Initiation of Coverage
September 25, 2012
SPECIALTY PHARMACEUTICALS

Equity Research

Irina Rivkind
212-915-1237
irivkind@cantor.com

Synergy Pharmaceuticals, Inc. (SGYP-$4.71)

Rating: BUY

Target Price: $7.00

Second in Line, but Not Second Best: Initiating with a BUY and $7.00 Price Target

REV	1Q	2Q	3Q	4Q
2011A	0.0A	0.0A	0.0A	0.0A
2012E	0.0A	0.0A	0.0E	0.0E
2013E	—	—	—	—

EPS	1Q	2Q	3Q	4Q
2011A	(0.08)A	(0.10)A	(0.01)A	(0.12)A
2012E	(0.13)A	(0.17)A	(0.18)E	(0.17)E
2013E	—	—	—	—

FY	2011A	2012E	2013E
REV	0.0A	0.0E	0.0E
EV/REV	—	—	—
P/S	—	—	—
EPS	(0.30)A	(0.65)E	(0.88)E
P/E	(15.7)x	(7.2)x	(5.4)x

- **Synergy is benefiting from linaclotide excitement in the constipation/IBS-C market:** We believe that investors have been motivated by the attractiveness of the constipation/IBS-C market outlined by competitor Ironwood and view Synergy's plecanatide as an improved compound possessing similar efficacy with less diarrhea. We provide a fresh look at Synergy's data post-Linzess (linaclotide) approval. We think that the plecanatide market opportunity is attractive, albeit smaller.
- **Why we like SGYP but not IRWD:** (1) Economics appear more favorable for Synergy, which owns 100% of plecanatide commercial rights, while Ironwood has partnered linaclotide with three companies and keeps only a portion of the profits. (2) Synergy's operational expenses are more modest than Ironwood's. (3) The exit strategy for Synergy is more visible, in our view, and we believe that management plans to sell the asset rather than build out a large organization with future commercial and clinical risks.
- **Valuation is based on a weighted average of two outcomes (weighted as 67%/33%):** (1) We assume 80% success probability for plecanatide in constipation and 50% success in IBS-C and employ DCF analysis (14% WACC, 0% terminal growth rate), which yields a hypothetical ~$10 PT; or (2) the plecanatide Phase IIb trial fails to demonstrate efficacy and shares plummet to cash value (<$1.00). This generates a risk-weighted PT of $7.00.
- **We are cautious because of the risk associated with slightly weaker efficacy data and early stage of development:** In spite of its chemical similarity to linaclotide, we believe that the efficacy of plecanatide could be somewhat weaker based on data from the small Phase IIa trial in chronic constipation. There are also limited data to support plecanatide's efficacy in IBS-C, and the efficacy signal on abdominal discomfort collected from the constipation trial was inconsistent with the data from the rest of the study. We believe that this clinical risk is already in the stock.

Current Statistics

Market Cap ($Mil)	**$310.0**	**Float Shares (Mil):**	**65.800**
Avg. Daily Trading Volume (3 mo.):	**320,939**	**Dividend Yield:**	**0.00%**
Shares Out (Mil):	**65.806**		

Company Description

Synergy Pharmaceuticals is a small developmental-stage pharmaceutical company focused on gastroenterology. Synergy is currently working to develop plecanatide (a GC-C agonist) for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome. The company also has two early-stage assets for the treatment of ulcerative colitis and shingles.

The Disclosure Section may be found on pages 33 - 35.

Summary

We initiate coverage with a BUY rating and $7.00 price target

Synergy is benefiting from Linzess excitement in the constipation/IBS-C market: We believe that Synergy investors have been motivated by the attractiveness of the constipation/IBS-C market outlined by competitor Ironwood and view Synergy's plecanatide as an improved compound possessing comparable efficacy to Linzess and improved tolerability. We urge investors to revisit their plecanatide assumptions with a fresh look at the available data following the FDA approval of Linzess. We think that the plecanatide market opportunity, while attractive, should initially be meaningfully smaller than Linzess's, given competitive dynamics and entrenched position of first-mover Linzess, though economics to Synergy are much more attractive since the company owns 100% of plecanatide rights. If Synergy is acquired by a larger company, we believe that the drug's competitive position could be improved via aggressive direct-to-consumer (DTC) promotion and more attractive pricing than Linzess. We launch with a BUY rating and $7.00 price target after taking into account the risk associated with plecanatide data release by year-end.

Why we like SGYP but not IRWD: We like SGYP as a stock while maintaining our SELL rating on IRWD for the following reasons: (1) drug economics are more favorable for Synergy, which owns 100% of plecanatide commercial rights, while Ironwood has partnered Linzess with three companies and is eligible to keep only a portion of the revenues and profits. (2) Synergy operational expenses are more modest than Ironwood's. (3) The exit strategy for Synergy is more visible, in our view, and we believe that management plans to sell the asset rather than build out a large organization with future commercial and clinical risks. (4) We believe that SGYP is fundamentally undervalued, even after risk-adjusting for the December catalyst, while IRWD looks expensive at these levels.

Visible exit opportunities are also attractive: Synergy valuation is highly dependent on the success of plecanatide, and the key catalyst for the company will arrive in December 2012, when data from the ongoing Phase IIb trial in chronic constipation become available. If December plecanatide data are positive, we would expect the company to become an attractive acquisition target to global pharmaceutical companies with an appreciation for the size of the worldwide constipation/IBS-C market. Under this scenario we would expect a significantly different valuation for the company due to reduced clinical risk, which is described in more detail in our report. If the drug fails to demonstrate efficacy, we believe that the price of the stock could decline to reflect the value of Synergy's cash position, since the company has only two early-stage assets for the treatment of shingles and ulcerative colitis, which have minimal value at this time, in our view.

We consider the risk based on limited efficacy data for plecanatide: While investors may be thinking that plecanatide is interchangeable with Ironwood's Linzess (based on chemical similarity but with lower incidence of diarrhea), we believe that the efficacy of the compound could be somewhat weaker based on data from Synergy's small Phase IIa trial in chronic constipation. There are limited data to support plecanatide's efficacy in IBS-C (though we are encouraged by the preclinical data on uroguanylin recently presented at an oral session during the Joint International Neurogastroenterology and Motility meeting in Italy). We are also cautious since the efficacy signal on abdominal discomfort collected from Synergy's Phase IIa constipation trial was inconsistent with the dose-response data from the rest of the study. Because of these risks, we assume a 33% probability of study failure in December.

Company History

Synergy Pharmaceuticals was operational in 2001 as a venture-backed company. At that time Dr. Kunwar Shailubhai, the company's Chief Scientific Officer, worked on the preclinical development of Synergy's GC-C agonist program for the treatment of colon cancer and GI diseases. Dr. Gary Jacobs joined Synergy as its CEO in 2003.

Callisto Pharmaceuticals acquired privately-held Synergy in 2003 in a merger and simultaneously went public. From 2003-2008 Callisto focused on cancer drug development and ignored its GC-C agonist assets. In 2008 Callisto stopped its cancer programs, spun off Synergy as its subsidiary, and executed a reverse merger with Pawfect Foods (a publicly held shell company). The newly created Synergy Pharmaceuticals is incorporated in Delaware.

Synergy issued 70% of the company's shares to Callisto, and Pawfect shareholders were granted the remaining 30%. In December 2011 Synergy held a 1-for-2 reverse stock split, which allowed the company to move from the Pink Sheets to the NASDAQ exchange. In July 2012 Synergy announced its pending merger with Callisto (which is expected to close in December 2012). Under this agreement, former Callisto shareholders will own approximately 38.3% of the combined company, and Synergy stockholders will own 61.7% of the combined entity. The Synergy stock issued to Callisto shareholders will be subject to an 18-month lockup period. We summarize the company's financing history in Exhibit 1 below.

Exhibit 1: Synergy Financing History

Date	Event	Funds Raised ($ in millions)	Financing Type
7-Jul-09	Private Placement	$7.1	Equity financing using ~10.1 million shares priced at $0.70 each
12-Nov-09	Private Placement	$8.6	Equity financing using ~12.3 million shares priced at $0.70 each
04-Oct-11	Registered Direct	$2.4	Equity financing using 1,105,293 units, each consisting of one share of common stock and one warrant to purchase 0.5 shares priced at $2.125 per unit.
14-Oct-11	Registered Direct	$0.5	Equity financing using 273,824 units, each consisting of one share of common stock and one warrant to purchase 0.5 shares priced at $2.125 per unit.
28-Oct-11	Registered Direct	$0.5	Equity financing using 235,294 units, each consisting of one share of common stock and one warrant to purchase 0.5 shares priced at $2.125 per unit.
15-Nov-11	Equity financing	$5.6	Sold 2,657,882 units, each consisting of one share of common stock and one common stock purchase warrant, priced at $2.125 per unit. Warrants are exercisable at $2.75 per share and expire after five years.
01-Dec-11	Reverse stock split	$0.0	1 for 2 reverse stock split
13-Dec-11	Secondary Offering	$17.3	Sold 2,156,250 units, each consisting of two shares of common stock and one common stock purchase warrant, priced at $8.00 per unit. Warrants are exercisable at $5.50 per share and expire after five years.
05-Jun-12	Secondary Offering	$51.8	11.5 million shares priced at $4.50 each

Source: Company reports and Cantor Fitzgerald research

Industry Overview

Synergy currently focuses on the treatment of constipation, constipation-predominant irritable bowel syndrome, and ulcerative colitis. Based on work conducted by Ironwood, a competitor company with a similar compound (Linzess), we estimate that approximately 15 million U.S. patients are potential initial targets for plecanatide, Synergy's lead product. At this time we expect that Ironwood's Linzess will be well-established in the U.S. market by the time that plecanatide launches and therefore expect that Synergy's initial market opportunity will be limited primarily to patients who are intolerant of Linzess due to diarrhea or other issues. This opportunity may exceed the 10% discontinuation rate we currently estimate for Linzess since approximately 27-29% of Linzess patients had their medication interrupted during open-label treatment lasting up to 18 months. Over time we believe that plecanatide could gain additional market penetration based on price competition as well as heavy patient outreach (if the drug is acquired by a large global pharmaceutical company).

