GALAXY
Statistical Analysis Plan

PROTOCOL NUMBER: GALAXY-OB-18

PROTOCOL TITLE: Multicenter Study of Patient-Reported Gastrointestinal Symptoms in People with Cystic Fibrosis (GALAXY)

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PREFACE

The Statistical Analysis Plan (SAP) as outlined in this document will be finalized prior to the analysis of final study data. The SAP contains all modifications and updates to the planned analyses that were outlined in the original study protocol. The analyses that will be generated for the final statistical report are outlined in this document. This plan details all a priori specified analyses that will be performed upon study completion and database lock, with detailed specifications for all tables, figures, and statistical models.

1. Overview

This is a prospective, multicenter, observational study designed to collect gastrointestinal (GI) related data in patients with cystic fibrosis (CF).

Eligible participants were consented and enrolled in the study at the Enrollment or Baseline Visit. At the visit, the participant or parent/guardian completed the patient reported outcome surveys (PROs) using their mobile device (e.g., smartphone or tablet). The PROs consist of four questionnaires: Patient Assessment of Constipation-Symptoms (PAC-SYM), Patient Assessment of Gastrointestinal-Symptoms (PAGI-SYM), Patient Assessment of Constipation Quality of Life (PAC-QOL) and the disease-specific questionnaire. The disease-specific questionnaire included the Bristol Stool Scale and collected information on presence of fecal incontinence, stool quality and stool frequency.

At the Baseline Visit, weight and height were collected in addition to medical history and concomitant medication information. The participant or parent/guardian completed the PROs outside-the-clinic setting per the Schedule of Events using their mobile device. Participants were on study for up to 29 days.

2. Report Generation

2.1 Data Flow

An electronic data capture system, Medidata Rave, was utilized for collection of study data. Study personnel at each site entered data from a participant's visit onto the protocol-specific Case Report Form (eCRF). Study participants were not be identified by name in the study database or on any data capture screens, however, they were identifiable by a unique participant identification number. Only study personnel at the individual sites were able to link the study ID to the participant's name. The Medidata Rave eCOA/ePRO system, a regulatory compliant system which allows participants in a study using Medidata Rave EDC to complete and submit forms and data for patient-reported outcomes electronically on a mobile device to the Medidata Rave EDC System, was also utilized. Study personnel at each site registered study participants using their unique identification number which generated an activation code unique to that participant. Study site personnel provided the participant with their activation code. The study participant downloaded the Medidata Rave eCOA/ePRO app to their mobile device and used their unique activation code to create their ePRO login and password.

The following schedule of events shows the schedule and data collected at the baseline visit and outside-of-clinic follow-up.

	Baseline Visit (Day 1)	Day 7 (+ 1 day)	Day 14 (+ 1 day)	Day 28 (+ 1 day)
Informed Consent	X			
Review Eligibility	X			
CFF Registry ID, CF Diagnosis, and Demographics	X			
Medical History/GI History	X			
Concomitant Medication Review	X			
Height	X			
Weight	X			
Assist with downloading mobile application for completing questionnaires	X			
Complete PAC-SYM, PAGI-SYM, and disease-specific questionnaires on mobile device	X	X	X	X
Complete PAC-QOL	X			X

After data was entered into the study database, data validation checks were applied on a regular basis. Queries were entered, tracked, and resolved through the system directly. The study database was updated in accordance with the resolved queries. All changes to the study database were documented in an audit trail.

2.2 Report Generation

The final statistical report will describe and provide justification for any deviations from the original statistical analysis plan as described in the protocol. Analyses will be performed using the most current versions of SAS software or R. All programs used to produce this report will be documented, tested, and archived. All tables, figures, and listings will be validated before considered final.

2.3 Definition of the Analysis Populations

Enrollment:

An enrolled participant was defined as a participant who had met all eligibility criteria, and fully completed (i.e. no question left unanswered) at least one of the ePRO questionnaires (PAC-SYM, PAGI-SYM, PAC-QOL, and disease-specific) at baseline.

Baseline:

Baseline refers to the enrollment visit of enrolled participants, at which informed consent was given, eligibility was met, and medical history was collected.

Follow-up weeks:

Follow-up occurred at week 1 (day 7, +1), week 2 (day 14, +1), and week 4, (day 28, +1). These were outside-of-clinic, i.e. participants are asked to complete the ePRO via their mobile devices. The questionnaires took approximately 10 minutes to complete. For participants ≥ 2 years of age to < 12 years of age, the parent/guardian completed the questionnaire. For participants ≥ 12 years of age, the participant completed the questionnaire.

Protocol-defined constipation:

Per protocol, constipation is defined as < 3 bowel movements in the past week and/or Bristol Stool type 1 or 2.

3. Overview of Planned Analyses

Unless otherwise noted, the endpoints of this study are mostly descriptive, with all continuous outcomes such as symptom severity and PRO scores evaluated using descriptive statistics such as mean, median, standard deviation, and 95% confidence intervals. Presence/absence of symptoms will be shown as percentages and corresponding 95% confidence intervals calculated using the Wilson method. Longitudinal models will be mixed-effect models with participant-specific random effect and compound symmetry covariance structure. Except where otherwise noted, all tests will be two-sided and statistical significance will be determined at the 0.05 level. No adjustment for multiple comparisons will be made.

3.1 Enrollment and Study Follow-up Completion

Participant progressing through the study (enrollment, follow-up, and analysis populations) will be graphically displayed in a CONSORT diagram. The number of participants screened, eligible, and completing the study throughout the follow-up period will be summarized overall and by site.

The corresponding descriptive summaries are outlined in Appendix A, Section A.1

3.2 Participant Demographics and Baseline Characteristics

Baseline demographics and clinical characteristics are descriptively summarized overall and by age group (less than 18, or 18 and above). Summarized characteristics include age, sex, race, ethnicity, CFTR genotype, sweat chloride at diagnosis, pancreatic sufficiency, modulator use, as well as other important GI or constipation medications. Comparison with population from the CF registry will also be included.

The corresponding descriptive summaries are outlined in Appendix A, Section A.2.

3.3 Primary Endpoint

The primary endpoint of the study is the percentage of scheduled out-side-the-clinic assessments with at least one of the four PROs fully completed. Subgroup analysis on the primary endpoint is performed by age group.

The analysis on the primary endpoint is summarized in Appendix A, Section A.3.

3.4 Secondary Endpoints

3.4.1 The feasibility of ePRO surveys conducted outside-the-clinic setting:

1. At each scheduled outside-the-clinic assessment, number (%) of participants with at least one PRO fully completed
2. For each PRO, number (%) of participants with fully completed questionnaires at each scheduled outside-the-clinic assessment and overall
3. Number (%) of completed PROs by age and site

The corresponding analyses are outlined in Appendix A, Section A.3.

3.4.2 Prevalence and variability of GI symptoms:

Evaluation of PRO scores overall and by sub-scale at scheduled assessments:

4. Mean PRO score for PAC-SYM, PAGI-SYM, and PAC-QOL
5. Within- and across-participant variability of PRO scores

Descriptive statistics will be used to visually summarize the total scores and domain scores over time, and by age group. Longitudinal summaries will be provided, using mixed-effect models with participant-specific random intercepts. The corresponding analyses are outlined in Appendix A, Section A.4.

Evaluation of the prevalence of protocol-defined constipation:

6. Number (%) of enrolled participants with any occurrence of protocol-defined constipation during 1 month of follow-up (the period prevalence)

Descriptive statistics will be used to summarize the protocol-defined constipation, as well as other information from the disease-specific questionnaire over time, and by age group. The corresponding analyses are outlined in Appendix A, Section A.5.

Evaluation of the frequency and severity of each GI symptom at scheduled assessments and overall:

7. Number (%) of participants with presence of GI symptom
8. Distribution of severity scores of GI symptom
9. Mean severity score of GI symptom
10. Mean severity score of GI symptom
11. Distribution of stool frequency and type by Bristol Stool Scale

12. Change in distribution of GI symptoms and stool frequency/type from baseline visit overall

Pre-specified GI symptoms of interest, i.e. particular questions from the ePROs, are identified. Descriptive statistics will then be used to summarize the distributions of these GI symptoms overall, by age group, and the change from baseline. The corresponding analyses are outlined in Appendix A, Section A.5.

Evaluation of PAC-SYM, PAGI-SYM, and PAC-QOL scores by protocol-defined constipation:

13. Mean total and domain scores (also mean difference and 95% confidence interval) comparing participants with and without protocol-defined constipation

Descriptive statistics will be used to summarize the total and domain scores by protocol-defined constipation. Longitudinal summaries will be provided, using mixed-effect models with participant-specific random intercepts, as well as fixed effects for weekly protocol-defined constipation status, visit, and age group. The predictor of interest is the protocol-defined constipation status. The corresponding analyses are outlined in Appendix A, Section A.5.

Evaluation of alternative CF-specific definitions of constipation:

14. Examine alternative definitions of constipation that are CF specific based on correlation with PRO questionnaires and maximizing the area under the receiver operating characteristic (ROC) curve for PAC-SYM scores
15. Number (%) reporting constipation based on patient self-assessment. Examine concordance of self-reported constipation against protocol/alternate definitions using Cohen's kappa coefficient

The corresponding analyses are outlined in Appendix A, Section A.6.

