		47BF 65BM 55WM	(b) (6)	44-49 80-83 48-50	Fluid overload (80-83), hypertension (80-83) Chest pain (48-50, 68) Pleural effusion (48-50) Hypertension (48-50) Blood urea increased (57-85) Fungal skin infection (85-ET)	Drug interrupted
Total Congestive Heart Failure Requiring Hospitalization	3/400 (0.75%) 0.063/PY	0/151 (0%) 0/PY					
New-onset Atrial Arrhythmias							
Atrial fibrillation	2		65BM 49WM		42-ET 6	Hypotension (42-49) Bradycardia (32-ET) Hypermagnesemia (84-ET) Coded as non-cardiac chest pain, required hospitalization	
Atrioventricular block (Second Degree)	1		85WM		29	Diarrhea (6-15)	
Total Atrial Arrhythmias	3/400 (0.75%) 0.063/PY	0/151 (0%) 0/PY					
Miscellaneous CV Events Requiring Hospitalization							
Artery dissection	1		47WM		7	Arteriosclerosis AV block, 1st degree Cardiac bifurcation	

						stenosis	
Total Miscellaneous Serious CV Events	1/400 (0.25%) 0.021/PY	0/151 0% 0/PY					
Venous Thromboembolism							
Graft thrombosis	4		43BM 50WF 52BF 32BM	(b) (6)	21-23 37-ET 34-42 70	Diarrhea (1-31), bronchitis (27-43) Diarrhea (21-ET), thirst (1-ET), Abdominal tenderness (1-ET) Vascular graft stenosis (34-47)	Required procedure Required procedure Required procedure
Shunt thrombosis	1		59BM		46	Vomiting (15-19), weight increased (14-ET), arteriovenous fistula site complication (5-ET)	
Medical device complication (clotted vascular access)	1		46BM		23-24	Diarrhea (2-29) Procedural complication (10-12)	
Steal syndrome (ischemia to vascular access)	1		65WM		49-77	Constipation (3-10) Burns, second degree (7-ET), diarrhea (24-60)	
Arteriovenous fistula thrombosis	1		25AM		50-53	Hyperphosphatemia (59-76)	Required procedure
Arteriovenous fistula complication (stenosis)	6		63AM 57WM 51WM		13-14 66-108 4	 Diarrhea (1-57) Dizziness (28-29) Fall (29) Pneumonia (19-26) Diarrhea (11-ET) Abdominal discomfort (5-7) Blurred vision (18) Pancytopenia (19-	Required procedure Required procedure Required procedure

				(b) (6)		ET)	
			69BF		36-39	Metabolic acidosis (19-ET) Blood calcium low (15-50), pruritus (32-ET), Diarrhea (8-17, 39-41)	Required procedure
			72WM		22	Diarrhea (2-ET)	Required procedure
			41BF		20	Ear infection (52-61)	Required procedure
Venous stenosis	1		76WF		60-77	Diarrhea (1-11), brachial arterial wall hypertrophy (60-77)	Procedure required
Pulmonary embolus	1		47BF		4-13	Non-cardiac chest pain (-2-4) Pain in extremity (3-4), bleeding from catheter site (66) Deep vein thrombosis (6-ET)	Drug interrupted Resolved
Deep vein thrombosis	2		88WM		15-23	Nasal fracture (8-9), humerus fracture (8-16)	
			52BF		54-61	Hyperphosphatemia (64-71), pulmonary edema (54-61), respiratory distress (54-61), chronic kidney disease (54-61), vulvovaginal pruritus (57-64), bacterial vaginosis (57-64), cellulitis (36)	
Arterio-occlusive disease	1		43F		7-8	Diarrhea (5-26)	Occluded cephalic vein
Total Venous Thromboembolisms	19/400 (4.7%) 0.36/PY	0/151 (0%) 0/PY					
Total Significant Cardiovascular AEs	32/400 (8.0%)	1/151 (0.66%)					

	0.68/PY	0.09/PY					
Total Cardiovascular Events without Graft Complications	17/400 (4.2%) 0.36/PY	1/151 (0.66%) 0.09/PY					

Source: Dr. Mannick

DCRP comments on analyses

We identified two issues to consider when interpreting these analyses. The first is whether the studies that were pooled should be pooled; the second is whether the appropriate terms were pooled.

- *Studies:* As we understand, DGIEP's analyses pooled data from three studies conducted in ESRD patients. In brief, studies D5611 and D5613 were placebo-controlled, dose-ranging studies of 4- and 9 to 10-weeks treatment duration, respectively. Study TEN-02-201 was a randomized withdrawal study in which all subjects were initially treated with different doses/dosing regimens of tenapanor for 8 weeks and then randomized to placebo or study drug for 4 weeks. Given its design, we do not think the safety data from Study TEN-02-201 is easily interpretable or should be pooled with the tenapanor and placebo data from the other trials.

- *Terms:* As noted by the cardiology reviewer, Dr. Grant, the cardiology terms that were pooled reflect disparate events, some of which are not well suited to capture the medical concept of interest (e.g., a hypercoagulable state). We have similar concerns with some of the access-related events that were pooled in the analysis.

In light of these issues, Dr. Nhi Beasley, a clinical analyst in DCRP, reanalyzed the data in ESRD patients to evaluate for a potential hypercoagulability signal. For this analysis, Dr. Beasley pooled studies D5613 and D5611. The results of her analysis, shown below, do not reveal an obvious imbalance between study arms using the narrow and broad SMQs for embolic and thrombotic events. We further note that thrombotic events/access related events are not unexpected events in the ESRD population.