Other companies in this space include Sucampo, with Amitiza (which is also indicated for chronic constipation and IBS-C); Shire Pharmaceuticals, with rights to Resolor (which is marketed for chronic constipation in Europe); and Ferring, a private Swiss company that in-licensed A3309, a Phase III drug

for chronic constipation, from privately-held Albireo. Salix Pharmaceuticals is developing Xifaxan for diarrhea-predominant irritable bowel syndrome, which would not compete with plecanatide, but the company is also exploring potential indications in IBS-C that are still in an early stage.

Synergy recently acquired a Phase II asset for the treatment of herpes zoster (or shingles) from Bristol-Myers Squibb, which obtained the product via its recent Inhibitex acquisition. Competitors in this space include generic antiviral agents such as acyclovir, valacyclovir and famcyclovir. Additionally, Merck has launched Zostavax, a herpes zoster vaccine indicated for prevention of herpes zoster in individuals ≥50 years old while GSK is conducting Phase III trials on its own herpes zoster vaccine. At this time Synergy's shingles drug is still fairly early stage and should not be a focus for investors, in our view.

Company Overview

CC NDA to be filed in 2015; revenues expected in 2016

Plecanatide is the crux of the Synergy story

Plecanatide is a synthetic peptide designed to mimic uroguanylin, a naturally occurring gastrointestinal hormone, which is expressed mainly in the small intestine. Uroguanylin activates a biological process that leads to the secretion of fluid into the intestinal lumen and helps increase gastrointestinal motility and reduce inflammation. Plecanatide is more potent than uroguanylin and is a Guanylate Cyclase-C (GC-C) agonist that binds to the same receptors targeted by uroguanylin and is believed to alleviate the abdominal discomfort and bloating associated with constipation, as well as to relieve abdominal pain associated with IBS-C. Interestingly, there are GC-C receptors in other anatomical areas including the eye and the lung, and management believes that there could be other indications for plecanatide that could be explored in colon cancer, obesity, and asthma.

Plecanatide is an oral capsule that is administered once-daily and is covered by a composition of matter patent (7,041,786) that expires on March 25, 2023, and a second composition of matter patent (7,799,897) expiring on June 9, 2022 (both of which are subject to patent term extension to ~2025). Plecanatide is also eligible for five years of New Chemical Entity market exclusivity as well as an additional 6-months pediatric exclusivity. The composition of matter patent has also been granted in Europe, Eurasia, and Japan.

Management believes that plecanatide may be difficult to copy since the drug is not systemically absorbed (thus making it difficult to demonstrate bioequivalence via PK trials). Competitor Ironwood has contested the European composition of matter patent for plecanatide by arguing that plecanatide is identical to uroguanylin (which is already patented) and has managed to narrow the patent to include fewer potential forms of the drug. Ironwood has also obtained its own method of use patent on plecanatide, but recently licensed this patent to Synergy for a low single-digit royalty. Separately, Synergy recently filed a request with the USPTO to re-examine Ironwood's patent 7,704,947, which covers a group of peptides but following the new licensing agreement with Ironwood, the company is not expected to pursue this request further.

Synergy is conducting a Phase IIb trial of plecanatide in the treatment of chronic constipation, with results expected in December 2012. The company plans to initiate a dose-ranging Phase II trial of plecanatide by the end of September in the IBS-C indication (and is filing an IND in October). To date, we have limited clinical evidence that this drug alleviates abdominal pain, though effectiveness is strongly suggested by plecanatide's chemical structure and data from Linzess, a similar compound that has demonstrated efficacy in IBS-C. Management also pointed out that a recent oral presentation from the Joint International Neurogastroenterology and Motility Meeting highlighted animal data in mice in which uroguanylin reduced nociceptor mechanosensitivity at levels that were comparable to Linzess (maximum effect of 61% reduction for uroguanylin vs. 59% reduction for Linzess). Given plecanatide's chemical similarity to uroguanylin, we believe that these data may be an early validation of plecanatide's potential efficacy in treating gastrointestinal pain. Management noted that the

constipation NDA would be submitted in 2015 at the earliest and has not given guidance around the timing of the IBS-C submission. We summarize the key company catalysts in Exhibit 2 below.

Exhibit 2: Key Synergy Pharmaceutical Catalysts

Date	Product	Indication	Milestone/Event
2012			
Sep-12	Plecanatide	IBS-C	Begin Phase IIB trial in IBS-C
Dec-12	Plecanatide	Chronic Constipation	Phase IIB data (may count as Phase III trial)
2013			
early 2013	Plecanatide	Chronic Constipation	End of Phase II meeting with FDA
early 2013	Plecanatide	Chronic Constipation	Begin second Phase III trial(s)
2H:13	Plecanatide	IBS-C	Data from first Phase IIB trial
2014			
early 2014	Plecanatide	Chronic Constipation	Data from Phase III
2015			
2015	Plecanatide	Chronic Constipation	NDA Submission

Source: Company reports and Cantor Fitzgerald estimates

We are optimistic about plecanatide's lack of a diarrhea signal

In a Phase I trial of 71 healthy volunteers, plecanatide was safe and well tolerated at doses ranging from 0.1 mg to 48.6 mg. Interestingly, 12.7% of plecanatide-treated patients in this trial reported diarrhea (defined as an increase in bowel movements per day compared to baseline) though none of the diarrhea was severe, even at the highest doses. Management indicated that placebo-treated patients also experienced diarrhea in this trial, and we think that this result was related to the fact that the drug was tested in non-constipated patients in this Phase I trial.

Synergy also reported results from a Phase IIa trial of plecanatide in Chronic Idiopathic Constipation. The study evaluated four cohorts of plecanatide administered once-daily (0.3 mg, 1.0 mg, 3.0 mg and 9.0 mg) versus placebo, in a 14-day trial of 78 patients. Patients were enrolled using Rome III criteria. The primary endpoint was safety, and secondary endpoints included PK, time to first bowel movement after first daily dose, changes in bowel habits, and quality of life. We summarize the study safety results in Exhibit 3 below and have attached the related scientific poster in the Appendix. Based on results from this small trial, it appears there is no diarrhea signal (which was noted in 4.8-14.3% of linaclotide-treated patients in the 4-week 310-patient Phase IIb constipation trial of Linzess[1] and also in 10-16.7% of linaclotide-treated patients in the smaller 42-patient Phase IIa trial[2]).

Based on the early diarrhea data, we believe that the ongoing Phase IIb clinical trial may demonstrate that plecanatide has lower diarrhea rates than Linzess (reported to be in the 16-20% range in the Linzess product label). We also point out that 27-29% of patients enrolled in long-term, open-label trials of Linzess had their dose reduced or suspended due to adverse events (which consisted primarily of diarrhea). In our revenue models we therefore assume that plecanatide has better diarrhea tolerability than Linzess and model plecanatide capturing the Linzess diarrhea discontinuation patients as Synergy's primary targets in the first few years of launch.

[1] Lembo, AJ, et al. Linaclotide Significantly Improved Bowel Habits and Relieved Abdominal Symptoms in Adults with Chronic Constipation: Data from a Large Four-week Randomized, Double-blind, Placebo-controlled Study. Late Breaker Submission. Digestive Disease Week, 2008.

[2] Johnston, JM, et al. Linaclotide Improves Bowel Habits and Patient Reported Outcomes in Subjects with Chronic Constipation. Abstract presented at American College of Gastroenterology, 2006.