3.4.3 Current management of GI symptoms:

16. Number (%) of all participants receiving treatment at baseline
17. Number (%) of all participants initiating treatment at baseline
18. Number (%) of all participants receiving treatment by medication class/type
19. Among participants with GI symptoms and constipation, number (%) receiving treatment
20. Change in distribution of GI symptoms and stool frequency/type by GI treatment at baseline
21. Mean PRO scores (also mean differences and 95% confidence interval) by GI treatment at baseline
22. Among participants receiving or initiating treatment for constipation, mean absolute change in PRO scores over time overall and by medication type/class

The corresponding analyses are outlined in Appendix A, Section A.7.

3.5 Adverse Events

Adverse Events, including Serious Adverse Experiences, will not be collected as part of this study.

Appendix A: Table and Figures

A.1 Summary of Enrollment and Study Follow-up Completion

Exhibit 1.1 Summary of Enrollment

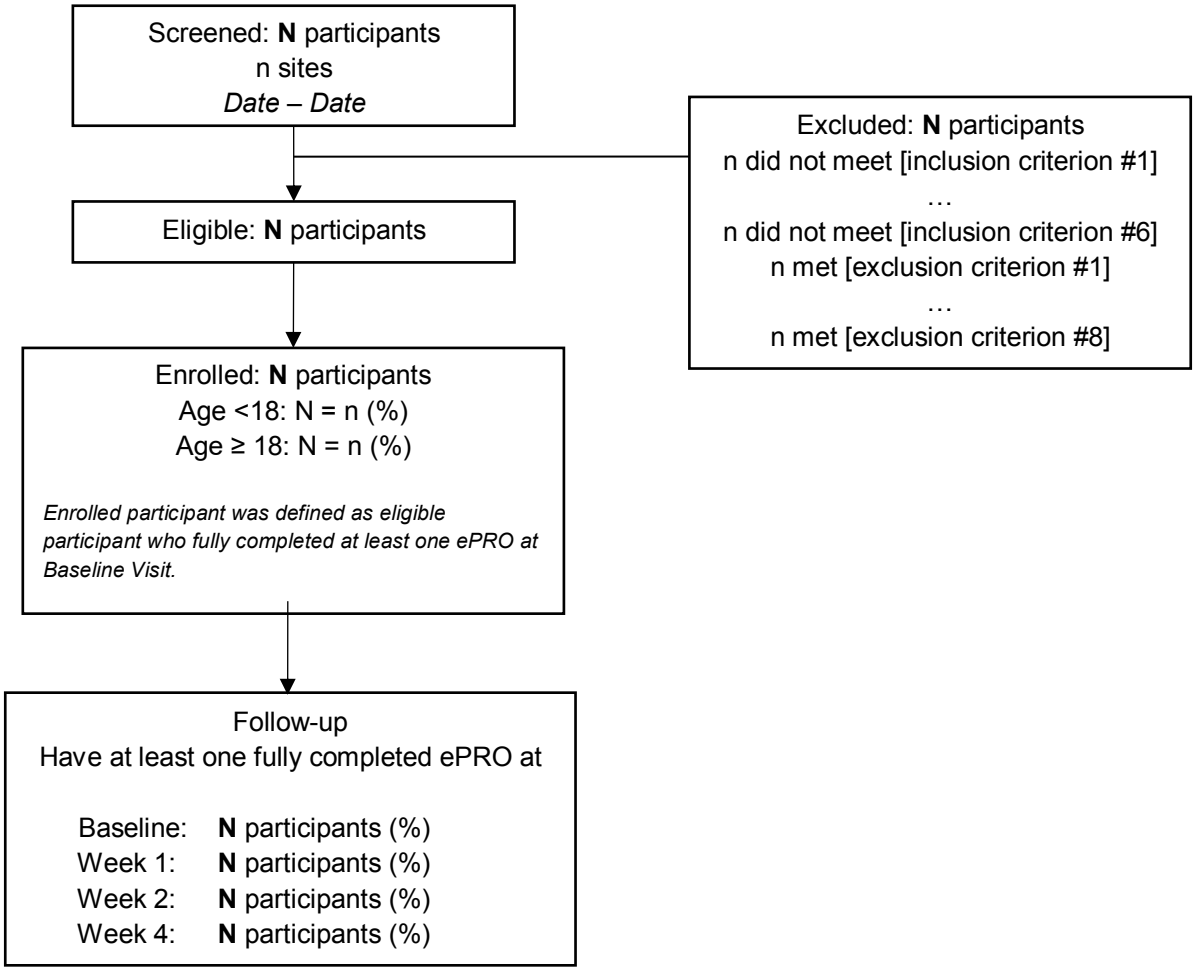
This table summarizes the number of participants screened, eligible, enrolled, and max follow-up by site.

Site	Screening Visits [1]	Participants Screened	Eligible [2]	Enrolled [3]	Follow-up [4]			
					Baseline	Week 1	Week 2	Week 4
Site 1 Site 2 … Site s								
Total								

[1] Participants could be screened multiple times. The total number of screening visits is provided followed by the number of unique participants screened.
[2] Eligibility is defined as all participants who passed inclusion/exclusion criteria.
[3] Enrollment is defined as all eligible participants who have at least one ePRO questionnaire fully completed at baseline.
[4] The number of participants who fully completed at least one ePRO questionnaire at each week of follow-up.

Exhibit 1.2 CONSORT diagram

This is a CONSORT diagram that summarizes enrollment and study follow-up completion overall.



A.2 Summary of Participant Demographics and Baseline Characteristics

Exhibit 2.1: Demographics and Baseline Characteristics.

This table summarizes demographic and baseline characteristics of the enrolled participants, in comparison with CF population from the registry.

		Age Category		All Enrolled Participants [1] (N=n)	Fully Completed at Least One ePRO at all Follow-up Weeks (N=n)	CF Registry (N=n)
		Age < 18 (N=n)	Age ≥ 18 (N=n)			
Sex at Birth, n (%)	Female					
	Male					
Age Distribution, n (%)	<6 years					
	≥6 – 12 years					
	≥12 – 18 years					
	≥18 – 24 years					
	≥24 – 30 years					
	≥30 years					
	Mean (SD)					
	Median					
	Min, Max					
Race, n (%)	White					
	American Indian or Alaska Native					
	Black or African American					
	More than One Race					
	Unknown or Not Reported					
Ethnicity, n (%)	Hispanic or Latino					
	Not Hispanic or Latino					

		Age Category		All Enrolled Participants (N=n)	Fully Completed at Least One ePRO at all Follow-up Weeks (N=n)	CF Registry (N=n)
		Age < 18 (N=n)	Age ≥ 18 (N=n)			
Genotype, n (%)	F508 Heterozygous					
	F508 Homozygous					
	Other/Unknown					
Mutation Class, n (%)	I-III					
	IV-V					
	Unknown					
Sweat Chloride at Diagnosis (mEq/L)	Mean (SD)					
Weight (kg)	Mean (SD)					
Height (cm)	Mean (SD)					
Pancreatic Sufficiency [2], n (%)	Insufficient					
	Sufficient					
	Unknown					
Modulator Use, n (%)	None					
	Ivacaftor					
	Ivacaftor/Lumacaftor					
	Ivacaftor/Tezacaftor					
	Ivacaftor/Tezacaftor/Elexacaftor					

[1] 'All Enrolled Participants' are those who met study eligibility criteria and fully completed at least ePRO at baseline visit (Visit 1).
[2] Pancreatic Insufficient is defined as PERT use and/or fecal elastase or other diagnostic test at baseline.
Note on missing demographic data

A.3 Summary of ePRO Completion

Exhibit 3.1.x Completion of ePRO Questionnaires – [All or Subgroups Defined by Age here]

This table summarizes ePRO completion rate across baseline and follow-up weeks. "Fully completed" a questionnaire is defined as having responded to all questions with no missing responses.

Week	PAC-SYM	PAGI-SYM	PAC-QOL	Disease-Specific	Fully Completed at Least One ePRO	Fully Completed all ePROs
Baseline (N=n)	n (%)					
Week 1 (N=n)	n (%)		X			
Week 2 (N=n)	n (%)		X			
Week 4 (N=n)	n (%)					
All follow-up weeks	n (%)					

Note: PAC-QOL was only collected at Baseline and Week 4.

Exhibit 3.1.1 Completion of ePRO Questionnaires – All Participants
Exhibit 3.1.2 Completion of ePRO Questionnaires – Age <18 Years
Exhibit 3.1.3 Completion of ePRO Questionnaires – Age ≥18 Years

Exhibit 3.2.1 Missing Data for ePROs by Follow-up Week and Participant

This figure helps to visualize the number of not-fully-completed ePROs at each week by participant. Data for each study participant is represented by a row. The color indicates the number of not-fully-completed ePROs at each week. For example, at baseline, enrolled participants are defined as those with eligibility and fully completed at least one ePRO. Hence, for each participant at baseline, there can only be zero, one, two, or three ePROs missing. Similarly, since PAC-QOL is not collected at Weeks 1 and 2, there can only be zero, one, two, or three ePROs missing.