SMQ (Narrow Search)		*Tenapanor (N = 180)*			*Placebo (N = 69)*		
Level 1	*Level 2*	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Embolic and thrombotic events		8	5	2.8	1	1	1.5
Embolic and thrombotic events	Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous* §	3	3	1.7	0	0	0
Embolic and thrombotic events	Embolic and thrombotic events, venous*†	2	2	1.1	0	0	0

*Broad Search gives the same results; § SMQ includes the following PTs among others: Arteriovenous fistula occlusion, Arteriovenous fistula thrombosis, Arteriovenous graft thrombosis, Artificial blood vessel occlusion, Shunt occlusion, Shunt thrombosis, Vascular graft occlusion, Vascular graft thrombosis, Graft thrombosis; † SMQ includes PTs such as Deep vein thrombosis, Deep vein thrombosis postoperative, Pulmonary embolism, Embolism venous.

Given the results of this analysis, the minimal systemic absorption of the drug, and, as we understand, the absence of a signal in other studies that were conducted as part of the tenapanor development program, we do not think further action or evaluation of this issue is needed at this time.

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/s/

SHEN XIAO
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ALIZA M THOMPSON
03/13/2019 09:40:47 AM

NORMAN L STOCKBRIDGE
03/13/2019 09:49:15 AM

Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 211801
Submission Number	0001
Submission Date	9/12/2018
Date Consult Received	10/30/2018
Clinical Division	DGIEP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review under IND 108732 dated 05/26/2015 in DARRTS;
- Previous QT-IRT review under IND [redacted] (b) (4)
- Summary of clinical pharmacology (Submission 0001);
- Study D5611C00005 clinical trial report and cardiac safety report (Submission 0001); and
- Proposed label (Submission 0001).

1 SUMMARY

No significant QTc prolongation effect of tenapanor was detected in this QTc assessment.

The effect of tenapanor was evaluated in Study D5611C00005. The highest dose evaluated was 180 mg single dose and 90 mg BID for 7 days, which is expected to cover two-times the worst-case exposure scenario at the time of this review (in patients with severe renal impairment, section 3.1). Because of the minimal systemic exposure of tenapanor, exposure-response analysis was performed on the major metabolite, AZ13792925. The data from Study D5611C00005 was analyzed using exposure-response analysis as the primary analysis, which did not suggest that tenapanor/AZ13792925 is associated with significant QTc prolonging effect at the highest exposure evaluated (90 mg BID on Day 7) (refer to section 4.5) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (section 3.1), bias assessment (section 4.2.2), central tendency analysis (section 4.3) and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

Treatment	AZ13792925 Concentration (ng/mL)	ΔΔ (ms)	90% CI (ms)
AZD1722 180 mg QD (SD)	19.6	-1.02	(-3.6, 1.5)
AZD1722 15 mg BID	10.3	-2.08	(-4.4, 0.3)
AZD1722 30 mg BID	13.5	-1.71	(-4.1, 0.7)
AZD1722 60 mg BID	36.3	0.88	(-2.4, 4.1)
AZD1722 90 mg BID	48.7	2.28	(-1.8, 6.3)

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable

2 PROPOSED LABEL

The sponsor did not propose label language related to QT prolongation risks. QT-IRT propose the following language. The proposal is a suggestion only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology At 3 times the mean maximum exposure of the 50 mg BID dose, there were no clinically relevant effects on the QTc interval.
Reviewer's comments: The maximum mean exposure achieved in this QTc assessment (48.7 ng/mL in the 90 mg BID treatment arm) is approximately 3 times that reported in healthy subjects taking the to-be-marketed formulation (i.e. 16.3 ng/mL).

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Tenapanor (AZD1722) is an NHE3 inhibitor, reducing sodium uptake in the intestinal tract. In the current submission, the sponsor seeks approval for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) in adults. The proposed therapeutic dose is 50 mg BID. Tenapanor is also under clinical development for the treatment of hyperphosphatemia in patients with end stage renal disease on dialysis (IND (b) (4). The highest therapeutic dose for the renal disease is 30 mg BID.

Previously the QT-IRT reviewed a TQT waiver request under IND 108732 (DARRTS 05/26/2015). At the time of review, $C_{max,ss}$ at the therapeutic dose (i.e. 50 mg BID) was determined to be at the sub-nanomolar scale. The QT-IRT agreed that a TQT study would not be necessary based on minimal systemic exposure, available non-clinical and clinical cardiac safety information, and a lack of clinical evidence of QTc changes in Study D5611C00005.

In 2018, a QT assessment was requested under IND (b) (4) as systemic exposure of the major metabolite was determined to be 20.9 ng/mL at the 45 mg BID dose level in patients with end stage renal disease. In May 2018, the QT-IRT reviewed a QT assessment plan based on Study D5611C00005 (IND (b) (4) Study D5611C00005 was a Phase 1 study in healthy volunteers. Japanese subjects were administered a single dose of 180 mg tenapanor (Cohort 1, originally designed for once daily doses) with 6 subjects on active drug and 2 on placebo, or twice-daily doses (BID) of tenapanor for 7 days in the multiple ascending dose (MAD) cohorts: 15 mg BID (Cohort 2), 30 mg BID (Cohort 3), 60 mg BID (Cohort 4), or 90 mg BID (Cohort 5) with 12 subjects on active drug and 3 on placebo in each dose group. In a separate group,

Caucasian subjects (Cohort 6; 12/3 active/placebo) were dosed with 90 mg BID tenapanor for 7 days. It was concluded that Study D5611C00005 could potentially serve as a substitute of a TQT study for the proposed clinical dose of 30 min BID for the renal disease indication.