Exhibit 3: Plecanatide Phase IIa Safety Data

Adverse Event	Placebo (n=20)	Plecanatide 0.3 mg (n=14)	Plecanatide 1.0 mg (n=14)	Plecanatide 3.0 mg (n=15)	Plecanatide 9.0 mg (n=15)
Abdominal Cramping	1 (5.0%)	0	0	0	0
Abdominal Pain	1 (5.0%)	0	0	0	0
Bloating	0	0	0	0	1 (6.7%)
Diarrhea	4 (5.0%)	0	0	0	0
Flatulence	2 (10.0%)	0	0	0	0
Nausea	0	1 (7.1%)	0	0	1 (6.7%)

Source: Company reports and Cantor Fitzgerald estimates

We believe that plecanatide is somewhat less potent than Linzess based on a comparison of results from two small Phase IIa trials

We are cautious on efficacy based on our own analysis of the company's data

Synergy reported that plecanatide treatment generated an improvement in complete spontaneous bowel movements (CSBM), spontaneous bowel movements (SBM), straining scores, and patient global assessment scores for abdominal discomfort, constipation severity, and overall relief. More than 50% of patients taking plecanatide in this trial had their first bowel movement within seven hours relative to 16 hours for placebo-treated patients. Plecanatide treatment was also associated with a numerical increase in Bristol Stool Score (indicating that patient stools had softened with drug treatment, a desirable effect in constipated patients). Due to the small sample size of the group, none of the results were deemed to be statistically significant.

We attempted to compare the plecanatide Phase IIa data with a very similar trial conducted by Ironwood in 42 patients (see Appendix for Johnston poster). We summarize our findings in Exhibit 4 below. Synergy did not provide exact numbers for their results, so we had to estimate the numbers based on a visual inspection of the graphs presented in scientific posters and company presentations.

Exhibit 4: Comparison Of Two Phase IIa Trials of Plecanatide and Linzess

	Linzess (all doses) n=42	Linzess 300 mcg dose only (n=7)	Placebo	Placebo-subtracted Difference (all doses)	Placebo-subtracted Difference (300 mcg dose)		Plecanatide (1 mg dose) n=15	Plecanatide (3 mg dose) n=15	Plecanatide (9 mg dose) n=15	Placebo	Placebo-subtracted Difference
Change in SBM/week after 14-days	4.66-6.18	5.41	2.76	1.90-3.42	2.65		4.1	2.9	4.1	2.1	0.80-2.0
Change in CSBM/week after 14 days	2.16-3.19	2.9	1.30	0.86-1.89	1.6		3.3	2.1	2.7	1.7	0.40-1.60
BSFS Score Increase after 14-days	1.50-2.70	1.6	0.50	1.00-2.20	1.1		1.6	1.7	1.6	0.8	0.80-0.90
SBM Responder after 14-days	71-100%	71%	44%	27-56%	27%		N/A	N/A	N/A	N/A	N/A
CSBM Responder after 14-days	40-43%	43%	11%	29-32%	32%		N/A	N/A	N/A	N/A	N/A

SBM=spontaneous bowel movement; CSBM=complete spontaneous bowel movement; BSFS=Bristol stool form scale

Sources:

(1) Johnston JM et. al, Complete Spontaneous Bowel Movement Frequency as a Primary Outcome Measure in Patients with Chronic Constipation and Healthy Volunteers Treated with Linaclotide. Poster 628 presented at American College of Gastroenterology 2007.

(2) Johnston JM et. al, Linaclotide Improves Bowel Habits and Patient Reported Outcomes in Subjects with Chronic Constipation. Abstract presented at the American College of Gastroenterology, 2006.

(3) Johnston JM et al, Pilot Study on the Effect of Linaclotide in Patients With Chronic Constipation. Am J Gastroenterol 2009;104:125-132; doi:10.1038/ajg.2008.59

(4) Shailubhai, K et. al, A Phase IIa Randomized, Double Blind, Placebo-Controlled, 14-Day Repeat, Oral, Range-Finding Study to Assess the Safety, Pharmacokinetic and Pharmacodynamic Effects of Plecanatide (SP-304) in Patients with Chronic Idiopathic Constipation (Protocol No. SP-SP304201-09). Poster 762 presented at the American College of Gastroenterology, 2010.
Note: Plecanatide data points are estimates based on interpretation of graphs; company did not provide actual numbers

(5) Cantor Fitzgerald estimates

Our observations are as follow:

(1) *Plecanatide appears less potent than Linzess:* The placebo-subtracted differences in plecanatide-treated patients were generally lower than those for Linzess (all doses) as well as the 300 mcg Linzess dose alone (which is the only dose that made it to registration for Linzess), which suggests that plecanatide may be slightly less efficacious. Management believes that this study was under-powered to detect a difference between drug and placebo since it was an ascending dose design, but we don't think that this caveat fully explains the result. Management also looks to the absolute magnitudes of change post-treatment as being relatively comparable to Linzess's changes, but we again don't think that this is a good way to view the data since the FDA is primarily concerned with the changes from baseline relative to placebo measures, rather than absolute magnitudes of change.

(2) *Abdominal discomfort dose-response data do not compare well to Linzess:* We note that the 1 mg plecanatide dose, which was strongest across the board for constipation endpoints, unexpectedly demonstrated the weakest efficacy signal for abdominal discomfort (though still quite superior to placebo), whereas the 0.3 mg dose, which was mostly ineffective for other constipation measures, was effective for abdominal discomfort. What makes us even more concerned about the lack of dose-response in the abdominal discomfort endpoint is that in the 42-patient Linzess trial, all Linzess groups had a greater improvement in abdominal discomfort than placebo, as summarized in the Johnston 2007 poster presented in the Appendix. The fact that there was minimal difference between the relatively benign 0.3 mg dose and the strongest 9.0 mg dose is concerning as Synergy moves towards its IBS-C program, which is likely to include the 9.0 mg dose. Because we don't know how plecanatide will behave in IBS-C patients and its early stage of development for this indication, we risk-adjust the plecanatide IBS-C revenues to account for a 50% probability of success. We expect more clarity on abdominal discomfort after the release of the Phase IIb chronic constipation data in December. Management is comforted by a recent oral presentation that described how urogunaylin, a chemically similar molecule to plecanatide, demonstrated comparable pain reduction to Linzess in mice. While these data are intriguing, we would like to see more robust evidence in man.

Exhibit 5: Phase IIa Plecanatide Abdominal Discomfort Endpoint (after 14 days of treatment)

		Dose			
Endpoint	Placebo	0.3 mg	1.0 mg	3.0 mg	9.0 mg
Absolute Change in Percent of Subjects Reporting an Improvement in Abdominal Discomfort from Baseline	6	45	28	39	47

Source: Shailubhai, K et. al, A Phase IIa Randomized, Double Blind, Placebo-Controlled, 14-Day Repeat, Oral, Range-Finding Study to Assess the Safety, Pharmacokinetic and Pharmacodynamic Effects of Plecanatide (SP-304) in Patients with Chronic Idiopathic Constipation (Protocol No. SP-SP304201-09). Poster 762 presented at the American College of Gastroenterology, 2010. Cantor Fitzgerald estimates
Note: Plecanatide data points are estimates based on interpretation of graphs; company did not provide actual numbers

(3) *Lack of a dose response in constipation is not troubling yet:* Endpoint data for the 1.0 mg dose were stronger than those for the 3.0 mg dose and relatively similar to the 9.0 mg dose. Management indicated that the 3.0 mg dose had the most severe constipation at baseline, which may have contributed to the worse performance of that patient group throughout the trial. Additionally, management pointed out that it just needs to identify a single successful dose in the ongoing Phase IIb constipation trial to move forward with the program. We accept this argument. We gain comfort from comparing these data in 78 patients to the 42-patient Phase II Linzess trial, in which Linzess also failed to demonstrate a dose-response relationship for stool frequency responder endpoints (failed to demonstrate dose-response for SBM and but did demonstrate this relationship for CSBM). In a larger 310-patient Phase II trial of Linzess for chronic constipation, Ironwood was able to demonstrate a dose response relationship for endpoints such as SBM and CSBM frequency but not for the more critical CSBM Responder endpoint. We therefore conclude that plecanatide is likely showing a similar trend.

(4) *We have no evidence supporting plecanatide's CSBM responder efficacy.* Synergy did not report SBM or CSBM responder rates in their study, which is serving as the primary endpoint in the ongoing

Phase IIb trial, so we have no way to predict how robust the responder rates could be. Management indicated that they had conducted the analyses but the data were so high as to be nonsensical, which was why they were not reported. In contrast, Ironwood reported the Linzess responder rates. This may be a less significant finding, but we wanted to highlight that investors have never seen the trend for the primary endpoint in the ongoing plecanatide constipation study.

(5) *Plecanatide should have had stronger data trends than Linzess:* The Synergy Phase IIa trial was conducted in almost double the number of Linzess Phase IIa patients (78 patients in the Synergy trial vs. 42 patients in the Linzess study) so the variability in this trial should be smaller, yet the data look worse overall.

Additionally, we spoke with an investigator participating in the ongoing plecanatide pivotal trial at Digestive Disease Week and learned that patients did not appear to be responding to the medication. Since the physician is still blinded, this comment should be taken in context. However, it directionally supports the idea that there could be some risk in demonstrating efficacy for plecanatide if the drug is slightly less potent than Linzess. Management countered that it has been in active communication with multiple investigators who believe that the drug is working well and are enthusiastic about signing on for other studies of the compound.

