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Pharmacodynamic and Clinical Endpoints for Functional Colonic Disorders: Statistical Considerations

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Abstract

Background—Intra- and inter-subject coefficients of variation (COV) of scintigraphic colonic transit (SCT) are well characterized. SCT response to therapy predicts clinical efficacy of experimental medications in lower functional gastrointestinal disorders (FGID).

Aim—To compare COVs for bowel function with pharmacodynamic (PD) colonic transit geometric center (GC) as endpoints in lower FGID studies.

Methods—We evaluated data from placebo arm of 9 phase IIA, parallel-group, clinical trials of PD effects of linaclotide, dextroglutamide, renzapride, elobixibat, ROSE 010, and chenodeoxycholate in lower FGID with constipation, and pexacerfont, VSL#3, and colessevelam in lower FGID with diarrhea. Patients completed daily diaries for at least 7 days of stool frequency, consistency (7-point Bristol Stool Form Scale), and ease of passage (7-point scale from manual disimpaction to incontinence). Seventeen patients received placebo in 2 separate studies allowing assessment of intra-patient COVs. We calculated sample sizes required to demonstrate a 30% effect size for colonic transit, stool frequency, consistency and ease of passage for patients with lower FGID with constipation and, separately, diarrhea.

Results—COV_{inter} from 87 patients and COV_{intra} from 17 patients are reported. Generally, COV_{intra} is somewhat greater than COV_{inter}. The COVs for PD endpoints are lower than for clinical endpoints; however, clinically relevant effects can be identified with modest (~50%) increases in the sample size using parallel-group design studies.

Conclusion—Phase IIA studies that incorporate clinical and PD endpoints are feasible in lower FGID associated with constipation or diarrhea. Crossover design would require lower sample size for most endpoints compared to parallel-group studies.

Keywords

transit; constipation; diarrhea; parallel; crossover

Introduction

The cost of drug development is leveraged by the long duration from concept to marketing, and the considerable costs of phase II and III trials. It is estimated that less than 20% of

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drugs that make it beyond animal pharmacology and toxicology actually make it to presentation and final regulatory approval; in fact, the estimated clinical approval success rate for compounds originating from the pharmaceutical company itself over a 20-year period (1993–2004) was 32% for large molecules and 13% for small molecules [1]. Through June 2009, among 120 GI/metabolism drugs, the success rate was 3.3% [1]. The average expenditure on drugs in human clinical trials is around \$27 million per year, with \$17 million per year on drugs in Phase I, \$34 million on drugs in Phase II, and \$27 million per year on drugs in Phase III of the human clinical trials [2]. For drugs entering human clinical trials for the first time between 1989 and 2002, the estimated cost per new drug was \$868 million [3].

Some of the greatest expenses occur when drugs are dropped at the end of multicenter clinical trials in phase IIB or, even worse, phase III. We believe that the drug development programs (for agents affecting motility, transit, secretion or microbiome) would be considerably enhanced by the availability of valid approaches that deliver an accurate and reliable decision: “go” or “no go”.

Validated biomarkers and surrogate endpoints are available for few indications [4], and none are approved in the context of lower functional gastrointestinal disorders (FGIDs).

Our focus is on development of novel approaches to enhance the efficiency of drug development in lower FGIDs. We believe that colonic transit by scintigraphy has been shown to have well-characterized performance characteristics, including intra- and inter-subject coefficients of variation (COV), responsiveness to therapy, and prediction of efficacy of experimental medications (motility-modifiers, or secretagogues or a combination probiotic) in phase IIB or III trials in patients with FGIDs [5]. In these studies, we have usually described the clinical effects of medications, though the sample size was not sufficient to exclude type II errors. The general goal of this study was to appraise whether phase IIA studies could be designed in the target population of lower FGIDs associated with either constipation or diarrhea (assessed separately) to demonstrate efficacy of an investigational drug using the validated pharmacodynamic (PD) endpoints in combination with clinical validation. Such an approach would have the potential to identify the doses to be taken to phase III trials, to skip phase IIB clinical trials, and to reduce the time taken to develop new drugs for colonic motility disorders. In general, it is considered that the intra-individual COV (COV_{intra}) is smaller than the interindividual COV (COV_{inter}) and, therefore, the sample size for crossover studies is generally assumed to be smaller than for parallel-group design studies. However, there are only limited data regarding these COVs to inform the design of trials in drug development programs.