***Reviewer's comment**:*

- *The highest clinically relevant exposure for AZ13792925 at the 50 mg BID dose has not been fully evaluated. There are inconsistent reports on the steady state exposure of AZ13792925 at the 50 mg BID dose and on the effect of intrinsic/extrinsic factors on AZ13792925 exposure.*
  1) *PK linearity has not been formally evaluated. Steady state exposure of the 50 mg BID dose is not readily available from Study D5611C00005. Note that this study used a capsule formulation while the commercial product is a tablet formulation.*
  2) *In Study D5612C0001, 50 mg BID tenapanor was administered to patients with IBS-C for 12 weeks. AZ13792925 Cmax was reported as 10.9 ng/mL on Day 85 (derived from sparse PK data).*
  3) *In Study TEN-01-103, AZ13792925 Cmax on Day 14 in healthy volunteers was reported to be 16.3 ng/mL at 50 mg BID dose level (n=28, to-be-marketed formulation).*
  4) *Renal clearance is the major elimination route for AZ13792925. Sponsor claims that exposures to tenapanor and/or AZ13792925 in stage 3 chronic kidney disease (CKD) patients and end stage renal disease patients (CKD-5D) are similar to healthy volunteers. In Study D5611C00001, 45 mg BID tenapanor was administered for 7-28 days to patients with end stage renal disease. The reported Cmax at steady state was 20.9 ng/mL (n=26). Assuming linear PK between 45 and 50 mg BID dose level, $C_{max,ss}$ at the 50 mg BID dose level would be 23.2 ng/mL in this population. These numbers are approximately two-fold of the value that the sponsor has proposed to include in the product label (i.e. 11 ng/mL).*
  5) *AZ13792925 was primarily formed by metabolism by CYP3A4 and CYP3A5. Concomitant medication with strong CYP3A inducers may increase the exposure of AZ13792925. The effect of CYP3A inducers has not been evaluated.*
- *The sponsor also reported less than 20% mean reduction in hERG current amplitude in vitro with tenapanor concentration up to 10 µM. Tenapanor inhibited hCav1.2/ß2/a2d (ICaL) at an IC50 of 4.67 µM. The IC50 values of AZ13792925 on hKv11.1 (hERG), hKv4.3/hKChIP2.2 (hIto), hKv7.1/hKCNE1 (hIKs), and hNav1.5 were 16.5, 27.3, 14.8, and > 33.3 µM, respectively. The estimated safety margin based on IC50 values would be >10000 for tenapanor and AZ13792925 at the highest recommended dose level (50 mg BID).*

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Not applicable

3.2.1.1.1 QT bias assessment

The sponsor did not conduct QT bias assessment.

3.2.2 Categorical Analysis

The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.4 for additional details.

3.2.3 Safety Analysis

No deaths or SAEs were reported. No discontinuations due to an AE were reported.

One (1) subject reported TEAEs in the AZD1722 SD group (headache, decreased appetite). The most common (at least 2 events recorded) TEAEs among AZD1722-treated subjects in the MAD cohorts were diarrhoea (2), oropharyngeal pain (2), rash (2) and skin irritation (2). Of these most commonly reported TEAEs, none were reported in the placebo cohorts. No apparent dose relationship was seen with regard to the incidence of these commonly reported AEs. The most common (at least 2 events recorded) TEAEs among AZD1722-treated subjects in the Caucasian cohort receiving the highest dose given (90 mg bid) was diarrhoea (2). This AE did not occur in the Caucasian placebo cohort.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

3.2.4 Exposure-Response Analysis

The sponsor conducted exposure-response analysis for Cohort 1, Cohort 2-5, Cohort 6, Cohort 1-5, and Cohort 2-6, separately. The linear mixed-effects model included ΔQTcF as the dependent variable, plasma concentration of AZ13792925 and centered baseline QTcF as covariates, treatment (active = 1 or placebo = 0) and time since first dose as categorical factors, and a random intercept and slope per subject. The models were used to predict mean effect and 2-sided 90% CI for ΔΔQTcF at the geometric mean Cmax at each dose level.

The analyses based on Cohort 1 or Cohort 6 alone did not suggest significant concentration-QTc relationship. The analyses should be interpreted with caution given the small sample size and narrow exposure range.

Sponsor's analyses based on Cohort 2-5, Cohort 1-5, and Cohort 2-6 predicted a mean effect less than 10 ms in all treatment arms. The maximum predicted value of mean effect was 6.11 ms in the 90 mg BID dose group using data from Cohort 2-5. All the models predicted an upper bound of 90% CI greater than 10 ms in the 90 mg BID treatment arm and less than 10 ms in the other groups.

The reviewer's analysis included data from all treatment arms and included study day as a covariate in the linear mixed effect model. Reviewer's analysis suggests a lack of small

effect (i.e. 10 ms) at the maximum evaluated exposure level (i.e. Day 7 on 90 mg BID). Please see section 4.5 for additional details.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate (i.e. mean < 10 bpm) were observed (see Sections 4.3.2 and 4.5).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment

QT bias assessment was conducted by evaluating the relationship between the difference between the sponsor provided QT measurements and the automated algorithm used by the ECG Warehouse and the mean of the two measurements (BA-slope). The resulting BA-slope by treatment (active/placebo/overall) is presented for QTcF (Table 2) and QT (Table 3). This analysis does not suggest the presence of significant negative treatment bias.

Table 2: QTcF bias assessment by treatment

Treatment	# of ECGs	Mean (sd), ms	Slope [95% CI], ms per 100 ms
Overall	9955	-4.51 (8.28)	5.25 [4.63 to 5.87]
Treatment	7977	-3.98 (8.61)	8.37 [7.71 to 9.04]
Placebo	1978	-6.65 (6.4)	-1.93 [-3.22 to -0.63]

Table 3: QT bias assessment by treatment

Treatment	# of ECGs	Mean (sd), ms	Slope [95% CI], ms per 100 ms
Overall	9955	-4.47 (8)	0.64 [0.21 to 1.07]
Treatment	7977	-3.95 (8.29)	1.87 [1.42 to 2.33]
Placebo	1978	-6.56 (6.27)	-3.48 [-4.49 to -2.46]