Data from the ongoing Phase II/III constipation trial will report out in 4Q:12 and are expected to serve as a key make-or-break event for the company

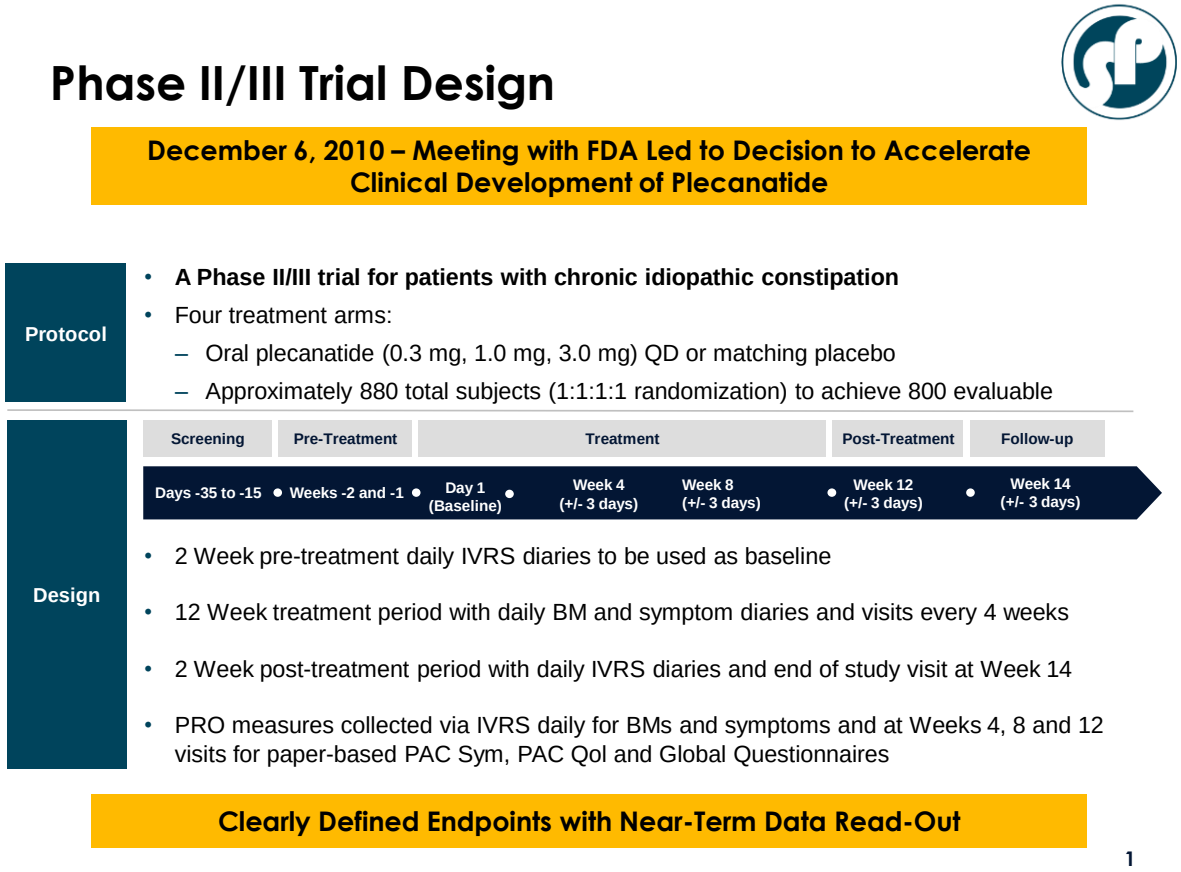
In October 2011 Synergy announced dosing of its first patients in a 12-week Phase II/III pivotal trial of plecanatide in 880 chronic constipation patients who meet modified Rome III criteria. This study is assessing the safety and efficacy of three doses of plecanatide (0.3 mg, 1.0 mg, and 3.0 mg) versus a placebo comparator arm. The trial measures the following endpoints:

- **FDA-mandated primary endpoint:** Synergy aims to detect at least a 10% difference in Overall Complete Spontaneous Bowel Movement between the plecanatide and placebo groups to meet its primary endpoint. The endpoint is defined using responder analyses (≥ 3 CSBMs/week, with increase ≥ 1 CSBMs/week). Patients will need to meet these criteria for at least 9 of 12 weeks and 3 of the last 4 weeks in the trial to be considered a monthly responder. An overall responder must achieve these criteria in two of the three months of treatment, and one of these months must be the last month of the treatment period. In other words, the product must demonstrate durability of efficacy.
- **Secondary endpoints:** SBM, time to first bowel movement, straining, stool consistency, pain, abdominal discomfort, bloating, quality of life and constipation symptoms (using patient reported outcomes), and safety.

We note that plecanatide study patients are taking the drug without regard to any food restrictions. The Linzess label indicates that the drug should be taken on an empty stomach, at least 30 minutes prior to the first meal of the day since dosing after a high-fat breakfast could result in looser stools and a higher stool frequency. If plecanatide can be well-tolerated without this food effect, we believe that it could prove to be a competitive differentiator once the drug reaches the market.

We summarize the study design in Exhibit 6 below. Synergy recently announced that it had completed study enrollment in this trial on August 13 and is on track to report our results in 4Q:12. We estimate that last patient last visit will occur in mid-late November, and database cleanup could delay top-line results until the last week in December.

Exhibit 6: Plecanatide Phase IIb Trial Design



BM= bowel movement; IVRS=Interactive Voice Response Services (telephone diaries); PRO=patient reported outcome; PAC Sym=Patient Assessment of Constipation Symptoms; PAC QoI=Patient Assessment of Constipation Quality of Life Questionnaire (older questionnaires used to benchmark plecanatide against older products)

Source: Company reports

If plecanatide results are positive, we would expect Synergy to be acquired outright by a global pharmaceutical company that would take over drug development activities. Otherwise, management is planning an end of Phase II meeting with the FDA in early 2013 followed by a second pivotal Phase III trial in constipation, with data in early 2014, an NDA filing in 2015, and launch in 2016 for constipation only. We believe that a deal could take place at any time along this spectrum.

We note that Synergy has already conducted genotoxicity and reproductive toxicity studies, as well as a QT trial in monkeys. There was no safety signal in any of these trials. Furthermore, management indicated that it does not expect to need to conduct drug interaction trials since plecanatide is not systemically absorbed. Linzess received a black box warning cautioning against use in pediatric patients and caused deaths in neonatal mice that is being investigated further in post-marketing trials. Synergy management indicated that it needs to conduct further pre-clinical work in plecanatide to test for this signal but does not believe that the drug will have similar issues.

Synergy is also pursuing the IBS-C market

Management is also planning to initiate a Phase IIb trial of plecanatide for IBS-C in 2H:12. We believe that the drug needs to be approved for both indications in order to remain competitive with Linzess. Top-line data for this trial are expected at the end of 2013. Management has not provided guidance about NDA filing at this time. The FDA has recently issued a final guidance on irritable bowel syndrome clinical trials, so Synergy will have a very clear blueprint of the necessary work that will be required to get FDA approval. We summarize the key inclusion criteria and endpoints from the final guidance document in Exhibit 7 below.

Exhibit 7: Summary of FDA's Recommended IBS Trial Designs by IBS Subtype

IBS Subtype	Co-Primary Endpoints	Entry Criteria (Rome III IBS diagnostic criteria)	Weekly Responder Definition*
IBS-C	Pain Intensity and Stool Frequency	**Pain Intensity:** Weekly average of worst daily abdominal pain (in past 24 hours) score of ≥ 3.0 in a 0 to 10 point scale AND **Stool Frequency:** < 3 complete spontaneous bowel movements (CSBM) per week.	**Pain Intensity:** Decrease in the weekly average of worst abdominal pain in the past 24 hours score (measured daily) of ≥ 30% compared with baseline weekly average AND **Stool Frequency:** Increase of 1 or more CSBM per week compared with baseline.
IBS-D	Pain Intensity and Stool Consistency	**Pain Intensity:** Weekly average of worst daily abdominal pain (in past 24 hours) score of ≥ 3.0 in a 0 to 10 point scale AND **Stool Consistency:** At least one stool with a consistency of Type 6 or Type 7 Bristol stool score	**Pain Intensity:** Decrease in the weekly average of worst abdominal pain in the past 24 hours score (measured daily) of ≥ 30% compared with baseline AND **Stool Consistency:** A ≥50% reduction in the number of days per week with at least one stool that has a consistency of Type 6 or 7 compared with baseline

* response has to be sustained for at least 50% of the days or weeks in treatment to be categorized an overall responder.

Source: www.FDA.gov and Cantor Fitzgerald research

We expect plecanatide to target Linzess failures in a large constipation/IBS-C market

Given that plecanatide is at least three years behind Linzess, we expect that Ironwood and partner Forest Laboratories will capture the majority of the segment being targeted by Synergy. With aggressive sampling and favorable formulary coverage, we think that Linzess will be able to lock up approximately 20% of the chronic constipation and IBS-C patients who are currently seeing a physician and taking prescription medications. We therefore expect plecanatide to be used primarily by patients who are unable to tolerate Linzess due to its well-established diarrhea side effect. We expect the remainder of patients to be treated with Amitiza, laxatives, and antidepressants.

Synergy management believes that it may have a COGS advantage over Linzess, with a less costly manufacturing process that could allow it to compete with Linzess on price and capture additional market share. A potential acquirer may also invest more heavily in DTC promotion than the Ironwood/Forest partnership, which could also provide an incremental benefit to Synergy. We include these opportunities in our model.