The aims of the current study were to appraise the COVs of bowel function endpoints in patients with lower FGIDs associated with either constipation or diarrhea, and to compare them with the COVs of the validated PD endpoints. A secondary aim was to assess reproducibility of colonic transit measurements and the relationship between colonic transit and bowel functions. The current study focused on patients randomized to the placebo arms of the pharmacodynamic studies [6–14]. This analysis incorporated some of the data previously included in the report by Deiteren et al. [15], which assessed 147 IBS patients and 46 healthy subjects who had received placebo or active treatment.

Methods

The study was approved by Mayo Clinic Institutional Review Board. All subjects were checked for general research authorization as per Minnesota state law, and only those without denial of research authorization were included in the present study.

Design

We evaluated data from 9 previously published phase IIA clinical trials of the PD effects of drugs (linaclotide, dexloxyglumide, renzapride, elobixibat, VSL#3, pexacerafont, ROSE 010, colesevelam and chenodeoxycholate) [6–14] in patients with lower FGIDs: constipation-predominant irritable bowel syndrome (IBS-C) or functional constipation (FC), and diarrhea-predominant irritable bowel syndrome (IBS-D). The primary endpoint of those studies was colonic transit geometric center at 24 hours. Patients completed daily diaries (Figure A in Appendix) for at least 7 days, documenting each bowel evacuation, the stool consistency based on 7 point Bristol stool form scale, and 7 point ease of passage ranging from manual disimpaction to incontinence. For the purpose of this analysis, we included only the placebo treatment arms, and all studies employed a parallel-group design. Among these patients, 17 had been assigned to the placebo arm in two studies conducted a median 37 months apart (range 2–90 months), and this provided an opportunity to assess intra-patient COV for the GC and bowel functions.

The colonic transit measurement is based on our well established method which has been described in detail in the literature [16], including its performance characteristics in patients with lower FGIDs [15] and prediction of responsiveness [5].

Statistical Analysis

The data for colonic transit (GC at 24 and 48 hours) and daily diary based assessment of bowel function were summarized for all 87 patients using the initial study in each patient and, separately, for the 17 patients using the data from their two studies. Estimates of inter-subject and intra-subject coefficients of variation (COV) were computed for each endpoint and for the two subgroups of lower FGIDs with either constipation or diarrhea. Inter-subject COV (%) was computed as $100 \times \text{SD}$ divided by the mean. For intra-subject COV, $100 \times \text{SD}$ of the deltas (first study vs. second study) was divided by the overall mean of the within subject means (over their two studies). The estimated variations (standard deviations) were then used to estimate the sample sizes required to detect a 30% effect size (with 80% power) for colonic transit, stool consistency and number of stools per day. We selected 30% effect size because, using the pharmacodynamic endpoint of GC24, this effect size has typically predicted responsiveness of bowel dysfunction when tested in phase IIB or III clinical trials [5].

Results

Demographics and relationship of bowel function clinical endpoints

Demographics of the patients with lower FGIDs, either constipation ($n=55$ IBS-C or FC) or IBS-D ($n=32$), included in the study are shown in Table I. There were significant correlations between mean daily stool consistency and mean daily stool frequency and mean ease of passage in the entire cohort of 87 patients (Figures 1 and 2, and Table II which shows Spearman correlation coefficients of all clinical and transit endpoints). Seventeen participants (2 IBS-D, 15 lower FGIDs with constipation) had two studies performed; all 17 were females and their mean (SD) age was 40 years [10].

Inter-individual variation

Endpoint data and $\text{COV}_{\text{inter}}$ from 55 IBS-C/FC patients and 32 IBS-D patients with at least one study are shown in Table IIIA and IIIB, respectively. Note that the COV is lower for pharmacodynamic endpoints (GC24h and 48h) than for stool frequency and consistency endpoints, although stool consistency variation was similar to that of GC24h. In patients

with lower FGIDs with constipation, GC24h has a lower COV_{inter} than GC48h; in contrast, in patients with IBS-D, the GC48h has the lower COV_{inter} .