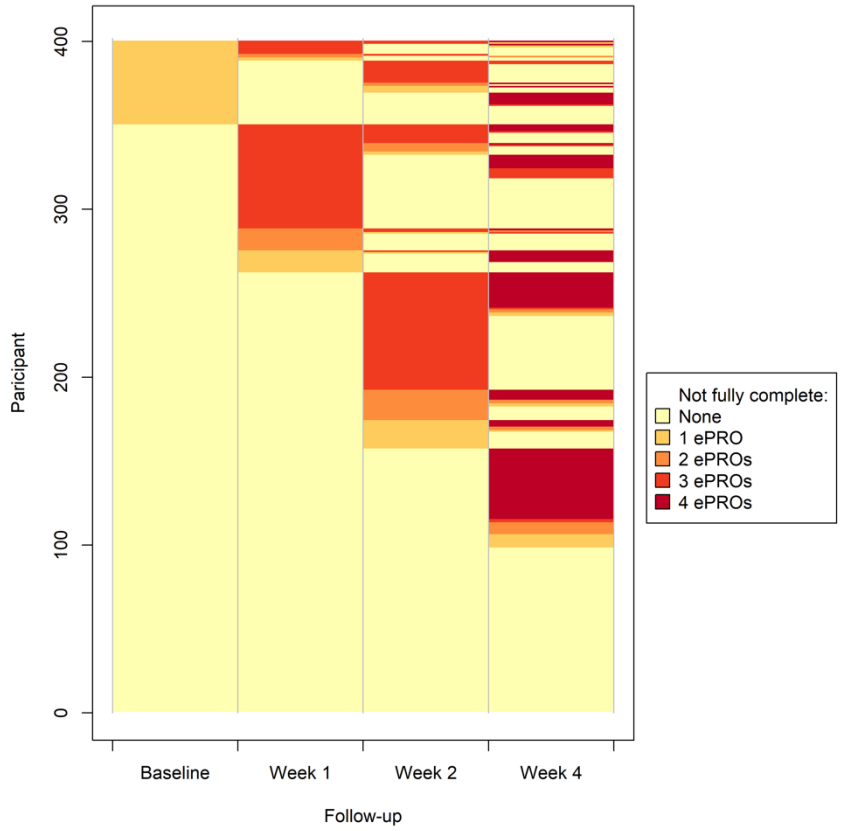


Exhibit 3.2.2 Missing Data for ePROs by Participant with Age < 18
Exhibit 3.2.3 Missing Data for ePROs by Participant with Age ≥ 18

Exhibit 3.3 Completion of ePROs by Site

This table summarizes ePRO completion by site

Site	Number of Participants	Fully Completed at Least One ePRO at All Follow-Up Weeks (Weeks 1,2 & 4)	Fully Completed all ePROs at All Follow-Up Weeks (Weeks 1, 2 & 4)
Site 1 Site 2 … Site s			
Overall			

A.4 Summary of PAC-SYM, PAGI-SYM, and PAC-QOL Scores

Exhibit 4.1 Distributions of Total Scores for PAC-SYM, PAGI-SYM, and PAC-QOL for All Participants

This figure summarizes the total scores for PAC-SYM, PAGI-SYM, and PAC-QOL at each week and overall, for all participants.

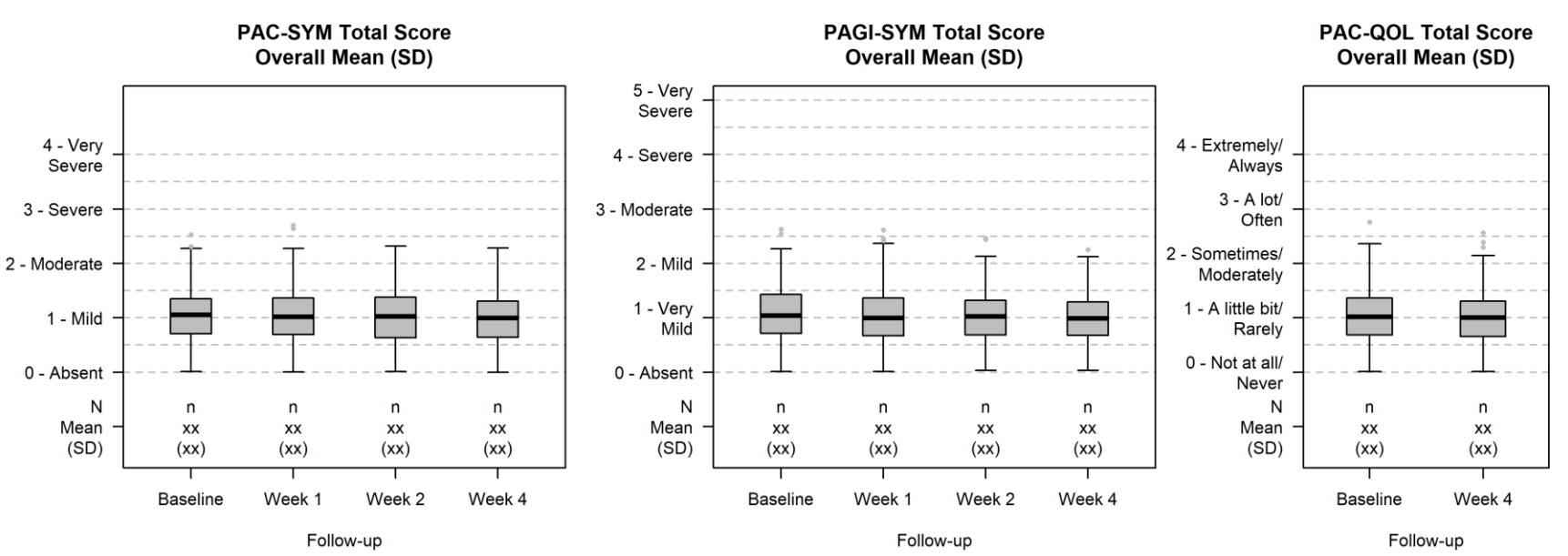


Exhibit 4.2 Distributions of Total Scores for PAC-SYM, PAGI-SYM, and PAC-QOL by Age

This figure summarizes the total scores for PAC-SYM, PAGI-SYM, and PAC-QOL at each week and overall, by age group.

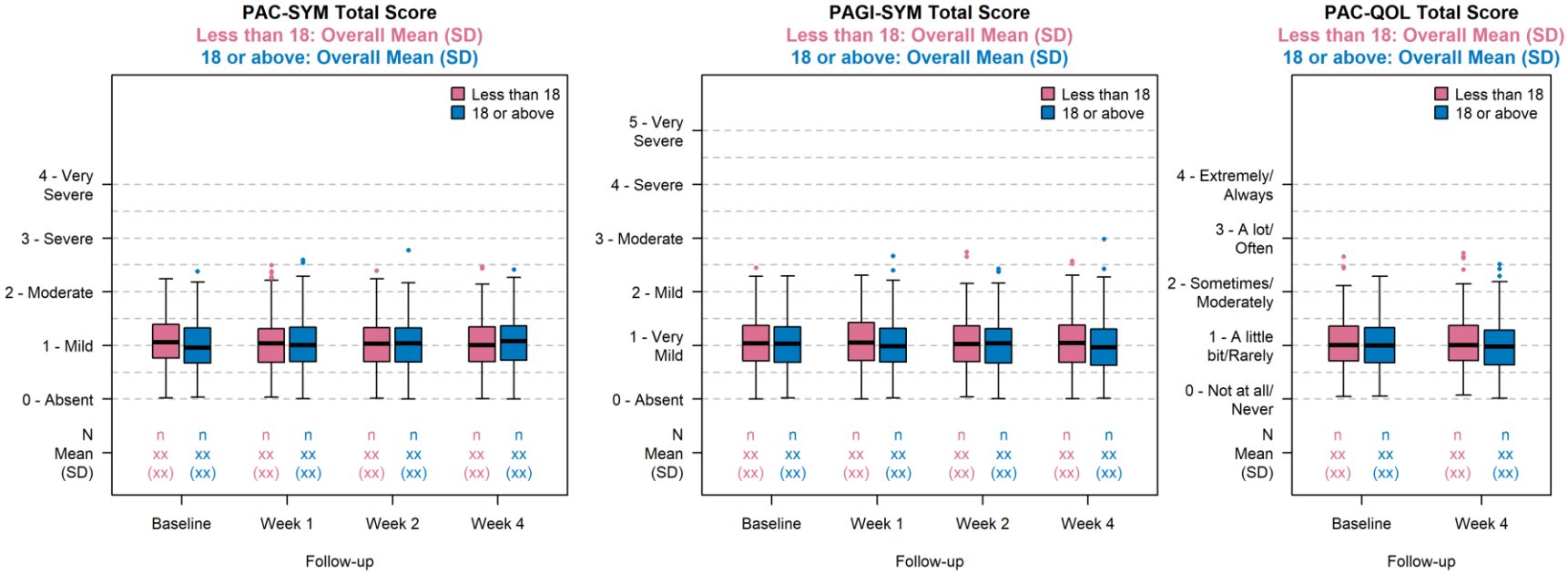


Exhibit 4.3.x Distributions of [ePRO] Domain Scores by Week

This figure summarizes the distributions of domain scores for [ePRO] by week.