We derive the U.S. constipation/IBS-C market

Based on prior work conducted by Ironwood, we know that there are 10 million patients who are already taking some form of constipation/IBS medication, are dissatisfied with treatment, and are seeking medical attention. These patients are expected to utilize 3 prescriptions per year (for a total 30 million prescriptions). Another way of looking at this market is that there are approximately 55-60 million 30-day over-the-counter (OTC) prescriptions (according to Ironwood who looked at Nielsen, IRI, and IMS Health Cabinet data). Of these prescriptions, Ironwood and partner Forest Laboratories estimate that it is possible to convert approximately 20% from OTC to prescription (11-12 million prescriptions) based on prior conversion rates of OTC H2 blockers to proton pump inhibitors in the GERD market. There are an additional 9 million prescriptions for constipation products (prescription laxatives and Amitiza). Using these two methodologies, we estimate that the overall market is based on approximately 20-30 million prescriptions and is valued at $4.4-6.5 billion (assuming ~$218 net cost/prescription). If plecanatide gains approval in both CC and IBS-C, we think the brand could capture $1.2 billion in the U.S. market.

U.S. Chronic Constipation (CC)

We summarize our assumptions for the plecanatide U.S. CC market opportunity in Exhibit 8 below. Our scenario models a CC plecanatide opportunity of approximately $660 million by 2023. We assume that plecanatide only captures the subset of patients who cannot tolerate Linzess treatment and model net pricing of $7.25/day and peak treatment duration of ~133 days (Sucampo estimated average length of Amitiza therapy as 155 days vs. 132 days of Zelnorm use). We risk-adjust our estimates by 80% under the best case scenario used in our valuation. This analysis yields risk-adjusted peak revenues of $526 million to Synergy for the constipation indication.

Constipation-Predominant Irritable Bowel Syndrome (IBS-C)

We currently assume an IBS-C launch a year behind CC, though management has not confirmed timelines. We summarize our assumptions for the plecanatide U.S. IBS-C market opportunity in Exhibit 9 below. We think that the IBS-C indication is riskier for plecanatide given that there is no proof-of-concept data in this indication and the efficacy signal for the abdominal discomfort endpoint in the previously discussed plecanatide Phase IIa trial in chronic constipation was not robust. Still, based on the chemical structure of plecanatide and its similarity to Linzess, as well as the recently presented animal data in uroguanylin, we believe it would be irresponsible to overlook an IBS-C indication. We model a market opportunity of approximately $499 million by 2023 and risk-adjust the probability of success by 50% to account for even higher clinical risk in this indication. This analysis yields risk-adjusted revenues of $250 million to Synergy for the IBS-C indication.

Exhibit 8: U.S. Chronic Constipation Market Opportunity (numbers are in millions)

US Market	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Chronic Constipation												
US Adult Population (in millions)	238.8	241.0	243.2	245.3	247.5	249.8	252.0	254.3	256.6	258.9	261.2	263.6
Percent with Chronic Constipation	15.5%	15.5%	15.5%	15.5%	15.5%	15.5%	15.5%	15.5%	15.5%	15.5%	15.5%	15.5%
Chronic Constipation Patients	37.0	37.4	37.7	38.0	38.4	38.7	39.1	39.4	39.8	40.1	40.5	40.9
Percent CC with Abdominal Symptoms	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%
Percent Seeing a Doctor	40%	40%	40%	40%	40%	40%	40%	40%	40%	40%	40%	40%
Treatment-seeking Patients	8.1	8.2	8.3	8.4	8.4	8.5	8.6	8.7	8.7	8.8	8.9	9.0
Percent Receiving Rx Medications	33%	33%	33%	33%	33%	33%	33%	33%	33%	33%	33%	33%
Potential Linzess Patients	**2.7**	**2.7**	**2.7**	**2.8**	**2.8**	**2.8**	**2.8**	**2.9**	**2.9**	**2.9**	**2.9**	**3.0**
Percent Discontinuing Treatment	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Plecanatide Patients	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**
Additional Plecanatide Market Penetration					**0.0%**	**0.5%**	**1.3%**	**2.1%**	**2.9%**	**3.7%**	**4.5%**	**5.3%**
Incremental Plecanatide Patients				**-**	**-**	**0.01**	**0.04**	**0.06**	**0.08**	**0.11**	**0.13**	**0.16**
Total Plecanatide Patients					**0.3**	**0.3**	**0.3**	**0.3**	**0.4**	**0.4**	**0.4**	**0.5**
Days Used				-	30.0	60.0	95.0	120.0	130.0	132.6	133.0	133.0
Price/Day					7.3	7.7	8.1	8.6	9.2	9.7	10.3	10.9
Plecanatide Chronic Constipation Revenue	**-**	**-**	**-**	**-**	**61**	**136**	**248**	**359**	**443**	**513**	**583**	**658**
Growth						**125%**	**82%**	**45%**	**24%**	**16%**	**14%**	**13%**
Risk Adjustment					**80%**	**80%**	**80%**	**80%**	**80%**	**80%**	**80%**	**80%**
Risk-Adjusted Plecanatide Revenues				**$ -**	**$ 48**	**$ 109**	**$ 198**	**$ 287**	**$ 355**	**$ 411**	**$ 466**	**$ 526**
Growth						**125%**	**82%**	**45%**	**24%**	**16%**	**14%**	**13%**

Source: Cantor Fitzgerald Estimates

Schoenfeld, PS. Symptom Frequency, Health Care Seeking Behavior, and Satisfaction with Therapy Among Chronic Constipation Patients: Results of a Population-Based Survey. P1089 presented at the 2010 American College of Gastroenterology.

Assumptions:

U.S. Adults (2009 Census data)

Percent with Chronic Constipation (prevalence is estimated at 12-19% of the population; we took the midpoint)

Percent with Abdominal Symptoms (62% of constipation patients had concomitant abdominal discomfort and 48% of patients experienced abdominal pain; we took the midpoint)

Percent seeing a Doctor (47% of CC patients in the 10,030-patient survey sponsored by Forest/Ironwood indicated they ever saw a doctor, and 41% saw a doctor in the last 12 months)

Percent Receiving Rx Medications (33% of medications taken ≥2 times per week by constipation patients in the 10,030-patient survey were prescription drugs)

Percent Discontinuing Treatment (Cantor Fitzgerald estimate based on Phase III overall discontinuation rates of 8-10% in the Linzess IBS-C trials)

Days Used (assuming a ramp up to 133 days/year based on 132 days/year of average Zelnorm use, which may be conservative if the drug is used like a PPI longer term)

Price/Day (assuming similar pricing to Amitiza and 6% annual price increases)

Exhibit 9: U.S. IBS-C Market Opportunity (numbers are in millions)

US Market	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
IBS-C												
US Adult Population (in millions)	238.8	241.0	243.2	245.3	247.5	249.8	252.0	254.3	256.6	258.9	261.2	263.6
Percent with IBS	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%	13.0%
IBS Patients	31.0	31.3	31.6	31.9	32.2	32.5	32.8	33.1	33.4	33.7	34.0	34.3
Percent with IBS-C	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%
IBS-C Patients	10.2	10.3	10.4	10.5	10.6	10.7	10.8	10.9	11.0	11.1	11.2	11.3
Percent Seeing a Doctor	60%	60%	60%	60%	60%	60%	60%	60%	60%	60%	60%	60%
Treatment-seeking Patients	6.1	6.2	6.3	6.3	6.4	6.4	6.5	6.5	6.6	6.7	6.7	6.8
Percent Receiving Rx Medications	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%
Potential Linzess Patients	**2.2**	**2.2**	**2.2**	**2.2**	**2.2**	**2.3**	**2.3**	**2.3**	**2.3**	**2.3**	**2.4**	**2.4**
Percent D/C	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Initial Plecanatide Patients	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**
Additional Plecanatide Market Penetration						**0.0%**	**0.5%**	**1.3%**	**2.1%**	**2.9%**	**3.7%**	**4.5%**
Incremental Plecanatide Patients					-	-	**0.01**	**0.03**	**0.05**	**0.07**	**0.09**	**0.11**
Total Plecanatide Patients						**0.2**	**0.2**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**
Days Used						30.0	60.0	95.0	120.0	130.0	132.6	133.0
Price/Day						7.7	8.1	8.6	9.2	9.7	10.3	10.9
Plecanatide IBS-C Revenue	-	-	-	-	-	**52**	**117**	**212**	**307**	**379**	**440**	**499**
Growth							**125%**	**82%**	**45%**	**24%**	**16%**	**14%**
Risk Adjustment						**50%**	**50%**	**50%**	**50%**	**50%**	**50%**	**50%**
Risk-Adjusted Plecanatide Revenues						**$26**	**$58**	**$106**	**$154**	**$190**	**$220**	**$250**
Growth							**125%**	**82%**	**45%**	**24%**	**16%**	**14%**

Source: Cantor Fitzgerald estimates

Chey WD, et al. Frequency and Bothersomeness of Symptoms, Health Care Seeking Behavior, and Satisfaction With Therapy in IBS-C Patients Meeting ROME II Criteria: Results of a Population-Based Survey. P1275 presented at the 18th United European Gastroenterology Week, October 23-27, 2010.