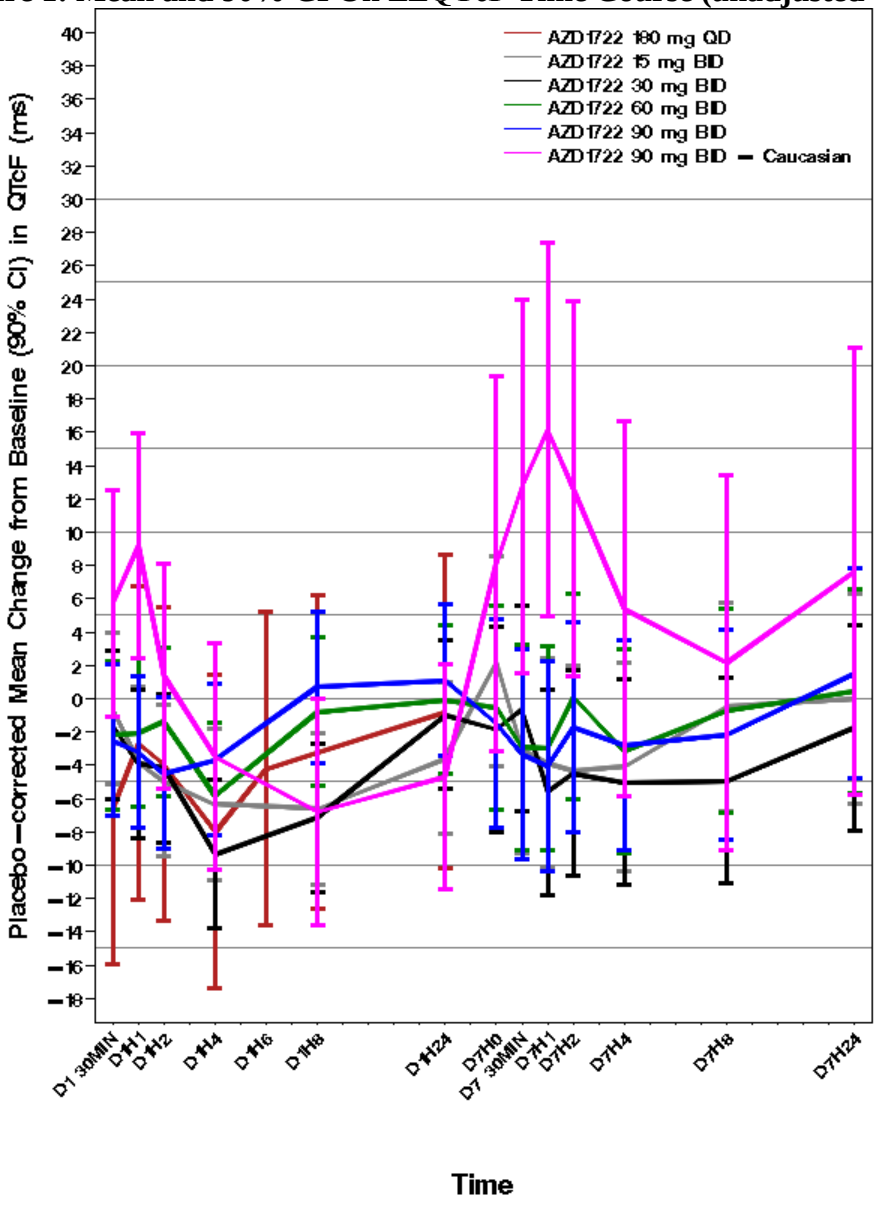
4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

The statistical reviewer used mixed effect model to analyze the ΔQTcF. The model includes treatment, time point, and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. Cohort 1, Cohorts 2–5 with placebo pooled, and Cohort 6 were analyzed separately. Results were similar to that of the sponsor's analysis. The largest upper bounds of 90% CI for placebo-corrected mean change from baseline in QTcF (ΔΔQTcF) were less than 10 ms for cohort 1 and cohorts 2-5, respectively. The largest upper bound of 90% CI for ΔΔQTcF in Cohort 6 was above 10 ms; however, the value was not reliable due to small number of subjects (12 subjects on active and 3 subjects on placebo) in the cohort.

The following figure displays the time profile of ΔΔQTcF for different treatment groups in Cohorts 1-6.

Figure 1: Mean and 90% CI On ΔΔQTcF Time Course (unadjusted CIs).