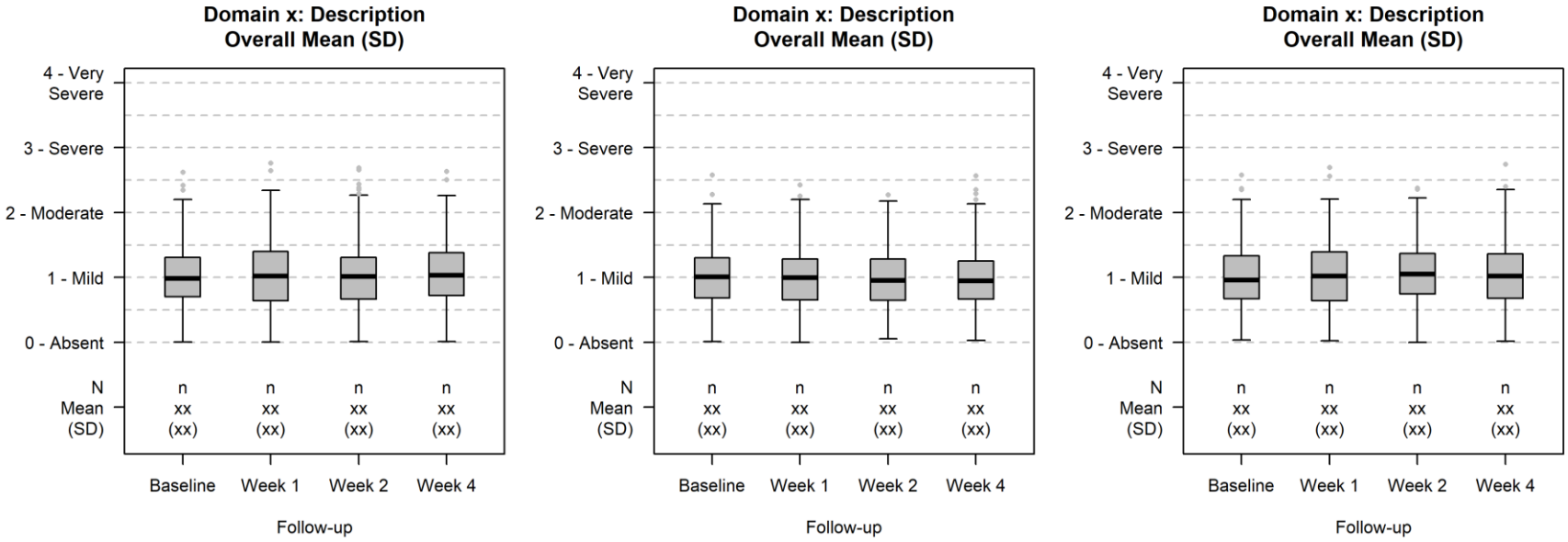


Exhibit 4.3.1 Distributions of PAC-SYM Domain Scores by Week
Exhibit 4.3.2 Distributions of PAGI-SYM Domain Scores by Week
Exhibit 4.3.3 Distributions of PAC-QOL Domain Scores by Week

Note:

- PAC-SYM and PAC-QOL are 5-point scale while PAGI-SYM is 6-point scale
- PAC-SYM has 3 domains, PAGI-SYM has 6 domains, and PAC-QOL has 4 domains

Exhibit 4.4.x Distributions of [ePRO] Domain Scores by Age Group

This figure summarizes the domain scores for [ePRO] at baseline and follow-up weeks by age group.

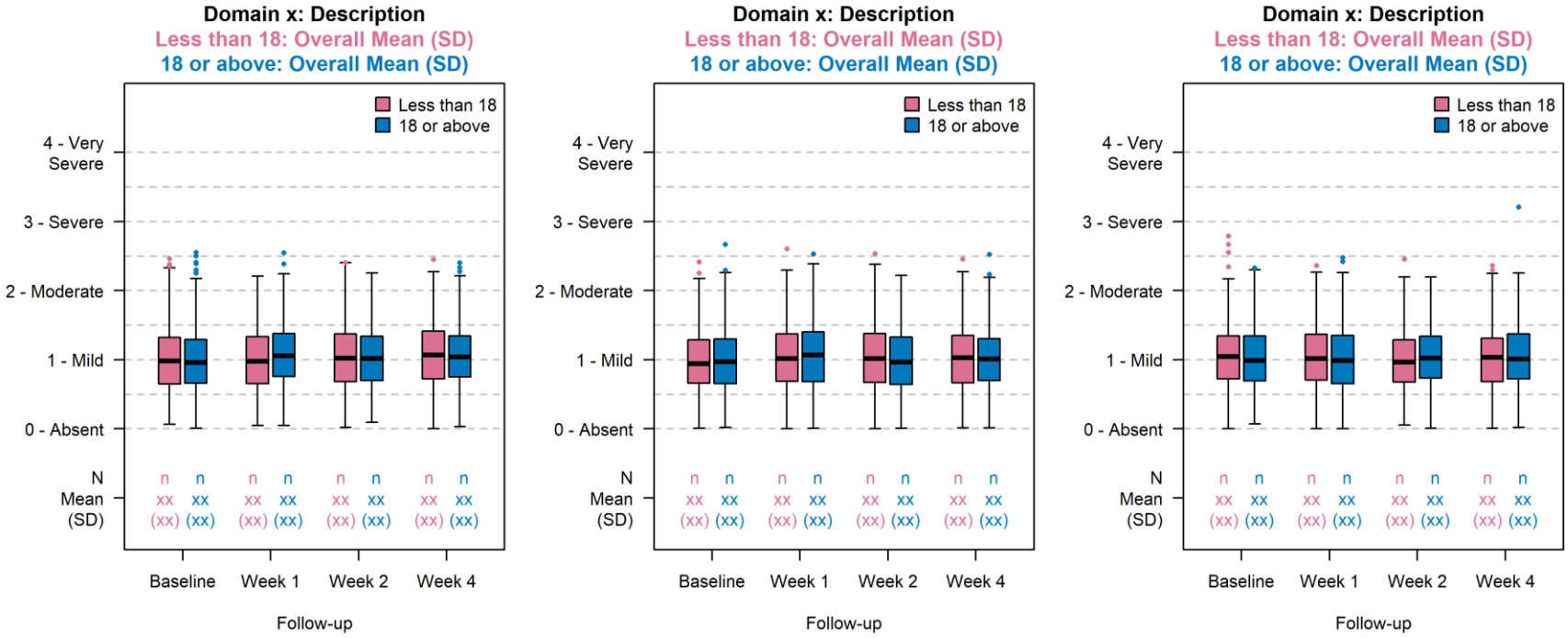


Exhibit 4.4.1 Distributions of PAC-SYM Domain Scores by Week and Age Group
Exhibit 4.4.2 Distributions of PAGI-SYM Domain Scores by Week and Age Group
Exhibit 4.4.3 Distributions of PAC-QOL Domain Scores by Week and Age Group

Note:
- PAC-SYM and PAC-QOL are 5-point scale while PAGI-SYM is 6-point scale
- PAC-SYM has 3 domains, PAGI-SYM has 6 domains, and PAC-QOL has 4 domains

Exhibit 4.5.1 Model-based Summary of PAC-SYM, PAGI-SYM, and PAC-QOL Total and Domain Scores

This figure provides model-based summaries of the total and domain scores, for all participants and subgroups stratified by age. The estimates are obtained from mixed-effect models with participant-specific random intercepts.

	Less than 18 Years Old (N=n)		18 Years Old and Above (N=n)		All Participants (N=n)	
	Mean (SD)	95% Confidence Interval	Mean (SD)	95% Confidence Interval	Mean (SD)	95% Confidence Interval
PAC-SYM						
Total Score (NN=nn)	**x.x (x.x)**		**x.x (x.x)**		**x.x (x.x)**	
Abdominal Symptoms (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Rectal Symptoms (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Stool Symptoms (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
PAGI-SYM						
Total Score (NN=nn)	**x.x (x.x)**		**x.x (x.x)**		**x.x (x.x)**	
Nausea/Vomiting (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Post-Prandial Fullness/Early Satiety (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Bloating (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Upper Abdominal Pain (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Lower Abdominal Pain (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Heartburn/Regurgitation (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
PAC-QOL						
Total Score (NN=nn)	**x.x (x.x)**		**x.x (x.x)**		**x.x (x.x)**	
Physical Discomfort (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Psychosocial Discomfort (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Worries and Concerns (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Satisfaction (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	

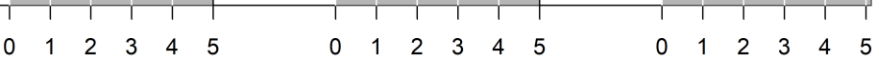


Exhibit 4.5.2 Comprehensive Model-based Summary of PAC-SYM, PAGI-SYM, and PAC-QOL Total and Domain Scores

This table is an extended version of Exhibit 4.5.1 with further details on the model-based summaries of the total and domain scores, for all participants and subgroups stratified by age, including the within-subject and between-subject variance estimates. The estimates are obtained from mixed-effect models with participant-specific random intercepts.