Assumptions:

U.S. Adults (2009 Census data)

Percent with IBS (prevalence is estimated at 10-15% of the population; we took the midpoint)

Percent with IBS-C (prevalence is estimated at 9.7-33%; we used the upper endpoint, a more common assumption)

Percent seeing a Doctor (69% of IBS-C patients in the 10,030-patient survey sponsored by Forest/Ironwood indicated they ever saw a doctor, and 57% saw a doctor in the last 12 months)

Percent Receiving Rx Medications (35% of medications taken ≥2 times per week by IBS-C patients in the 10,030-patient survey were prescription drugs)

Percent Discontinuing Treatment (Cantor Fitzgerald estimate based on Phase III overall discontinuation rates of 8-10% in the IBS-C trials)

Days Used (assuming a ramp up to 133 days/year based on 132 days/year of average Zelnorm use, which may be conservative if the drug is used like a PPI longer term)

Price/Day (assuming similar pricing to Amitiza and 6% annual price increases)

Other thoughts on the U.S. market:

Synergy will not need to build the market
Ironwood plans to educate physicians regarding the urgency of changing the current treatment paradigm and will employ social media to promote Linzess to patients. We therefore believe that the market will be sufficiently educated regarding constipation and IBS-C by the time that plecanatide enters the market. Furthermore, we believe that primary care physicians will have had ample opportunity to trial Linzess and Amitiza by the time that plecanatide launches and will be familiar with the shortcomings of those medications. For these reasons, we think that Synergy or its potential acquirer would not need to spend as much on plecanatide as Ironwood will need to invest as a first-to-market compound.

We do expect meaningful barriers to formulary access
Since plecanatide is expected to enter the U.S. market at a time when Linzess is solidly established, we expect significant barriers to access when the drug first launches into the U.S. market. We would envision the restrictions to take the form of step edits (patients first have to fail a generic laxative and Linzess, which we assume will gain Tier 2 access) and therefore expect plecanatide to occupy a Tier 3 position. We think that Synergy may need to implement co-pay assistance cards with significant rebates to maintain affordability, which could further cut into profitability. We do think that the company may be able to get some leverage if it is able to offer more attractive pricing than Linzess.

International opportunities are expected to make a modest contribution
While prevalence of gastrointestinal disease and treatment patterns in Europe are relatively similar to that of the U.S., we expect lower demand in the Asian market based on our review of epidemiologic data. Japanese patients currently rely on laxatives and a variety of prokinetic agents that are not approved in the U.S., and we expect a smaller contribution from this market.

We assume a smaller market opportunity in Europe and Japan
We model a smaller market in Europe and Japan due to reference pricing and first-mover advantage of Ironwood. Since Synergy will be the second market entrant in this class, the company will likely inherit Linzess pricing, which should be somewhat deteriorated several years following launch. The European market is also constrained since DTC promotion is forbidden, which may make it more challenging to roll out plecanatide and promote its hypothetical tolerability advantages to patients.

We summarize our assumptions for the E.U. market in exhibits 10-11 below. Our model assumes approximately 0.9 million potential plecanatide patients, and risk-adjusted peak revenues of $142 million across both CC and IBS-C indications. We model a 50% discount to U.S. drug prices along with gradual price declines over time. While we don't think that Synergy will pursue a chronic constipation indication (since pricing would be referenced to inexpensive generic laxatives), we still believe that the drug would be used off-label in the constipation patients. We risk-adjust both CC and IBS-C revenues by 50% in the E.U. since the success of plecanatide is tied to the IBS-C outcome in this market.

.

Exhibit 10: E.U. IBS-C Market Opportunity Assumptions (numbers are in millions)

European Market	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
IBS-C											
EU Adult Population (millions)	401.6	402.4	403.2	404.0	404.8	405.6	406.4	407.3	408.1	408.9	409.7
Percent with IBS	11.0%	11.0%	11.0%	11.0%	11.0%	11.0%	11.0%	11.0%	11.0%	11.0%	11.0%
Percent with IBS-C	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%
IBS-C Patients	11.0	11.1	11.1	11.1	11.1	11.2	11.2	11.2	11.2	11.2	11.3
Percent Seeking Treatment	60.0%	60.0%	60.0%	60.0%	60.0%	60.0%	60.0%	60.0%	60.0%	60.0%	60.0%
Treatment-seeking Patients	6.6	6.6	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.8
Percent Receiving Rx Medications	45.0%	45.0%	45.0%	45.0%	45.0%	45.0%	45.0%	45.0%	45.0%	45.0%	45.0%
Potential Linzess Patients	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Percent D/C	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Plecanatide Patients -	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**
Additional Plecanatide Market Penetration						**0.0%**	**0.5%**	**1.2%**	**1.9%**	**2.6%**	**3.3%**
Incremental Plecanatide Patients						**-**	**0.02**	**0.04**	**0.06**	**0.08**	**0.10**
Total Plecanatide Patients						**0.3**	**0.3**	**0.3**	**0.4**	**0.4**	**0.4**
Days Used						30.0	60.0	95.0	120.0	130.0	132.6
Price/Rx						4.1	3.7	3.3	3.0	2.7	2.4
Plecanatide IBS-C Revenue -	-	-	-	-	-	**37**	**70**	**106**	**128**	**133**	**129**
Growth								**52%**	**21%**	**3%**	**-3%**
Risk Adjustment						**50%**	**50%**	**50%**	**50%**	**50%**	**50%**
Risk-Adjusted Plecanatide Revenues						**$ 18**	**$ 35**	**$ 53**	**$ 64**	**$ 66**	**$ 65**
Growth							*89%*	*52%*	*21%*	*3%*	*-3%*

Source: Cantor Fitzgerald estimates

Chey WD, et al. Frequency and Bothersomeness of Symptoms, Health Care Seeking Behavior, and Satisfaction With Therapy in IBS-C Patients Meeting ROME II Criteria: Results of a Population-Based Survey. P1275 presented at the 18th United European Gastroenterology Week, October 23-27, 2010.

Assumptions:

E.U. Adult Population age 15-65 (Wolfram Alpha)

Percent with IBS-C (24.1% as estimated by Wilson in a survey of 8,386 UK patients)[3]

Percent seeing a Doctor (IBS-C literature estimates range from 56-63%)[4][5]

Percent Receiving Rx Medications (33-35% of medications taken ≥2 times per week in the 10,030 U.S. patient survey were prescription drugs; we assume a higher rate in E.U. for IBS)

Percent Discontinuing Treatment (Cantor Fitzgerald estimate based on Phase III overall discontinuation rates of 8-10% in the IBS-C trials)

Days Used (assuming a ramp up to 134 days/year based on 132 days/year of average Zelnorm use, which may be conservative if the drug is used like a PPI longer term)

Price/Day (assuming 50% discount to U.S. pricing, with a 10% annual price decline due to pricing pressure)

[3] Wilson, S. et al. Prevalence of irritable bowel syndrome: a community survey. British Journal of General Practice. 2004. 54, 495-502.

[4] Wilson, S. et al. Prevalence of irritable bowel syndrome: a community survey. British Journal of General Practice. 2004. 54, 495-502.

[5] Hungin APS, et al. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther 2003; 17: 643-650.

Exhibit 11: E.U. CC Market Opportunity Assumptions (numbers are in millions)

European Market		2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Chronic Constipation												
EU Adult Population (millions)	0	401.6	402.4	403.2	404.0	404.8	405.6	406.4	407.3	408.1	408.9	409.7
Percent with Chronic Constipation		7.7%	7.7%	7.7%	7.7%	7.7%	7.7%	7.7%	7.7%	7.7%	7.7%	7.7%
Chronic Constipation Patients		30.9	31.0	31.0	31.1	31.2	31.2	31.3	31.4	31.4	31.5	31.5
Percent Seeing a Doctor		35.0%	35.0%	35.0%	35.0%	35.0%	35.0%	35.0%	35.0%	35.0%	35.0%	35.0%
Treatment-seeking Patients		10.8	10.8	10.9	10.9	10.9	10.9	11.0	11.0	11.0	11.0	11.0
Percent Receiving Rx Medications		33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%
Potential Linzess Patients		**3.6**	**3.6**	**3.6**	**3.6**	**3.6**	**3.6**	**3.6**	**3.6**	**3.6**	**3.6**	**3.6**
Percent D/C		10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Plecanatide Patients	-	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**
Additional Plecanatide Market Penetration							**0.0%**	**0.5%**	**1.2%**	**1.9%**	**2.6%**	**3.3%**
Incremental Plecanatide Patients							**-**	**0.02**	**0.04**	**0.07**	**0.09**	**0.12**
Total Plecanatide Patients							**0.4**	**0.4**	**0.4**	**0.4**	**0.5**	**0.5**
Days Used		-	-	-	-		30.0	60.0	95.0	120.0	130.0	132.6
Price/Rx							4.1	3.7	3.3	3.0	2.7	2.4
Plecanatide Chronic Constipation Revenue		**-**	**-**	**-**	**-**	**-**	**44**	**83**	**127**	**154**	**159**	**155**
Growth								**89%**	**52%**	**21%**	**3%**	**-3%**
Risk Adjustment							**50%**	**50%**	**50%**	**50%**	**50%**	**50%**
Risk-Adjusted Plecanatide Revenues						**$ -**	**$ 22**	**$ 42**	**$ 64**	**$ 77**	**$ 80**	**$ 77**
Growth								*89%*	*52%*	*21%*	*3%*	*-3%*

Source: Cantor Fitzgerald Estimates

Schoenfeld, PS. Symptom Frequency, Health Care Seeking Behavior, and Satisfaction with Therapy Among Chronic Constipation Patients: Results of a Population-Based Survey. P1089 presented at the 2010 American College of Gastroenterology.