The lowest COV_{inter} observed was for ease of stool passage scores, but this is probably mostly relevant in patients with constipation. It is important to appreciate that, with a 50% increase in the number of participants per group (27 compared to 19), it would be possible to demonstrate 30% improvements in stool number and consistency in addition to the improved primary PD endpoint, which is colon GC at 24 hours. In IBS-C/FC, a smaller COV_{inter} was observed for GC48h than for GC24h due to the larger mean values of GC48h, despite greater variation in GC48h values. The number of subjects required to demonstrate a 30% difference in GC48h values (i.e. 0.76 units) is greater than for GC24h (i.e. 0.70 units); this is to be expected because the sample size is directly proportional to the variance and inversely proportional to the square of the difference between two groups, and the variance in this particular case dominates.

Intra-individual variation

Data from 15 IBS-C/FC patients who had two sets of data are shown in Table IIIC. Note that the COV_{intra} is lower for pharmacodynamic than for clinical (bowel movement and evacuation) endpoints. In addition, note that the COVs are comparable and sometimes higher for the COV_{intra} compared to COV_{inter} . The number of subjects in a paired study to detect the same 30% effect sizes are generally lower than in a parallel design study, including the primary endpoints of interest GC24h [20 per group (total 40 studies for a two-arm study) using a parallel-group design compared to 14 (total 28 studies) in a crossover design] and stool consistency [24 patients per group (total 48 studies) in a two-arm, parallel-group design compared to 18 patients studied twice (total 36 studies) in a two-period crossover design].

Reproducibility of colonic transit measurements

The Bland-Altman plots in Figure 3 show the differences in two measurements of colonic transit at 24 and 48 hours, relative to the mean result in the two measurements. Note that, for the vast majority of participants, the data are reproducible within 0.5 to 1 GC units at 24 hours and 1 SD unit at 48 hours, but that the variance is larger in patients with faster colonic transit (higher GC values).

Relationship of clinical endpoints and colonic transit

There were significant correlations between colon transit measurements at 24 and 48 hours and stool frequency (Figure 4) and stool consistency (Figure 5) in the cohort of 87 patients undergoing one study. In contrast (based on the data from the 17 patients with two studies), the correlations between per subject mean colonic transit and stool consistency (Figure 6) and stool frequency (data not shown) were not significant.

Discussion

Our study provides guidance on the potential design of early phase (IIA/IIB) clinical trials that are intended to provide proof of concept of medication efficacy or to inform decisions related to further drug development or selection of doses to be pursued in pivotal phase III trials required for regulatory approval. In the past, we had demonstrated that the measurement of colonic transit by scintigraphy provides a biomarker that predicts what drug and what doses will be efficacious in large, multicenter clinical trials based on patient response outcomes or clinical endpoints [5]. The current study builds upon those observations in several ways as it appraises, in combination, the application of clinical endpoints describing bowel function during pharmacodynamic studies based on

measurement of colonic transit. We appraised 87 patients with a spectrum of lower FGIDs with diarrhea or constipation. As expected in this spectrum of patients, there were significant associations between stool consistency and frequency, as well as stool consistency and ease of passage of stool. The measurement of colonic transit was generally reproducible when it was repeated [when conducted a median 37 months apart (range 2–90 months)] in 17 patients, though there was greater variation in patients with faster colonic transit; reproducibility is inferred from the COV_{intra} of 43.4% at 24 hours and 21.9% at 48 hours. The delta colonic GC24h and GC48h values from repeat studies showed no association with the time between studies. The significant relationship between colonic transit and stool frequency and consistency previously demonstrated in a cohort of 147 IBS patients and 46 healthy subjects evaluated in our laboratory [15] was confirmed in the current cohort of 87 patients, some of whom were included in the prior study. The relationship between transit and bowel functions was not significant in the small group of 17 participants when the analysis assessed the association of mean colonic transit at 24 or 48 hours and mean stool frequency and consistency. The latter observation may have been compromised by the smaller sample of 17 participants.

Our current studies provide novel insights on the variation in pharmacodynamic and clinical endpoints in patients with colonic disorders that result in altered bowel function. First, the COV_{inter} for clinical endpoints of stool consistency and frequency is larger than that of the PD endpoints, especially the GC24h which is applicable for studies in both diarrhea and constipation groups. Our experience with several trials conducted in the last decade shows that it is clearly feasible to conduct trials that incorporate both PD and clinical endpoints. A major objective when using these endpoints is to avoid type II errors. Our study provides information on the sample size necessary to demonstrate a clinically relevant effect size of 30%. Our study shows that the total number of studies required in parallel-group design studies is only about 50% larger than the sample size required for studies that evaluate exclusively the PD endpoint. The data also suggest that such proof of concept studies can be accomplished with sample sizes of these common disorders available at single or few centers where the methods used here can be easily standardized, especially for conditions such as the lower functional gastrointestinal disorders which may affect 15% of the population in many Western countries. This approach has the advantage that the study can be centralized, more easily administered and monitored for regulatory purposes, and the patients' physiological and clinical responses can be evaluated concurrently and correlated, rather than extrapolated from one PD group to a separate group of patients who participate in a clinical phase IIB trial focused exclusively on clinical endpoints.