	Age <18 Years (N=n)			Age ≥18 Years (N=n)			All Participants (N=n)		
	Mean (95% CI)	**Within-Subject Variance**	**Between-Subject Variance**	**Mean (95% CI)**	**Within-Subject Variance**	**Between-Subject Variance**	**Mean (95% CI)**	**Within-Subject Variance**	**Between-Subject Variance**
PAC-SYM Total Score (NN=nn)	x.x (x.x, x.x)	x.xx	x.xx						
Abdominal Symptoms (NN=nn)									
Rectal Symptoms (NN=nn)									
Stool Symptoms (NN=nn)									
PAGI-SYM Total Score (NN=nn)									
Nausea/Vomiting (NN=nn)									
Post-Prandial Fullness/Early Satiety (NN=nn)									
Bloating (NN=nn)									
Upper Abdominal Pain (NN=nn)									
Lower Abdominal Pain (NN=nn)									
Heartburn/Regurgitation (NN=nn)									
PAC-QOL Total Score (NN=nn)									
Physical Discomfort (NN=nn)									
Psychosocial Discomfort (NN=nn)									
Worries and Concerns (NN=nn)									
Satisfaction (NN=nn)									

A.5 Summary of Prevalence and Variability of GI Symptoms

Exhibit 5.1.1 Summary of Disease-Specific Questionnaire – All Participants

This table summarizes the GI disease-specific questionnaire for all participants. All questions were based on patient's experience in the last week.

		Baseline (N=n)	Week 1 (N=n)	Week 2 (N=n)	Week 4 (N=n)
Bowel Movements	<3 Bowel Movements	n (%)			
	≥3 Bowel Movements				
Self-Described Bowel Pattern:	Normal				
	Constipated				
	Diarrhea				
	Alternating Constipation and Diarrhea				
Bristol Stool Scale [1]:	1 (Hard Lumps) – 2				
	3 – 5				
	6 – 7 (Watery)				
	Missing				
Leakage of Stool:	Yes				
Protocol-Defined Constipation [2]:	**Yes**				

[1] Question for Bristol Stool Scale: describe what your stool looked like on most days in the last week when you had a bowel movement?
[2] Protocol-defined constipation is defined as less than 3 bowel movements and/or Bristol Stool type 1 or 2 in the past week

Exhibit 5.1.2 Summary of Disease-Specific Questionnaire – Age < 18
Exhibit 5.1.3 Summary of Disease-Specific Questionnaire – Age ≥ 18

Exhibit 5.2.1 Demographics and Baseline Characteristics by Protocol-Defined Constipation at Baseline.

This table summarizes demographics and baseline characteristics, stratified by protocol-defined constipation at Baseline Visit.

		Protocol-Defined Constipation at Baseline		All Enrolled Participants (N=n)	Fully Completed at Least One ePRO at all Follow-up Weeks (N=n)	CF Registry (N=n)
		Yes (N=n)	No (N=n)			
Sex at Birth, n (%)	Female					
	Male					
Age Distribution, n (%)	<6 years					
	≥6 – 12 years					
	≥12 – 18 years					
	≥18 – 24 years					
	≥24 – 30 years					
	≥30 years					
	Mean (SD)					
	Median					
	Min, Max					
Race, n (%)	White					
	American Indian or Alaska Native					
	Black or African American					
	More than One Race					
	Unknown or Not Reported					
Ethnicity, n (%)	Hispanic or Latino					
	Not Hispanic or Latino					

		Protocol-Defined Constipation at Baseline		All Enrolled Participants (N=n)	Fully Completed at Least One ePRO at all Follow-up Weeks (N=n)	CF Registry (N=n)
		Yes (N=n)	No (N=n)			
Genotype, n (%)	F508 Heterozygous					
	F508 Homozygous					
	Other/Unknown					
Mutation Class, n (%)	I-III					
	IV-V					
	Unknown					
Sweet Chloride at Diagnosis (mEq/L)	Mean (SD)					
Weight (kg)	Mean (SD)					
Height (cm)	Mean (SD)					
Pancreatic Sufficiency[1], n (%)	Insufficient					
	Sufficient					
	Unknown					
Modulator Use, n (%)	None					
	Ivacaftor					
	Ivacaftor/Lumacaftor					
	Ivacaftor/Tezacaftor					
	Ivacaftor/Tezacaftor/Elexacaftor					

[1] Pancreatic Insufficient is defined as PERT use and/or fecal elastase or other diagnostic test at baseline.
Note on missing demographic data

Exhibit 5.2.2 Summary of Period-Prevalence of Constipation with Disease-Specific Questionnaire Fully Completed at all Weeks

This table summarizes the period-prevalence of protocol-defined constipation, as well as other definitions of constipation. Only participants who fully completed the disease-specific questionnaire at baseline and all follow-up weeks were considered. Period prevalence is defined as occurrence of the symptom at any time from baseline to week 4.

	Age <18 Years (N = n)	**Age ≥18 Years (N = n)**	**All Participants (N = n)**
Protocol-Defined Constipation [1]:	% (95% CI)		
Self-Described Constipation[2]			
Constipation			
Alternating Constipation and Diarrhea			
Alternative Definition:			
Definition 1			
…			
Definition d			

[1] Protocol-defined constipation is defined as less than 3 bowel movements and/or Bristol Stool type 1 or 2 in the past week
[2] Self-described constipation is based on the second question on the disease-specific questionnaire

Note: See Appendix B for discussion regarding alternative definitions of constipation.

Exhibit 5.2.3 Summary of Period-Prevalence of Constipation with Disease-Specific Questionnaire Fully Completed at least once

Similar table as above with consideration of participants who fully completed the disease-specific questionnaire at least once.

Exhibit 5.3.1 Summary of GI Symptoms from PAC-SYM, PAGI-SYM, and PAC-QOL

This table summarizes the GI symptoms based on prespecified questions from PAC-SYM, PAGI-SYM, and PAC-QOL questionnaires. All questions were based on patient's experience in the last week.

		Baseline	Week 1	Week 2	Week 4	Overall [1]
Symptom 1	N [2]					
	Absent, n (%)					
	Mild, n (%)					
	Moderate, n (%)					
	Severe, n (%)					
	Very Severe, n (%)					
	Symptom Presence [3], n (%)					
	Symptom Score [4], mean (sd)					
Symptom 2	N [2]					
	Absent, n (%)					
	Mild, n (%)					
	Moderate, n (%)					
	Severe, n (%)					
	Very Severe, n (%)					
	Symptom Presence [3], n (%)					
	Symptom Score [4], mean (sd)					

[1] Overall results were aggregated over all participants weeks. Overall symptom score is obtained from a longitudinal model.
[2] Number of participants who completed the question at each week
[3] Symptom presence is defined as checking any severity level other than "Absent"
[4] Symptom score is defined based on the scoring rubric of each ePRO (max of 4 for PAC-SYM and PAC-QOL, and max of 5 for PAGI-SYM)

Note: Selected symptoms were prespecified from PAC-SYM, PAGI-SYM, and PAC-QOL questionnaires (see Appendix C for the complete list of prespecified symptoms of interest). Scoring of symptoms range from either 0-4 (PAC-SYM and PAC-QOL) or 0-5 (PAGI-SYM)

Exhibit 5.3.2 Summary of GI Symptoms from PAC-SYM, PAGI-SYM, and PAC-QOL – Age < 18 Years
Exhibit 5.3.3 Summary of GI Symptoms from PAC-SYM, PAGI-SYM, and PAC-QOL – Age ≥ 18 Years

Exhibit 5.4.x Change from Baseline for [GI Symptom]

The following table shows the change in distribution for each symptom (including stool frequency/type) from baseline at each follow-up week.

		Week 1 (N =) [1] (Mean Score = , 95% CI =)						Week 2 (N =) [2] (Mean Score = , 95% CI =)						Week 4 (N =) [3] (Mean Score = , 95% CI =)					
		Absent	Mild	Moderate	Severe	Very Severe		Absent	Mild	Moderate	Severe	Very Severe		Absent	Mild	Moderate	Severe	Very Severe	
Baseline (Mean =, 95% CI =)	Absent	n (%)	n (%)				n (%) Worsened	n (%)	n (%)				n (%) Worsened	n (%)	n (%)				n (%) Worsened
	Mild	n (%)						n (%)						n (%)					
	Moderate																		
	Severe																		
	Very Severe																		
		n (%) Improved				n (%) No Change		n (%) Improved				n (%) No Change		n (%) Improved				n (%) No Change	

[1] Consider participants with both baseline and Week 1 data
[2] Consider participants with both baseline and Week 2 data
[3] Consider participants with both baseline and Week 4 data

Note: One table per each symptom; PAC-QOL only has data for Baseline and Week 4

Exhibit 5.4 Change in GI Symptoms from Baseline

The following table shows the changes in GI symptoms from baseline at each follow-up week. This is a collapsed version with less details compared to the 5.4.x exhibits.

GI Symptom	Baseline Mean (95% CI)	Week 1					Week 2					Week 4				
		N [1]	Mean (95% CI)	Worsen – n (%)	No Change – n (%)	Improved – n (%)	N [1]	Mean (95% CI)	Worsen – n (%)	No Change – n (%)	Improved – n (%)	N [1]	Mean (95% CI)	Worsen – n (%)	No Change – n (%)	Improved – n (%)
Symptom 1	Mean (95% CI)	n	mean (CI)	n (%)	n (%)	n (%)	n	mean (CI)	n (%)	n (%)	n (%)	n	mean (CI)	n (%)	n (%)	n (%)
Symptom 2																
…																
Symptom s																

[1] N per each follow-up week is defined as the number of participants who had data at both baseline and the follow-up week.