Assumptions:
E.U. Adult Population age 15-65 (Wolfram Alpha)
Percent with Chronic Constipation (using estimates provided by Movetis)
Percent seeing a Doctor (30-40% see a doctor for constipation as per Movetis)
Percent Receiving Rx Medications (33-35% of medications taken ≥2 times per week in the 10,030 U.S. patient survey were prescription drugs)
Percent Discontinuing Treatment (Cantor Fitzgerald estimate based on Phase III overall discontinuation rates of 8-10% in the IBS-C trials)
Days Used (assuming a ramp up to 134 days/year based on 132 days/year of average Zelnorm use, which may be conservative if the drug is used like a PPI longer term)
Price/Day (assuming 50% discount to U.S. pricing, with a 10% annual price decline due to pricing pressure)

Japan is a smaller market

The prevalence of IBS in Japan ranges from 14.2-31%[6] [7]. If we apply a 15% estimate to Japan's adult population (127 million) to encompass both IBS and Chronic Constipation, we arrive at approximately 19 million patients. Using a blended assumption for 50% seeking treatment, 35% prescription drug use, and a 10% Linzess discontinuation rate, we would arrive at approximately **0.3 million patients** who are potential plecanatide candidates.

We model our assumptions for the Japanese market in Exhibit 12 below.

Exhibit 12: Japanese Market Opportunity Assumptions (numbers are in millions)

Japanese Market	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Japanese Population (millions)	127.0	126.7	126.5	126.2	126.0	125.7	125.5	125.2	125.0	124.7	124.5
Percent with IBS-C/CC	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
IBS-C /CC Patients	19.1	19.0	19.0	18.9	18.9	18.9	18.8	18.8	18.7	18.7	18.7
Percent Seeking Treatment	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
Treatment-seeking Patients	9.5	9.5	9.5	9.5	9.4	9.4	9.4	9.4	9.4	9.4	9.3
Percent Receiving Rx Medications	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%
Potential Linzess Patients	**3.3**	**3.3**	**3.3**	**3.3**	**3.3**	**3.3**	**3.3**	**3.3**	**3.3**	**3.3**	**3.3**
Percent D/C							10%	10%	10%	10%	10%
Plecanatide Patients	-	-	-	-	-	-	**0.3**	**0.3**	**0.3**	**0.3**	**0.3**
Additional Plecanatide Market Penetration							**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**
Incremental Plecanatide Patients							-	-	-	-	-
Total Plecanatide Patients							**0.3**	**0.3**	**0.3**	**0.3**	**0.3**
Days Used							30.0	60.0	95.0	120.0	130.0
Price/Rx							3.7	3.5	3.3	3.1	3.0
Plecanatide CC/IBS-C Revenue	-	-	-	-	-	-	**36**	**69**	**103**	**123**	**127**
Growth								**90%**	**50%**	**20%**	**3%**
Risk Adjustment							**50%**	**50%**	**50%**	**50%**	**50%**
Risk-Adjusted Japan Plecanatide Market Opportunity	-	-	-	-	-	-	**$ 18**	**$ 34**	**$ 52**	**$ 62**	**$ 63**
Growth								*90%*	*50%*	*20%*	*3%*

Source: Cantor Fitzgerald Estimates

Additional Assumptions:
Slight annual decline in Japanese population
Assuming blended risk of 50%

[6] Fujiwara, KM, et al. Prevalence of overlaps between GERD, FD, and IBS and impact on health-related quality of life. J. Gastroenterol Hepatol. 2010 Jun; 25(6): 1151-6.
[7] Shinozaki M, et al. High prevalence of irritable bowel syndrome in medical outpatients in Japan. J. Clin Gastroenterol. 2008 Oct; 42(9): 1010-6.

In China the prevalence of IBS is believed to be much lower than in western countries (4.6%) based on a survey of over 16,000 patients from five regions in China. [8] More affluent Asian cities like Singapore have a higher prevalence of 8.6%, while community subjects in India had low rates of IBS (4.2%)[9] yet higher rates of constipation (11.6%)[10]. Movetis estimated that there are 6 million patients in Asia and < 1 million patients in Latin America who are dissatisfied with laxatives, which represent additional markets for Synergy or its potential acquirer. We are not yet including revenue estimates from these countries in our assumptions.

Other intellectual property from GC-C agonists represents a potential source of future growth

Synergy is also developing SP-333, a second generation GC-C agonist for the treatment of ulcerative colitis. SP-333 is believed to be more stable than plecanatide and is designed for colonic delivery (rather than targeting the small intestine). Management believes that GC-C agonists have potent anti-inflammatory activity in animal models and that the compound may have a novel mechanism of action.

The company presented a poster on SP-333 at the American College of Gastroenterology in 2011 that demonstrated that oral administration of SP-333 ameliorated gastrointestinal inflammation through downregulation of pro-inflammatory cytokines, which makes the drug a potential candidate for the treatment of inflammatory bowel disease such as ulcerative colitis and Crohn's. Management also hypothesizes that GC-C agonists may delay progression of colitis into colon cancer via the same inflammatory downregulation mechanism. This is an area that may warrant further exploration. A composition of matter patent was issued on SP-333 in February 2011, and we are aware of three other issued patents for this compound.

The company filed the IND on SP-333 in September 2012 and plans to commence the first of several Phase I trials in October. This trial will be a single dose-escalation trial in healthy volunteers, which will assess safety, tolerability, and PK of the compound and establish whether the drug is systemically absorbed. Data from this first study could be available in early 2013, and management plans to follow up with future work in ulcerative colitis patients.

New addition is still in early stage development and has minimal value for now, in our view

FV-100 is a potent, orally available nuceleoside analogue that is being investigated for the treatment of herpes zoster (or shingles). This drug is believed to be more potent and to have a more rapid onset of antiviral activity than competitors such as acyclovir and valacyclovir. Another potential advantage of this drug is that it may be possible to administer it once-daily relative to the three times per day dosing schedule of its competitors. Management also hypothesizes that it may be feasible to administer FV-100 several days after the onset of a shingles outbreak rather than at the very beginning. All of these theoretical benefits still need to be demonstrated in well designed clinical trials.

Synergy acquired FV-100 from Bristol-Myers Squibb for an upfront payment of $1 million along with milestone payments covering FDA approval, single digit royalties, and sales milestones payable if the drug exceeds $125 million in sales. Synergy still needs to identify an ideal dose and dose schedule for this product and plans to conduct additional Phase II trials in 2013.

Prior owner Inhibitex conducted a Phase II trial on FV-100 in December 2010 which failed to attain statistical significance on its primary endpoint. The Phase II trial was a double-blind study comparing two different dosing arms of FV-100 to valacyclovir. The trial enrolled 350 patients, aged 50 years and older and randomized them to receive either 200 mg or 400 mg of FV-100 administered once daily or 1,000 mg valacyclovir dosed three times per day. The primary endpoint of the trial was herpes

[8] Zhao Y, et al. Dyspepsia and irritable bowel syndrome in China; a population-based endoscopy study of prevalence and impact. Aliment Pharmacol Ther. 2010 Aug;32(4): 562-72. Epub 2010 May 22.
[9] Gwee KA, Lu CL and Ghoshal UC. Epidemiology of irritable bowel syndrome in Asia: something old, something new, something borrowed. J Gastroenterol Hepatol. 2009 Oct; 24(10):1601-7.
[10] Makharia, G et al. Prevalence of Irritable Bowel Syndrome: A Community Based Study From Northern India. J Neurogastroenterol Motil, Vol 17. No 1 January 2011, p 82-87.

zoster pain as measured by the Zoster Brief Pain Inventory (ZBPI) over 30 days and secondary endpoints included herpes zoster associated pain over 90 days, herpes zoster lesion healing, and clinical lab results.
We summarize study safety and efficacy data in exhibits 13-14 below.