Second, the COV_{intra} is similar to the COV_{inter} , and it is reasonable to conclude, based on the estimated sample sizes documented in Table II, that parallel-group design studies are as powerful as crossover studies, since they are capable of detecting a clinically relevant effect size of 30%, with a moderate increase in sample size in parallel-design studies over the number that would be required in crossover studies. Conduct of parallel-group design studies essentially utilizes the same laboratory resources (e.g. transit measurements); Table IIA and IIC show that the total number of studies is modestly greater in a parallel-group compared to a crossover design. In conditions like lower FGIDs, which have high prevalence and therefore present less challenges in patient recruitment, the parallel design has additional advantages over the crossover studies.

There are several pitfalls associated with crossover studies. First, is the potential of an order effect, which would require that the study conclusions be confirmed by analysis of only the first treatments received by all participants. Second, is that, despite the washout period between the two study arms, patients would not have returned to the function or symptom loads that were present at entry into the first treatment period. This is particularly relevant in

the context of studies in which the analysis plan requires the use of baseline measurements as covariates in the analysis of treatment effects, as occurs in studies using PD endpoints.

A third observation, among the clinical endpoints, is that the COVs are slightly smaller for mean daily stool consistency than mean daily stool number. This supports the decision by FDA to use bowel movement consistency rather than stool number as the primary bowel function endpoint in PROs for irritable bowel syndrome [17].

The clinical endpoint with the lowest COV is ease of passage of bowel movements. In these single center studies, we are able to carefully exclude disorders of defecation dynamics by means of standardized questionnaires, interviews and examinations of patients, and evaluation of defecation dynamics. Therefore, the information provided from this study may not be generalizable to other centers without expertise in excluding an evacuation disorder. In addition, this symptom (ease of passage) will require further validation before it can be proposed for use as a primary endpoint for assessing clinical efficacy, despite the favorable sample size required to demonstrate a 30% effect.

Our analysis focused on estimated sample sizes to demonstrate an effect size of 30%; this was based on the observation that several drugs in development that had such an effect size were subsequently reported to have significant effects on bowel functions [5]. The data provided in the table could be used to estimate the sample size required for different effect sizes, e.g. 20 or 40%. While the colonic scintigraphy method is not widely available, similar studies could be conducted with other more generally available methods, such as radiopaque marker transit or wireless motility capsules. Regrettably, there are insufficient data on reproducibility and simultaneous measurement of bowel function in the literature to allow a similar analysis.

The estimated coefficients of variation and effect size calculations or number required to demonstrate a specific effect size in pharmacodynamics endpoints reflect the transit profile observed with scintigraphy, and the same question could be applied to alternative transit measurements such as radiopaque markers or motility/transit recording capsules if the coefficient of variation is estimated with those methods. The sample size estimate is a function of the size of the COV%, irrespective of the method used to measure transit. Therefore, we perceive this is a useful contribution for others doing such research, and the sample sizes studied (n=87) provide robust information about the clinical endpoints which would be generally relevant to studies not conducted using colonic transit scintigraphy.

In conclusion, the COVs for PD endpoints are lower than those for clinical endpoints; however, clinically relevant effects can be identified with a ~50% increase in the sample size in parallel-group design studies. COV_{intra} is not much smaller than COV_{inter} , implying that the sample size for crossover studies would not be dramatically lower than for parallel-group design studies. In particular, the observed SD of the deltas implies that the total number of studies in a crossover design would be somewhat lower for most endpoints than for parallel group design studies, although not sufficiently smaller to mitigate the potential pitfalls associated with using crossover studies. It is feasible to conduct simultaneous PD and clinical endpoint phase IIA studies which have the potential to reduce the need to include multiple dose arms in the large, more costly clinical phase IIB or III trials that are based on patient response outcomes.