Exhibit 5.5.1 Summary of PAC-SYM, PAGI-SYM, and PAC-QOL Total Score by Protocol-Defined Constipation

This figure summarizes the distribution of total scores for PAC-SYM, PAGI-SYM, and PAC-QOL by **weekly** protocol-defined constipation status

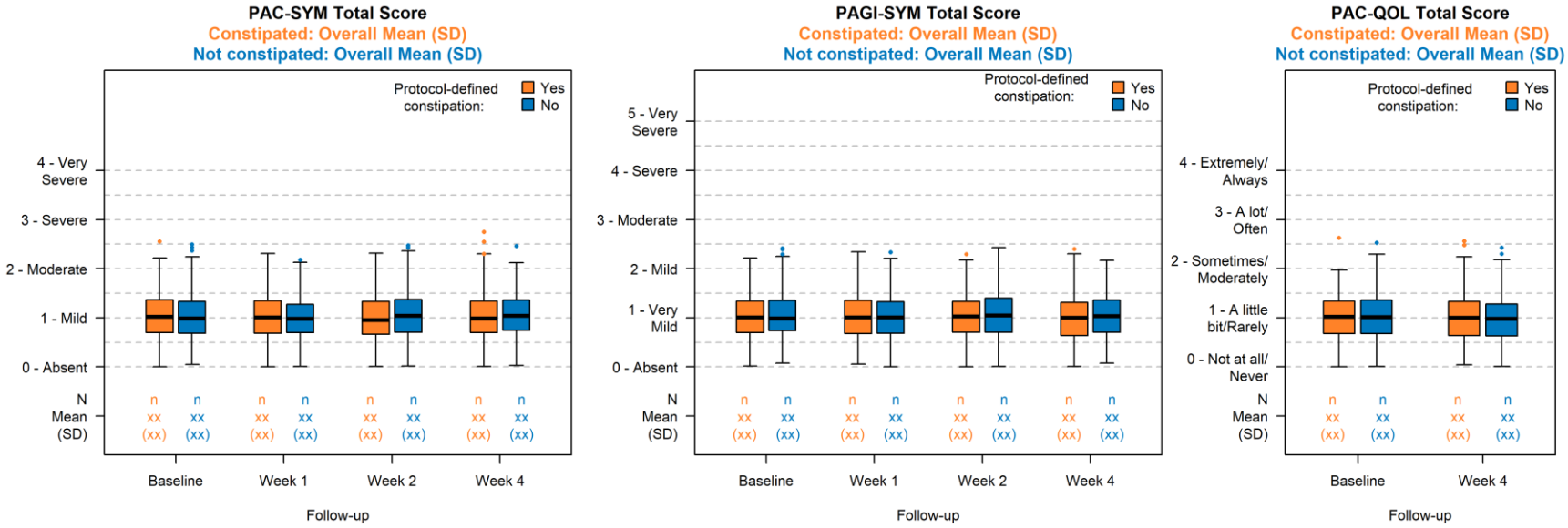


Exhibit 5.5.2 Summary of PAC-SYM, PAGI-SYM, and PAC-QOL Total Score by Self-Defined Constipation

Similar figure to Exhibit 5.5.1 but using self-defined constipation.

Exhibit 5.6.1 Model-based Summary of PAC-SYM, PAGI-SYM, and PAC-QOL Total and Domain Scores by Protocol-Defined Constipation

This figure provides model-based summaries of the total and domain scores, for all participants and by weekly protocol-defined constipation. The estimates are obtained from mixed-effect models with participant-specific random intercepts, as well as fixed effects for protocol-defined (weekly) constipation status, week, and age group. The predictor of interest is constipation status.

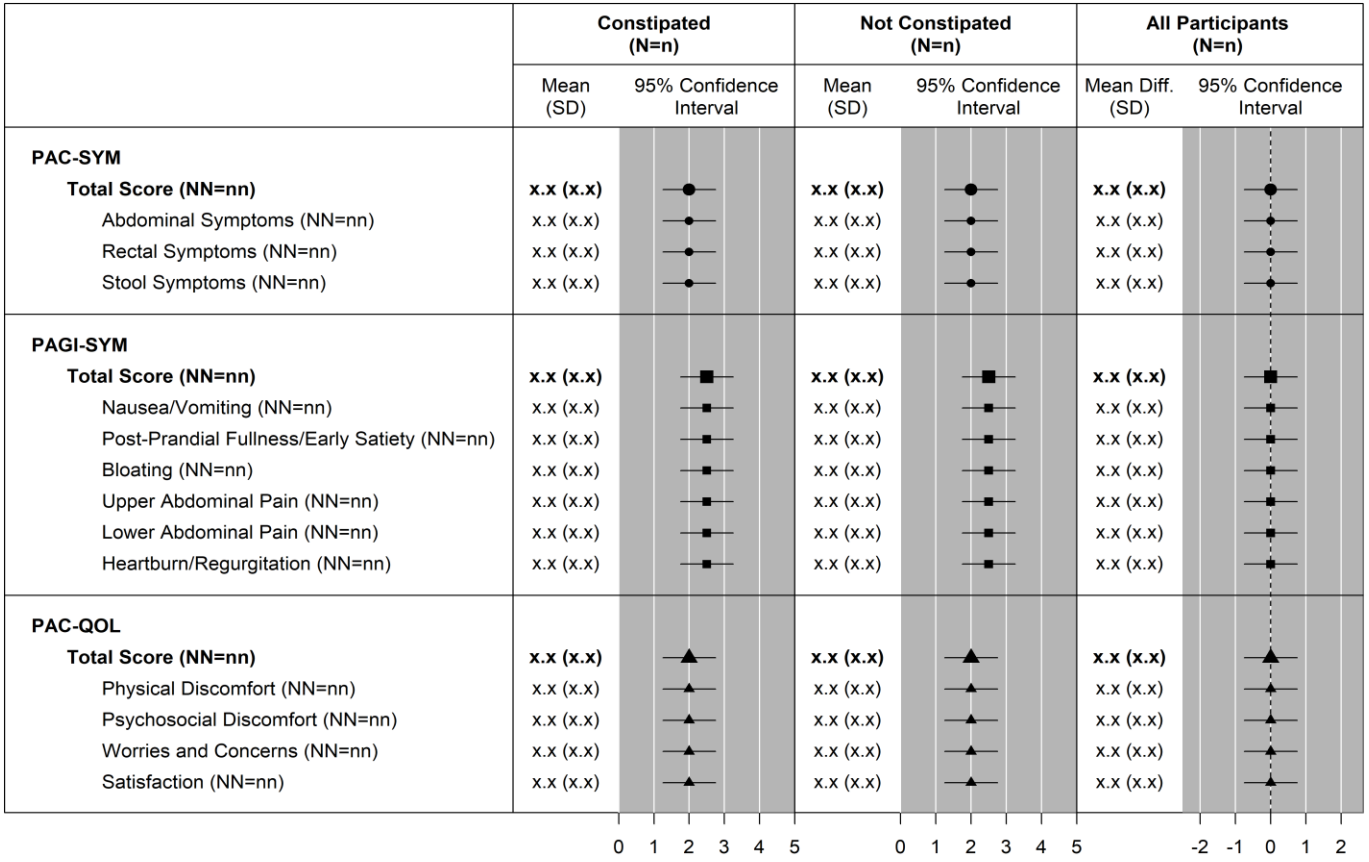


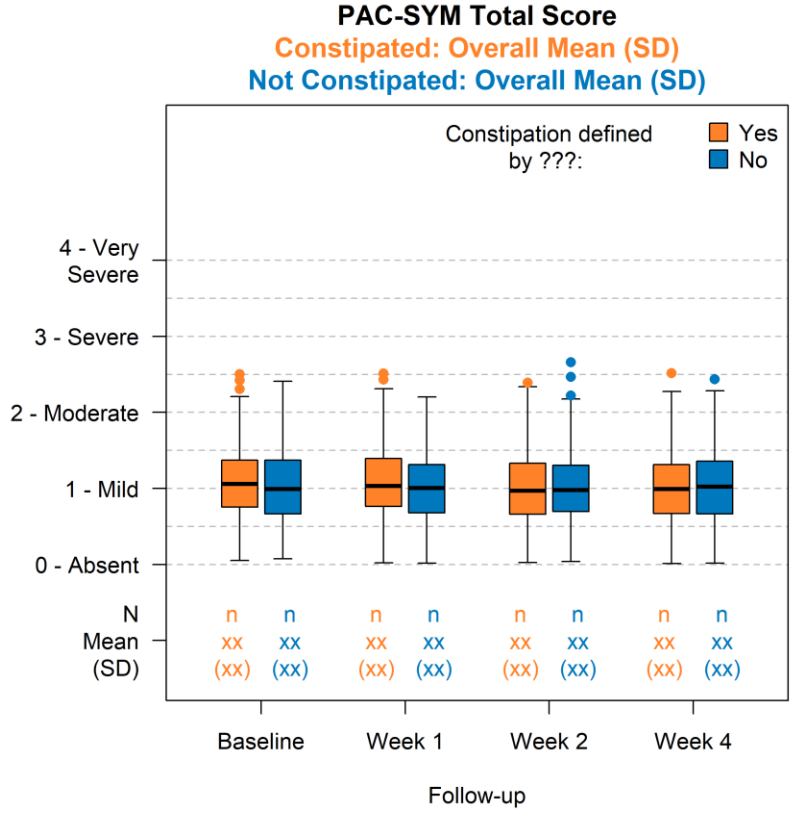
Exhibit 5.6.2 Model-based Summary of PAC-SYM, PAGI-SYM, and PAC-QOL Total and Domain Scores by Self-Defined Constipation

Similar figure to Exhibit 5.6.1 but using self-defined constipation.