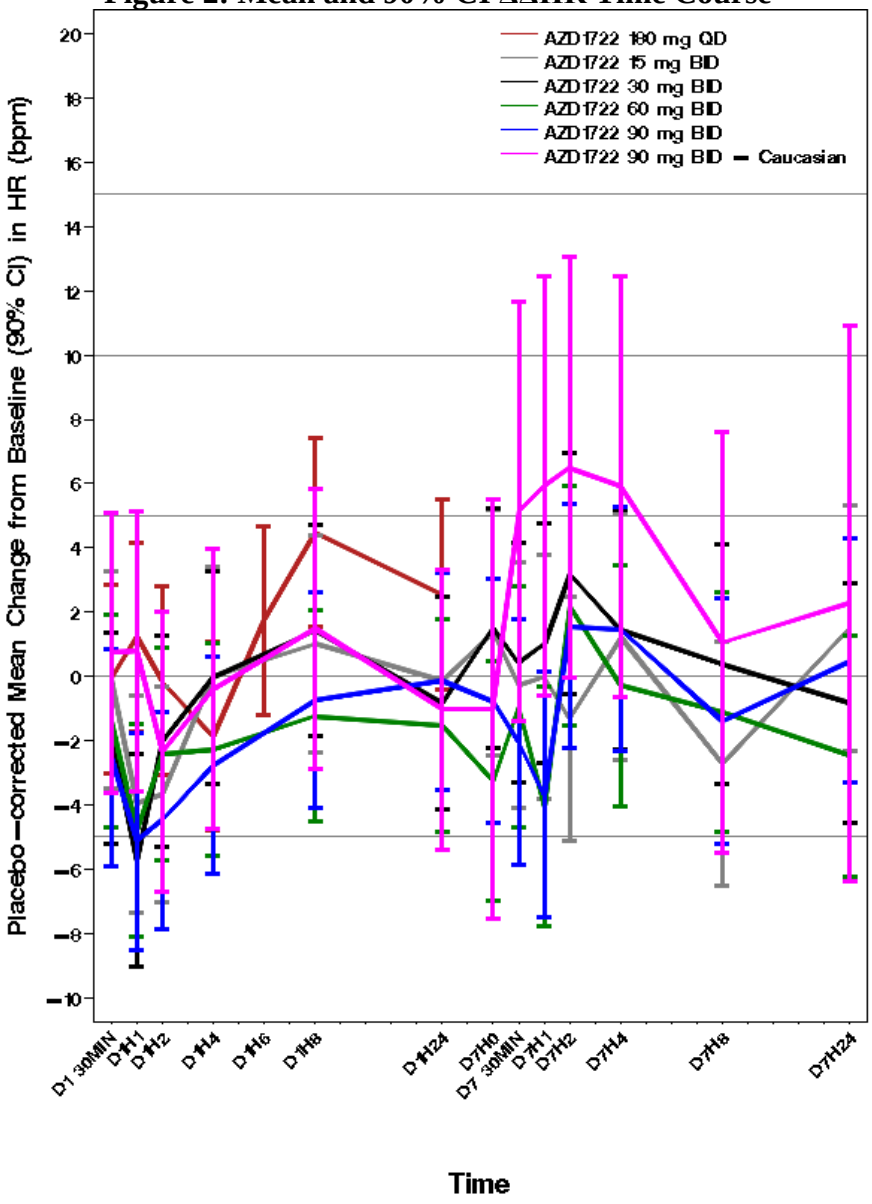
4.3.1.1 Assay sensitivity

Not applicable

4.3.2 HR

The same statistical analysis was performed based on HR (Figure 2). Results from the statistical reviewer's analysis are similar to that of the sponsor. The mean values for ΔΔHR were very small in Cohort 1 and Cohorts 2-5. Thus, No HR effect was found in Cohort 1 or Cohorts 2-5. Due to small number of subjects in Cohort 6, the upper bounds for ΔΔHR were not reliable.

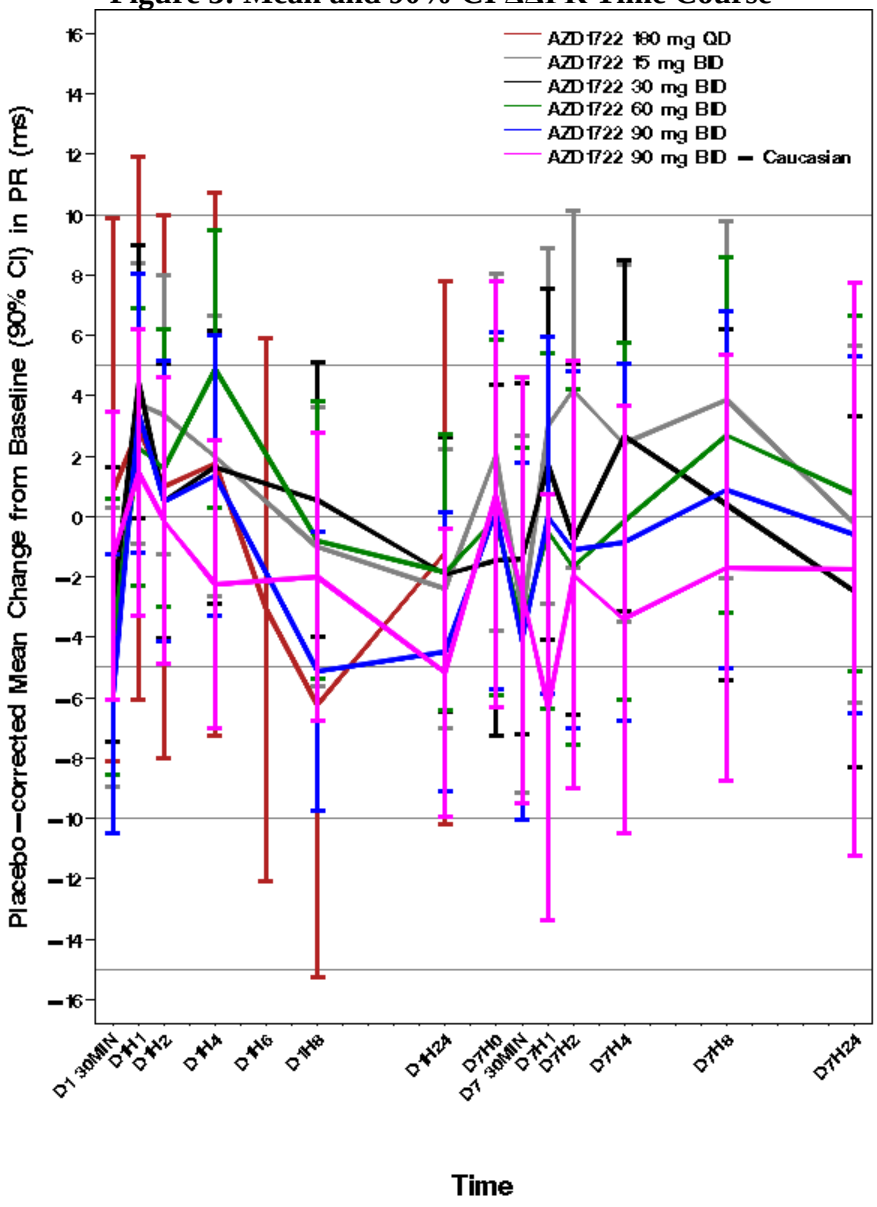
Figure 2: Mean and 90% CI ΔΔHR Time Course



4.3.3 PR

The same statistical analysis was performed based on PR interval (Figure 3). Results from the statistical reviewer's analysis are similar to that of the sponsor. Almost all 90% CIs for ΔΔPR did not exclude 0.