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APPENDIX

SAMPLE STOOL DIARY CARD

Daily Diary Date: 			
If you had no bowel movements today, please check this box: ☐ no bowel movements today.			
Please record the time you took the study medication today: : 			
	Describe the consistency of bowel movement	Describe the Ease of Passage of bowel movement	Did you feel like you completely emptied your bowels?
	1 hard lumps 2 lumpy sausage 3 cracked sausage 4 smooth sausage 5 soft lumps 6 mushy 7 watery	1 Manual Disimpaction 2 Enema needed 3 Straining needed 4 Normal 5 Urgent w/pain 6 Urgent w/pain 7 Incontinent	1 no 2 yes
1 ☐ am ☐ pm			
2 ☐ am ☐ pm			
3 ☐ am ☐ pm			
4 ☐ am ☐ pm			
5 ☐ am ☐ pm			
6 ☐ am ☐ pm			
7 ☐ am ☐ pm			

Have you had any unusual negative events today? No ☐ Yes ☐ (complete below)	
Event 	Mild / Moderate / Severe Resolved / Ongoing

Have you taken any medications other than those you routinely use today? No ☐ Yes ☐ (complete below)		
Medication 	Medication 	Medication
Dose 	Dose 	Dose
Frequency 	Frequency 	Frequency

Figure A.

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Figure 1. Relationship between mean daily stool consistency based on the 7-point Bristol Stool Form Scale ranging from 1 (pellety stool) to 7 (watery diarrhea) and frequency assessed by Spearman correlation (R_s).

Figure 2. Relationship between mean daily stool consistency based on the 7-point Bristol Stool Form Scale ranging from 1 (pellety stool) to 7 (watery diarrhea) and ease of stool passage assessed by Spearman correlation (R_s).

Figure 3. Reproducibility of colonic transit measurements assessed by Bland-Altman plots at 24 (A) and 48 (B) hours.

Figure 4. Relationship between colonic transit at 24 (A) and 48 (B) hours and mean daily stool frequency in the entire patient cohort (n=87) undergoing at least one study (Rs=Spearman correlation).

Figure 5.

Relationship between colonic transit at 24 (A) and 48 (B) hours and stool consistency based on the 7-point Bristol Stool Form Scale ranging from 1 (pellety stool) to 7 (watery diarrhea) in the entire patient cohort ($n=87$) undergoing at least one study (R_s =Spearman correlation).

Figure 6. Relationship of mean colonic transit at 24 (left) and 48 (right) hours and mean stool consistency in 17 patients undergoing two measurements (R_s =Spearman correlation).

Table IA

Demographics of Participants in the Study

	All participants (n=87)	IBS-C/FC (n=55)	IBS-D (n=32)
Age (years), mean $\pm$ SD	41 $\pm$ 12	40 $\pm$ 10	42 $\pm$ 14
Females, n (%)	83 (95)	55 (100)	28 (88)
BMI (Kg/m ²), mean $\pm$ SD	26.1 $\pm$ 4.4	26.0 $\pm$ 4.2	26.3 $\pm$ 4.9

Table IB

Demographics (at first study) of 17 Participants Who Underwent Two Studies

Age (years), mean $\pm$ SD	40 $\pm$ 10
Females, n (%)	17 (100)
BMI, mean $\pm$ SD	26.9 $\pm$ 3.2
Functional constipation/IBS-C, n (%)	15 (88)
Functional diarrhea/IBS-D, n (%)	2 (12)

Table II
Spearman Correlation Coefficients of Clinical and Pharmacodynamics Endpoints

Spearman Correlation Coefficients, N=87 (overall lower FGIDs)				
	Frequency	Consistency	Ease of Passage	GC 48
Stool Frequency	1.00000	0.37840 p=0.0003	0.33395 p=0.0016	0.57144 p<.0001
Stool Consistency	0.37840 p=0.0003	1.00000	0.73049 p<.0001	0.40795 p<.0001
Ease of Passage	0.33395 p=0.0016	0.73049 p<.0001	1.00000	0.33120 p=0.0017
Geometric Center at 24hrs	0.45588 p<.0001	0.37710 p=0.0003	0.35216 p=0.0008	0.80626 p<.0001
Geometric Center at 48hrs	0.57144 p<.0001	0.40795 p<.0001	0.33120 p=0.0017	1.00000