A.6 Summary of Alternative CF-Specific Definitions of Constipation

Exhibit 6.1.x Summary of PAC-SYM total score by constipation status defined by [protocol or specific rules]

This figure (one figure per one definition of constipation) shows how the distribution of PAC-SYM total score looks with different definition for constipation, and an in-sample ROC curve constructed by using PAC-SYM total score in a longitudinal model as a classifier for the corresponding weekly constipation status.



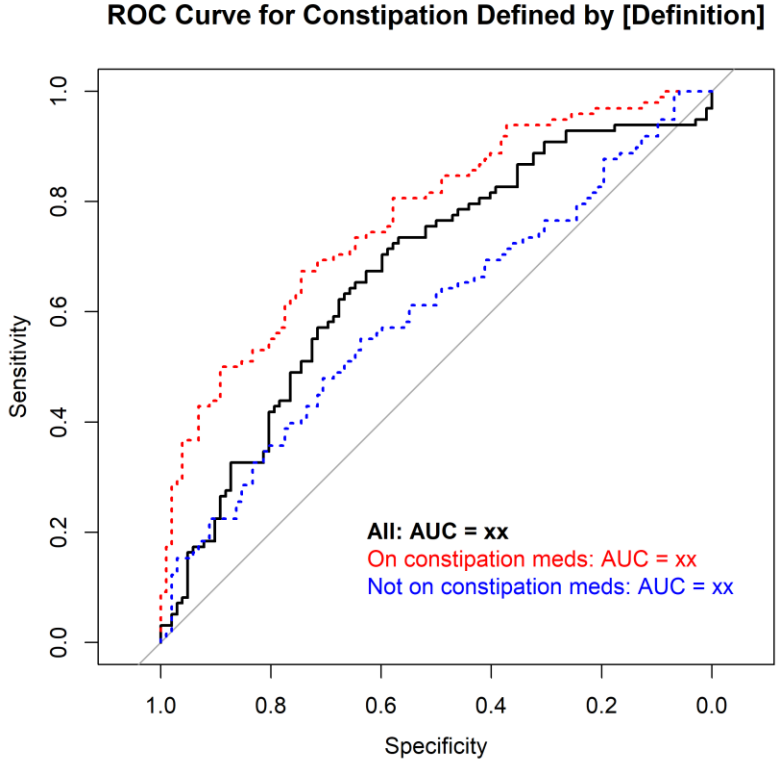


Exhibit 6.2.x Evaluation of Concordance between Self-Defined Constipation and Constipation Defined by [Protocol or Specific Rules]

This table shows the concordance between self-defined constipation and the definition of interest

			Self-Defined Constipation Yes	Self-Defined Constipation No	Cohen's Kappa
Constipation Definition of Interest:	**Baseline (N=n)**	**Yes**	n (%)		x
		No			
	Week 1 (N=n)	**Yes**			
		No			
	Week 2 (N=n)	**Yes**			
		No			
	Week 4 (N=n)	**Yes**			
		No			
	Overall (NN=nn)	**Yes**			
		No			

Exhibit 6.3.1 Evaluation of Protocol-Defined Constipation at Baseline and Constipation Treatment.

This table shows the relationship between constipation at baseline and constipation treatment. Constipation is defined per protocol.

		Constipation at Baseline (N=n)		No Constipation at Baseline (N=n)		All Participants at Baseline (N=n)	
		On Treatment (N=n)	Not on Treatment (N=n)	On Treatment (N=n)	Not on Treatment (N=n)	On Treatment (N=n)	Not on Treatment (N=n)
Week 1	Constipation	n (%)	n (%)				
	No Constipation	n (%)	n (%)				
	Unknown [1]	n (%)	n (%)				
Week 2	Constipation						
	No Constipation						
	Unknown [1]						
Week 4	Constipation						
	No Constipation						
	Unknown [1]						
All Follow-up Weeks [2]	Constipation						
	No Constipation						
	Unknown						

[1] Unknown status of constipation at each week is defined as incomplete Disease-Specific Questionnaire
[2] To summarize all follow-up weeks, constipation status implies that a participant had at least one or more week where they met the protocol definition of constipation.

Exhibit 6.3.2 Evaluation of Self-Defined Constipation at Baseline and Constipation Treatment.

This table shows the relationship between self-defined constipation at baseline and constipation treatment. Constipation is defined as choosing "Constipated" or "Alternating constipation and diarrhea" as answer for question 2 ("How would you describe your bowel pattern in the last week? (Select one)") on the Disease-Specific Questionnaire.

		Constipation at Baseline (N=n)		No Constipation at Baseline (N=n)		All Participants (N=n)	
		On Treatment (N=n)	Not on Treatment (N=n)	On Treatment (N=n)	Not on Treatment (N=n)	On Treatment (N=n)	Not on Treatment (N=n)
Week 1	Constipation	n (%)	n (%)				
	No Constipation	n (%)	n (%)				
	Unknown [1]	n (%)	n (%)				
Week 2	Constipation						
	No Constipation						
	Unknown [1]						
Week 4	Constipation						
	No Constipation						
	Unknown [1]						
All Follow-up Weeks [2]	Constipation						
	No Constipation						
	Unknown						

[1] Unknown status of constipation at each week is defined as either incomplete Disease-Specific Questionnaire or failure to answer question 2 on the Disease-Specific Questionnaire.
[2] To summarize all follow-up weeks, constipation status implies that a participant had at least one or more week where they met the self-defined definition of constipation.

Exhibit 6.4.x Model-Based Summary of Clearance of Constipation among Participants Who Had Constipation at Baseline Visit.

This exhibit reports statistical results for the clearance of constipation among participants who had constipation at baseline visit and had at least one follow-up Disease-Specific Questionnaire fully completed. Weekly clearance of constipation (1=yes, 0=no) is the outcome of interest in a generalized linear mixed model (GLMM) with either logit link (for odds ratio interpretation) or log link (for relative risk interpretation), participant-specific random effects, and adjustments for baseline constipation treatment, age group, sex, and week. In formula:

Weekly Clearance of Constipation (0/1) ~ Baseline Constipation Treatment + Age Group + Sex + Week + Participant-Specific Random Effect

Note: Constipation treatment at baseline was determined based on ATC coding of concomitant medications.

Exhibit 6.4.1 for Protocol-Defined Constipation
Exhibit 6.4.2 for Self-Defined Constipation

Exhibit 6.5.x Model-Based Summary of Emergence of Constipation among Participants Who Had No Constipation at Baseline Visit.

This exhibit reports statistical results for the emergence of constipation among participants who had no constipation at baseline visit and had at least one follow-up Disease-Specific Questionnaire fully completed. Weekly emergence of constipation (1=yes, 0=no) is the outcome of interest in a generalized linear mixed model (GLMM) with either logit link (for odds ratio interpretation) or log link (for relative risk interpretation), participant-specific random effects, and adjustments for baseline constipation treatment, age group, sex, and week. In formula:

Weekly Emergence of Constipation (0/1) ~ Baseline Constipation Treatment + Age Group + Sex + Week + Participant-Specific Random Effect

Note: Constipation treatment at baseline was determined based on ATC coding of concomitant medications.

Exhibit 6.5.1 for Protocol-Defined Constipation
Exhibit 6.5.2 for Self-Defined Constipation

A.7 Summary of Current Management of GI Symptoms

Exhibit 7.1 Summary of Treatment for GI Symptoms and Constipation at Baseline

This table summarizes the number of participants initiating treatment, receiving treatment (along with the medication type/class), or neither at baseline.

	Age Category		All Enrolled Participants (N=n)
	Age < 18 (N=n)	Age ≥ 18 (N=n)	
Neither Initiating nor Receiving Treatment	n (%)		
Initiating or Receiving GI Treatment			
Type of Treatment			
Non-Constipation			
Medication 1			
…			
Medication m			
Constipation			
Medication 1			
…			
Medication m			
Route			
GI Tube			
Others			

Note: missing data

Note: See Appendix D for a list of GI medications of interest. GI/Constipation medications were derived from all concomitant medications based on ATC coding.

Exhibit 7.2 Summary of GI Symptoms and Constipation by Receiving Constipation Treatment

This table summarizes GI symptoms and constipation status at baseline by receiving constipation treatment.