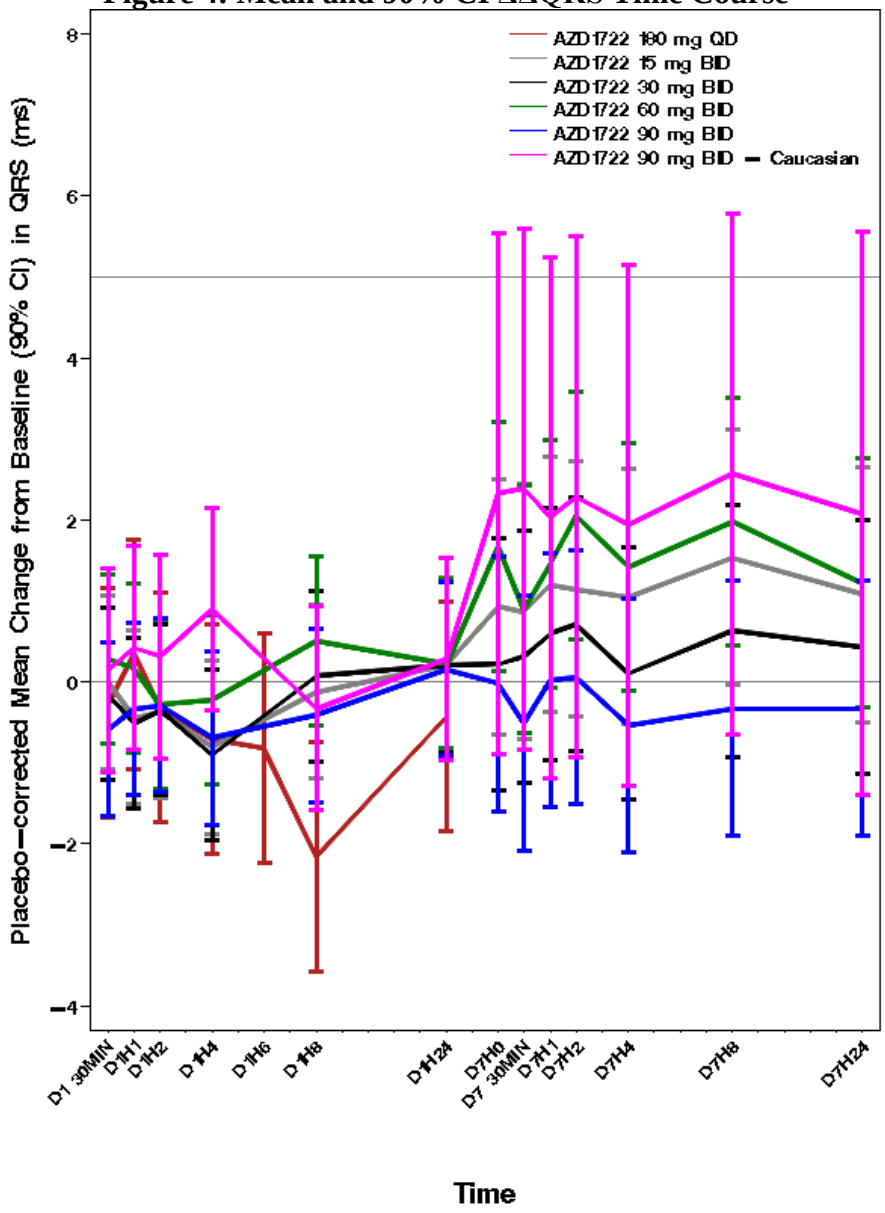
Figure 3: Mean and 90% CI ΔΔPR Time Course



4.3.4 QRS

The same statistical analysis was performed based on QRS interval (Figure 4). Results from the statistical reviewer's analysis are similar to that of the sponsor. The mean values for ΔΔQRS were very small for all active treatments in Cohorts 1-6.

Figure 4: Mean and 90% CI ΔΔQRS Time Course



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

Table 4 lists the number of subjects as well as the number of observations whose QTcF values were ≤450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms. The results are very similar to that of the sponsor except that the reviewer's analysis shows one more subject in active treatments experienced postbaseline QTcF values between 450 to 480 ms. The sponsor's outlier analysis results for QTcF were presented on page 107-108 of their cardiac safety report.

Table 4: Categorical Analysis for QTcF

	Total N		QTcF<=450 ms		450<QTcF<=480 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	81	81	80 (98.8%)	80 (98.8%)	1 (1.2%)	1 (1.2%)
All Active Treatments Pooled	66	815	63 (95.5%)	801 (98.3%)	3 (4.5%)	14 (1.7%)
All Placebo Pooled	17	200	17 (100%)	200 (100%)	0 (0.0%)	0 (0.0%)

Table 5 lists the categorical analysis results for ΔQTcF. No subject's change from baseline in QTcF was above 60 ms. The results are the same as that of the sponsor. The sponsor's outlier analysis results for ΔQTcF were presented on page 108-109 of their cardiac safety report.

Table 5: Categorical Analysis of ΔQTcF

	Total N		ΔQTcF<=30 ms		30<ΔQTcF<=60 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
All Active Treatments Pooled	64	794	62 (96.9%)	792 (99.7%)	2 (3.1%)	2 (0.3%)
All Placebo Pooled	17	200	17 (100%)	200 (100%)	0 (0.0%)	0 (0.0%)

Note: Total N for subject is the total number of subjects with non-missing values or changes for a specific ECG parameter.