Spearman Correlation Coefficients, N=55 (constipation lower FGIDs)				
	Frequency	Consistency	Ease of Passage	GC 48
Stool Frequency	1.00000	0.04068 p=0.7681	0.03241 p=0.8143	0.37002 p=0.0054
Stool Consistency	0.04068 p=0.7681	1.00000	0.62359 p<.0001	0.17469 p=0.2021
Ease of Passage	0.03241 p=0.8143	0.62359 p<.0001	1.00000	0.16257 p=0.2357
Geometric Center at 24hrs	0.29774 p=0.0273	0.12149 p=0.3769	0.21112 p=0.1218	0.75092 p<.0001
Geometric Center at 48hrs	0.37002 p=0.0054	0.17469 p=0.2021	0.16257 p=0.2357	1.00000

Spearman Correlation Coefficients, N=32 (diarrhea lower FGIDs)				
	Frequency	Consistency	Ease of Passage	GC 48
Stool Frequency	1.00000	0.44106 p=0.0115	0.38662 p=0.0288	0.32748 p=0.0673
Stool Consistency	0.44106 p=0.0115	1.00000	0.82258 p<.0001	0.28796 p=0.1100
Ease of Passage	0.38662 p=0.0288	0.82258 p<.0001	1.00000	0.42163 p=0.0162

Spearman Correlation Coefficients, N=32 (diarrhea lower FGIDs)					
	Frequency	Consistency	Ease of Passage	GC 24	GC 48
Geometric Center at 24hrs	0.25385 p=0.1609	0.37764 p=0.0331	0.42163 p=0.0162	1.00000	0.76191 p<.0001
Geometric Center at 48hrs	0.32748 p=0.0673	0.28796 p=0.1100	0.30210 p=0.0929	0.76191 p<.0001	1.00000

Table IIIA

Descriptive Statistics, Coefficients of Variation, and Number Required per Treatment Arm in a Parallel-group Design Study Conducted to Demonstrate Effect Size of 30% in Patients with Lower FGIDs Associated with Constipation

Endpoint	Mean $\pm$ SD	COV _{inter} %	#/group to show 30% effect* (number of units)
Transit GC24	1.98 $\pm$ 0.76	38.1	20/group (0.70)
Transit GC48	2.94 $\pm$ 1.00	33.9	29/group (0.76)
Stool #/day	1.09 $\pm$ 0.56	51.2	34/group (0.39)
Stool consistency	2.74 $\pm$ 1.15	41.8	24/group (0.95)
Stool ease of passage	3.46 $\pm$ 0.80	23.2	14/group (0.91)

COV_{inter} was calculated by SD/mean

* Difference as a percentage of overall mean

Table IIIB

Descriptive Statistics, Coefficients of Variation, and Number Required per Treatment Arm in a Parallel-group Design Study Conducted to Demonstrate Effect Size of 30% in Patients with IBS-D

Endpoint	Mean $\pm$ SD	COV _{inter} %	#/group to show 30% effect* (number of units)
Transit GC24	3.10 $\pm$ 1.12	36.0	32/group (0.80)
Transit GC48	4.41 $\pm$ 0.77	16.0	8/group (0.85)
Stool #/day	2.41 $\pm$ 1.29	53.6	67/group (0.73)
Stool consistency	3.96 $\pm$ 1.33	33.6	23/group(1.04)
Stool ease of passage	4.05 $\pm$ 0.66	16.3	8/group (1.04)

COV_{inter} was calculated by SD/mean

* Difference as a percentage of overall mean

Table IIIC

Descriptive Statistics (n=15), Coefficient of Variation, and Number Required per Treatment Arm to Demonstrate Effect Size of 30% in Patients with Lower FGIDs Associated with Constipation Undergoing Cross-over Study

Endpoint	Mean $\pm$ SD	SD of Deltas	COV _{intra} %	Total # to show 30% effect *
Mean transit GC24	1.98 $\pm$ 0.49	0.86	43.4	14
Mean transit GC48	3.01 $\pm$ 0.66	1.18	21.9	21
Mean stool #/day	1.09 $\pm$ 0.55	0.83	50.5	38
Mean stool consistency	2.52 $\pm$ 0.85	1.35	53.6	18
Mean stool ease of passage	3.61 $\pm$ 0.49	0.78	21.6	8

COV_{intra} was calculated by SD of deltas/overall mean

* Number of subjects in a crossover study to detect 30% effect sizes (number of units in Table IIA)