		Receiving Constipation Treatment	
		Yes (N = n)	**No (N = n)**
GI Symptoms	Symptom 1 (n = x)		
	Symptom 2 (n = x)		
	…		
	Symptom s (n = x)		
	Any Symptom (n = x)		
Protocol-Defined Constipation	Yes (n = x)		
Self-Defined Constipation	Yes (n = x)		
Other Definition of Constipation	Definition 1 (n = x)		
	Definition 2 (n = x)		
	…		
	Definition d (n = x)		

Note: missing data

Note: See Appendix B for a list of prespecified alternative definition of constipation.

Exhibit 7.3.x.y Change in [GI Symptom X] from Baseline among [Subgroups Defined by Constipation Treatment at Baseline]

This table is similar to the 5.4.x tables for each subgroup defined by constipation treatment at baseline (initiating/receiving or neither). The table shows the change in distribution for each symptom X (including stool frequency/type) from baseline at each follow-up week.

		Week 1 (N =) [1] (Mean Score = , 95% CI =)						Week 2 (N =) [2] (Mean Score = , 95% CI =)						Week 4 (N =) [3] (Mean Score = , 95% CI =)					
Baseline (Mean =, 95% CI =)		Absent	Mild	Moderate	Severe	Very Severe		Absent	Mild	Moderate	Severe	Very Severe		Absent	Mild	Moderate	Severe	Very Severe	
	Absent	n (%)	n (%)				n (%) Worsened	n (%)	n (%)				n (%) Worsened	n (%)	n (%)				n (%) Worsened
	Mild	n (%)						n (%)						n (%)					
	Moderate																		
	Severe																		
	Very Severe																		
		n (%) Improved				n (%) No Change		n (%) Improved				n (%) No Change		n (%) Improved				n (%) No Change	

[1] Consider participants with both baseline and Week 1 data
[2] Consider participants with both baseline and Week 2 data
[3] Consider participants with both baseline and Week 4 data

Exhibit 7.3 Changes in GI Symptoms from Baseline by Constipation Treatment

The following table shows the changes in GI symptoms from baseline at each follow-up week in subgroups defined by constipation treatment, i.e. not treated versus treated (initiating or receiving). This is a collapsed version with less details compared to the 7.3.x exhibits.

GI Symptom		Baseline Mean (95% CI)	Week 1					Week 2					Week 4				
			N [1]	Mean (95% CI)	Worsen – n (%)	No Change – n (%)	Improved – n (%)	N [1]	Mean (95% CI)	Worsen – n (%)	No Change – n (%)	Improved – n (%)	N [1]	Mean (95% CI)	Worsen – n (%)	No Change – n (%)	Improved – n (%)
Symptom 1	Not Treated	Mean (95% CI)	n	mean (CI)	n (%)	n (%)	n (%)	n	mean (CI)	n (%)	n (%)	n (%)	n	mean (CI)	n (%)	n (%)	n (%)
	Treated	Mean (95% CI)	n	mean (CI)	n (%)	n (%)	n (%)	n	mean (CI)	n (%)	n (%)	n (%)	n	mean (CI)	n (%)	n (%)	n (%)
Symptom 2	Not Treated																
	Treated																
…																	
Symptom s	Not Treated																
	Treated																

[1] N per each follow-up week is defined as the number of participants who had data at both baseline and the follow-up week.

Exhibit 7.4 Longitudinal Summary of PAC-SYM, PAGI-SYM, and PAC-QOL Total and Domain Scores by Constipation Treatment

This table provides longitudinal summaries of the total and domain scores, for all participants and subgroups stratified protocol-defined constipation. The estimates are obtained from mixed-effect models with participant-specific random intercept, as well as fixed effects for indicator of constipation treatment, week, and age group. The predictor of interest is the indicator of constipation treatment.

	On Constipation Treatment (N=n)		Not on Constipation Treatment (N=n)		All Participants (N=n)	
	Mean (SD)	95% Confidence Interval	Mean (SD)	95% Confidence Interval	Mean Diff. (SD)	95% Confidence Interval
PAC-SYM						
Total Score (NN=nn)	**x.x (x.x)**		**x.x (x.x)**		**x.x (x.x)**	
Abdominal Symptoms (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Rectal Symptoms (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Stool Symptoms (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
PAGI-SYM						
Total Score (NN=nn)	**x.x (x.x)**		**x.x (x.x)**		**x.x (x.x)**	
Nausea/Vomiting (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Post-Prandial Fullness/Early Satiety (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Bloating (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Upper Abdominal Pain (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Lower Abdominal Pain (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Heartburn/Regurgitation (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
PAC-QOL						
Total Score (NN=nn)	**x.x (x.x)**		**x.x (x.x)**		**x.x (x.x)**	
Physical Discomfort (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Psychosocial Discomfort (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Worries and Concerns (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
Satisfaction (NN=nn)	x.x (x.x)		x.x (x.x)		x.x (x.x)	
		0 1 2 3 4 5		0 1 2 3 4 5		-2 -1 0 1 2

A.8 Additional Exhibits for Consideration Given Data Availability and Feasibility

Exhibit: PAC-SYM, PAGI-SYM, and PAC-QOL total/domain scores by modulator use and types

Exhibits: Selected analysis on completion of ePROs, total/domain scores of PAC-SYM, PAGI-SYM, and PAC-QOL, summary of disease-specific questionnaire by 3 age groups: <12, ≥12 and <18, and ≥18 (Note: for participants <12 years old, parents or guardians would complete the ePROs)

Exhibits: Selected analysis by age groups corresponding to PROMISE for future comparison (less than 6, 6-11, 12+)

Exhibits: Repeat Exhibits 6.3-6.5 for specific symptoms of interest, e.g. nausea or bloating
Note: This depends on whether data are available for symptom-specific treatment.

Exhibit: Correlation across GI symptoms of interest

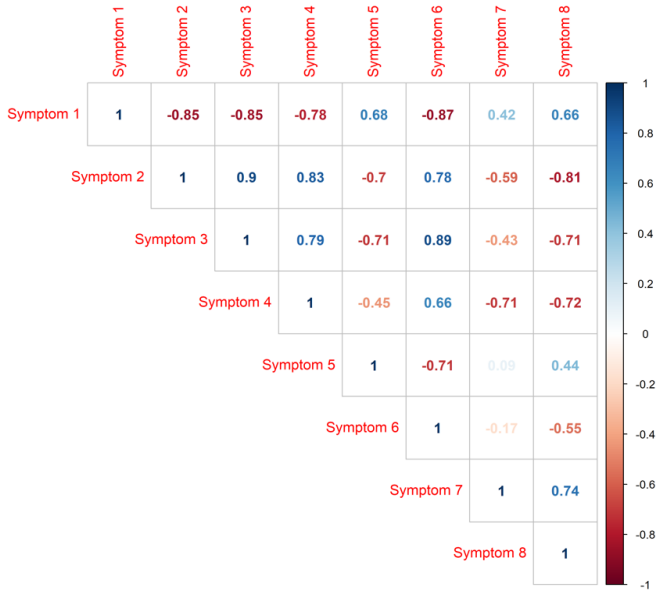


Exhibit: Comprehensive list of GI medications/treatments at baseline

Appendix B: Definitions of Constipation

Protocol-defined constipation: <3 bowel movements AND/OR BSS type 1 or 2.

Self-described constipation (based on disease-specific questionnaire)
- Definition 1: Answered “Constipated” for question 2 on disease-specific questionnaire
- Definition 2: Answered “Constipated” or “Alternating constipation and diarrhea” for question 2 on disease-specific questionnaire

Other alternative definitions to be considered:
- Proposed definition 1: <3 bowel movements (rationale: subset of the protocol definition)
- Proposed definition 2: BSS type 1 or 2 (rationale: subset of the protocol definition)
- Proposed definition 3: <7 bowel movements (rationale: the disease-specific questionnaire is a weekly survey, and having <7 bowel movements is equivalent to not having at least 1 bowel movement per day on average)

Appendix C: Pre-Specified GI Symptoms of Interest

PAC-SYM:

- Incomplete BMs (Q8)
- Straining or squeezing to try to pass a BM (Q11)
- Feeling you have to have a BM but cannot pass it (Q12)

PAGI-SYM:

- Regurgitation or reflux (fluid or liquid coming up) (Q18)
- Nausea (Q1)
- Vomiting (Q3)
- Upper abdominal pain (Q10)
- Loss of appetite (Q7)
- Stomach fullness (Q4)
- Bloating (Q8)
- Stomach for belly visibly larger (Q9)

Disease-specific questionnaire:

- Fecal incontinence

Appendix D: Medications of Interest

List of constipation medication/treatment of interest:

- Polyethelyne glycol, Miralax, PEG, etc.
- Senna/Ex-Lax
- Lubiprostone
- Fiber supplements
- Linaclotide

List of non-constipation GI medication/treatment of interest:

- Acid suppressing agents: Proton Pump inhibitors; H2-Receptor antagonists; Others
- Antiemetics and antinauseants
- Anti-gas
- Anti-inflammatory agents
- Antipasmodic
- Appetite stimulants
- Bile acid derivatives
- Dopamine antagonists
- Drugs for non-acid reflux GERD
- Multivitamins and mineral supplements
- Pancreatic enzymes: relizorb, oral
- Probiotics

<u>List of non-GI medication/treatment of interest:</u>

- Erythromycin
- Azithromycin
- Drugs used in diabetes