4.4.2 PR

The outlier analysis results for PR are presented in Table 6. No subject's PR was above 220 ms. The sponsor listed the number of subjects as well as the number of timepoints for PR >200 ms with an increase in ΔPR >25% on page 109-110 of their cardiac safety report; no outliers were reported for PR based on the sponsor's criteria.

Table 6: Categorical Analysis for PR

	Total N		PR<=200 ms		200<PR<=220 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	81	81	81 (100%)	81 (100%)	0 (0.0%)	0 (0.0%)
All Active Treatments Pooled	66	815	66 (100%)	815 (100%)	0 (0.0%)	0 (0.0%)
All Placebo Pooled	17	200	15 (88.2%)	197 (98.5%)	2 (11.8%)	3 (1.5%)

4.4.3 QRS

The outlier analysis results for QRS are presented in Table 7. Twenty-two subjects in the active treatment groups had QRS >110 ms, 14 of the 22 subjects' baseline QRS values were also >110 ms. The sponsor listed the number of subjects as well as the number of timepoints for QRS >120 ms with an increase in ΔQRS >25% on page 109-110 of their cardiac safety report; no outliers were reported for QRS based on the sponsor's criteria.

Table 7: Categorical Analysis for QRS

	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	81	81	64 (79.0%)	64 (79.0%)	17 (21.0%)	17 (21.0%)
All Active Treatments Pooled	66	815	44 (66.7%)	654 (80.2%)	22 (33.3%)	161 (19.8%)
All Placebo Pooled	17	200	12 (70.6%)	168 (84.0%)	5 (29.4%)	32 (16.0%)

4.4.4 HR

The outlier analysis results for HR are presented in Table 8. The sponsor listed the number of subjects as well as the number of timepoints for HR >100 bpm with an increase in ΔHR >25% and for HR <50 bpm with a decrease in ΔHR >25% on page 109-110 of their cardiac safety report; only one subject in tenapanor 90 mg BID group had large HR outliers based on the sponsor's criteria.

Table 8: Categorical Analysis for HR

Treatment Group	**Total N**	**HR<=100 bpm**	**HR>100 bpm**	**HR>45 bpm**	**HR<=45 bpm**
	Subj. #	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**
Baseline	81	81 (100%)	0 (0.0%)	76 (93.8%)	5 (6.2%)
All Active Treatments Pooled	66	65 (98.5%)	1 (1.5%)	64 (97.0%)	2 (3.0%)
All Placebo Pooled	17	17 (100%)	0 (0.0%)	16 (94.1%)	1 (5.9%)

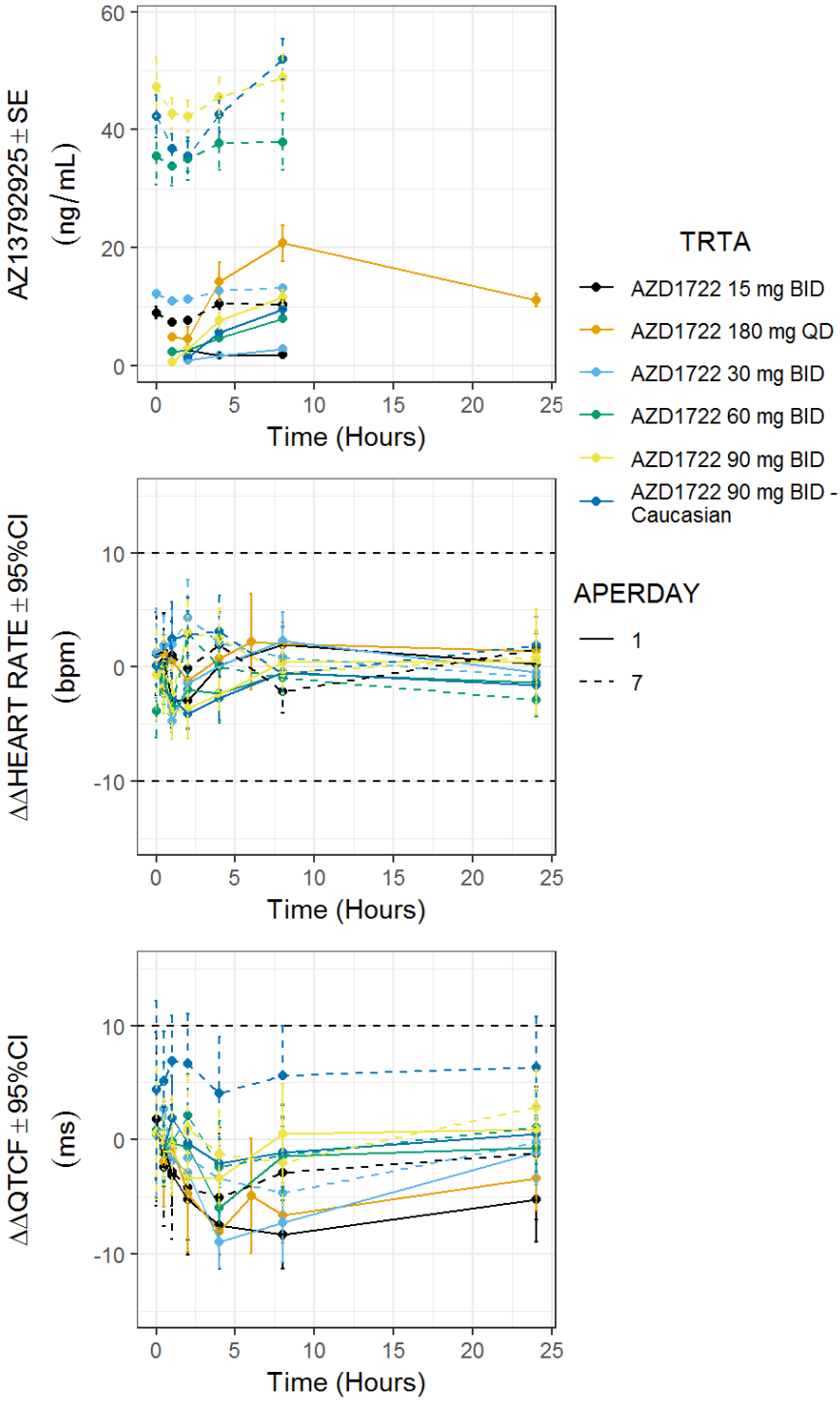
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between AZ13792925 concentration and ΔQTcF.

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between AZ13792925 plasma concentration and ΔQTcF and 3) presence of non-linear relationship.

An evaluation of the time-course of drug concentration and changes in ΔΔHR and ΔΔQTcF is shown in Figure 5, which shows an absence of significant changes in HR. The accumulation ratio for AZ13792925 concentration at 8-hour postdose is between 5-8-fold on Day 7 across 15-90 mg BID doses. AZ13792925 exposure are similar in Japanese and Caucasian subjects at the 90 mg BID dose level. While ΔΔQTcF profiles overlap across the evaluate dose ranges on Day 1 and 7, there appears to be a clear separation between ΔΔQTcF profile in Cohort 6, Day 7 vs the rest of treatment arms. Figure 5 does not appear to show significant hysteresis between ΔΔQTcF and AZ13792925 concentration.

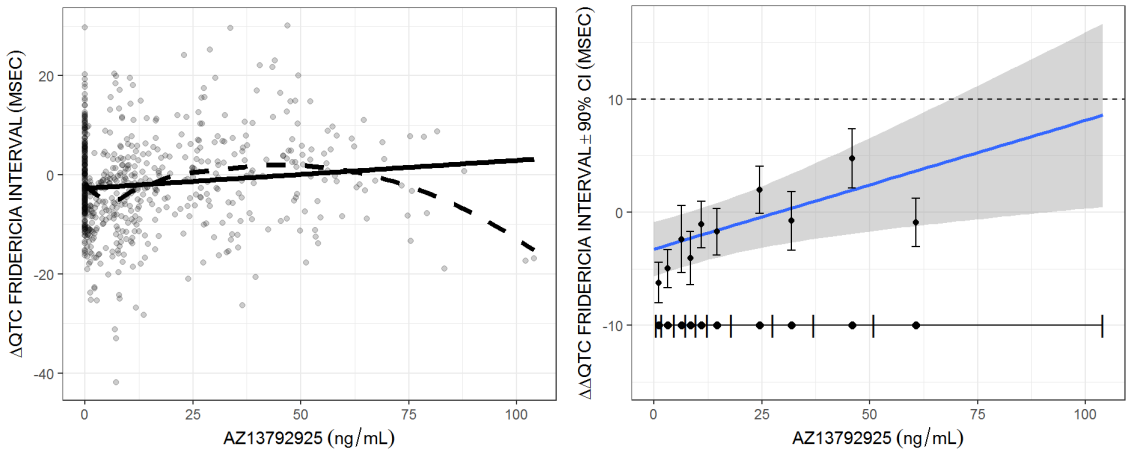
Figure 5: Time course of drug concentration (top), heart rate (middle) and QTcF (bottom)



After confirming the absence of significant heart rate changes and delayed QTc changes, the relationship between AZ13792925 concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 Left shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 6 Right. The model used ΔQTCF as the dependent variable, used active treatment, AZ13792925 concentration, time since last dose, study day, time and day interaction, and baseline adjustment as the fixed effects, and used subject ID as a random effect on the slope and intercept. The model suggests a significant treatment effect (-3.25 ms, p=0.03) and a positive exposure-response relationship (0.11 ms/(ng/mL), p=0.02). Predictions from the concentration-QTc model are provide in Table 1. Except for an underestimation in Cohort 6, the model predicted ΔΔQTcF are generally in agreement with observations from Cohort 1-5.

Figure 6: Assessment of linearity of concentration-QTc relationship and goodness-of-fit plot for QTc



The apparent difference in ΔΔQTcF profile in Cohort 6 might be introduced by factors other than drug exposure. In a sensitivity analysis, a concentration-QTc analysis was conducted using data from Cohorts 1-5 only. The treatment effect remains negative (-3.55 ms, p=0.03), the slope is positive (0.08 ms/(ng/mL), p=0.1), and the overall conclusion is similar to that derived from the complete dataset (Table 9). Therefore, it is concluded that concentration-QTc analysis suggests a lack of small effect (i.e. 10 ms) at the maximum evaluated exposure level (i.e. Day 7 on 90 mg BID).

Table 9: The Point Estimates and the 90% CIs (Cohorts 1-5)

Treatment	AZ13792925 Concentration (ng/mL)	ΔΔ (ms)	90% CI (ms)
AZD1722 180 mg QD (SD)	19.6	-1.91	(-4.6, 0.8)
AZD1722 15 mg BID	10.3	-2.69	(-5.2, -0.2)
AZD1722 30 mg BID	13.5	-2.42	(-4.9, 0.1)
AZD1722 60 mg BID	36.3	-0.53	(-4.0, 3.0)
AZD1722 90 mg BID	48.8	0.52	(-3.9, 4.9)

When the interaction between time and day is removed from the linear model, the treatment effects and slopes are generally similar, and the predictions support the overall conclusion based on the pooled dataset from Cohorts 1-6 or Cohorts 1-5.

4.5.1 Assay sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.3. No additional safety analyses were conducted.

4.7 OTHER ECG INTERVALS

No clinically significant changes in PR or QRS were observed.

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/s/

NAN ZHENG
01/25/2019 11:54:30 AM
Yuan Xu is the primary clinpharm reviewer.

YUAN XU
01/25/2019 11:55:39 AM

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