Exhibit 13: FV-100 Phase II Efficacy Data

	Primary Endpoint	Secondary Pain Endpoints	
Cohort	Least Squares Mean BOI30 days AUC ±S.E.	Least Squares Mean BOI90 days AUC ±S.E.	Incidence of PHN
3000 mg valacyclovir (n=109)	117.96 ±6.25	229.59 ±19.55	20.2%
200 mg FV-100 (n=107)	114.49 ±6.24	221.53 ±19.51	17.8%
400 mg FV-100 (n=113)	110.31 ±6.08	196.94 ±19.01	12.4%

Source: Company reports and Cantor Fitzgerald estimates

Exhibit 14: FV-100 Phase II Safety Data

Number (%) of Patients Reporting	200 mg FV-100 (n=117)	400 mg FV-100 (n=117)	3000 mg valacyclovir (n=116)
Any AE	46.2	54.7	42.2
Treatment-related AEs	20.5	25.6	19.8
Discontinuation of drug for AE	1.7	1.7	1.7
SAEs	0	4.3	3.4
Treatment-related SAEs	0	0	1.7

Source: Company reports and Cantor Fitzgerald estimates

We note that the trial failed to attain statistical significance on the primary endpoint and was not powered to detect a statistically significant difference in the secondary endpoints. However, management points out the numerically favorable trends in the FV-100 arm, especially with respect to reduction in incidence of PHN. Additionally, management believes that the trial failed to detect a difference in pain since concomitant analgesics were not controlled for in the trial. In the 400 mg FV-100 dose group, the most common adverse events were headache (13% of patients) and nausea (9%); no patient discontinued because of headache and one patient terminated due to nausea (grade 1). The most common adverse events in the valacyclovir cohort were nausea (6%) and upper abdominal pain (5%). We don't have any further details on the drug's safety profile but Inhibitex reported that FV-100 was generally well tolerated at both dose levels, with a similar adverse event profile as valacyclovir.

We are not forecasting sales for FV-100 at this time given the drug's early stage of development and uncertain future. Management wants to explore additional dosing regimens as well as to redesign trials to incorporate antiviral endpoints. Given that the company would need to pay out an additional milestone to Bristol Myers if sales exceeded $125 million per year, we view this level as a benchmark of success for the product. We note that this compound only demonstrates antiviral activity against herpes zoster and not other herpes viruses. Chief competitors to FV-100 would be generic treatments acyclovir, valacyclovir, and famcyclovir which are burdened by more frequent dosing schedules and longer duration of treatment. Inhibitex previously estimated that approximately 15-30% of prescriptions written for these three antiviral agents were for the treatment of herpes zoster (we estimate this to be approximately 2.75-5.5 million prescriptions).

Management

We highlight the qualifications of the Synergy management team below. We note that there is currently no commercial expertise in the group due to the early stage of the plecanatide development program and hypothesize that management plans to sell the company rather than build out a marketing division and promote the drug on its own.

Gary S. Jacob, Ph.D.
Dr. Jacob has served as the President, CEO and Director of Synergy since July 2008 and as Chairman of the privately held company from October 2003 until July 2008. He was previously at Monsanto/G.D. Searle, where he specialized in the field of Glycobiology and drug discovery. Dr. Jacob earned a B.S. in Chemistry from the University of Missouri, and holds a Ph.D. in Biochemistry from the University of Wisconsin–Madison. Dr. Jacob also serves on the Board of Directors of Trovagene, Inc.

Kunwar Shailubhai, Ph.D., M.B.A.
Dr. Shailubhai served as Synergy's Chief Scientific Officer since July 2008. From 2001-2008 he was responsible for the preclinical development of Synergy's GC-C agonist program for drugs to treat colon cancer and GI disorders and diseases. Dr. Shailubhai was with Monsanto Company from 1993-2000 where he was the Group Leader of the cancer chemoprevention group. Prior to Monsanto he served as a Senior Staff Fellow at the National Institutes of Health, and as an Assistant Professor at the University of Maryland. Dr. Shailubhai received his Ph.D. in microbiology from the University of Baroda, India and his M.B.A. from the University of Missouri, St. Louis.

Gail M. Comer, M.D.
Dr. Gail Comer joined Synergy in 2012 as the company's Chief Medical Officer. She is a board-certified gastroenterologist and hepatologist, with more than 14 years of experience in the pharmaceutical industry, which includes seven years at Abbott Laboratories, six years at Wyeth Research, and her most recent position as Senior Director at Pfizer. Prior to joining the pharmaceutical industry Dr. Comer was an Associate Professor of Clinical Medicine at The State University of New York at Stony Brook

Laura Barrow, Pharm. D.
Dr. Barrow joined Synergy in 2011 as SVP Clinical Operations and has more than 25 years of experience in the pharmaceutical industry, with seven years in clinical research at Hoffmann-La Roche; 17 years in project management at Bristol-Myers Squibb and a year as Worldwide Head of Clinical and Regulatory Standard Operating Procedures at Pfizer. Dr. Barrow holds a Pharm.D. from St. John's University.

Bernard F. Denoyer, C.P.A, M.B.A.
Bernard Denoyer has served as Synergy's SVP of Finance and Secretary since July 2008. He has simultaneously served as Callisto Pharmaceuticals' Senior Financial Officer and Secretary since January 2004. From 2001 through 2003 Mr. Denoyer provided interim CFO services to emerging technology companies. He served as CFO at META Group, Inc. from 1994 through 2000 and from 1990 to 1993 he served as VP Finance of Environetics, Inc. Mr. Denoyer received a B.A. in Economics from Fairfield University, earned his M.B.A. in Finance from the Columbia Business School and his CPA while at Ernst and Young.

Financial Performance and Outlook

Revenues: We model revenues for the company beginning in 2016 upon the launch of plecanatide in chronic constipation. We note that Consensus models revenues in 2015, even though the company indicated that it would submit its CC NDA in 2015 at the earliest. We also include incremental contribution from an IBS-C indication beginning in 2017 (one year behind CC revenues), as well as revenues in Europe and Japan in the outer years. Our revenue estimates are currently risk-adjusted to assume an 80% likelihood of approval in chronic constipation and a 50% likelihood of approval in IBS-C.

Gross Margins: We assume gross margins above 90% improving over time to the 94% range based on management's comments about its cost-effective production process and a comparison to estimated Linzess margins.

R&D: We model continued investment into the company's pipeline as Synergy works to gain approval for CC, and IBS-C; as well as advance SP-333 in ulcerative colitis and FV-100 for the treatment of shingles. We believe that spending will increase meaningfully in 2013 to support several ongoing clinical programs.

SG&A: We model some gradual SG&A increases from 2012-2015 associated with a growing organization, legal expenses, and financing expenses. Though we are not expecting Synergy to commercialize plecanatide alone, we are making financial assumptions to incorporate commercialization expenses for now.

Tax: We model standard 38% tax rates beginning in 2018 upon profitability.

Share Count: We model some increases to the share count associated with expected dilutive financing over the next four years. We do believe that Synergy will need to raise more cash to support its R&D program if it does not partner plecanatide or sell the company.

Cash: We expect the company to end 2012 with approximately $20 million in cash and short-term investments, which would necessitate more financing in 2013 to push forward with its research program.

Valuation

Our current valuation of the company is based upon weighted average of two scenarios:

(1) We utilize discounted cash flow analysis (DCF) with a weighted average cost of capital of 14% (to account for the high clinical risk), and a conservative 0% terminal growth rate which generates a hypothetical $10 price target. Under this scenario we assume positive data results in December and weight the probability of this outcome at 67%.
(2) The ongoing Phase IIb CC trial fails to identify at least one plecanatide dose that is statistically different from placebo, and the company valuation falls to reflect its cash position (<$1.00/share). We weight this negative outcome by a 33% probability.

We arrive at our $7.00 price target by utilizing a probability-weighted average of these two outcomes.

We check our assumptions by evaluating a potential takeout scenario of the company. If we assume that Synergy is acquired at a 3x multiple of discounted and risk–adjusted 2022 sales of $894 million then we derive a hypothetical price target of ~$10 which supports our BUY rating.

Risks

(1) Plecanatide may fail to demonstrate efficacy at any of the doses being tested in the ongoing Phase IIb trial for chronic constipation. If this is the case, we would expect the stock price to decline to reflect the cash position on the company's balance sheet with minimal additional value allocated for the pipeline assets.
(2) Plecanatide may fail to show any tolerability differentiation from Ironwood's Linzess based on data from the ongoing Phase IIb trial in chronic constipation.
(3) Management could fail to attract an acquirer for the company if data from the chronic constipation trial are not sufficiently robust.
(4) Synergy may pursue additional dilutive financing to support its clinical development programs in plecanatide, SP-333 and FV-100.
(5) Manufacturing issues could arise that delay or prevent FDA approval of plecanatide.
(6) Synergy faces regulatory approval risk for plecanatide in chronic constipation.
(7) Longer-term, plecanatide may fail to demonstrate efficacy in treating abdominal pain and may therefore fail to gain an IBS-C indication.
(8) The commercial opportunity for plecanatide may be limited due to competition from Linzess and managed care restrictions.

Exhibit 15: Synergy Income Statement (dollars in millions)

	2009	2010	2011	1Q:12A	2Q:12A	3Q:12E	4Q:12E	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Net Sales	-	-	-								-	48.5	134.8	297.1	487.9	659.1	793.3	894.0	981.2
COGS	-	-	-								-	4.8	12.7	26.1	40.0	50.1	55.5	57.2	56.9
Gross Profit	-	-	-	-	-	-	-	-	-	-	-	43.6	122.1	271.0	447.9	609.0	737.7	836.8	924.3
SG&A	4.5	6.6	6.7	1.7	1.9	2.0	2.1	7.7	9.3	13.0	16.0	90.0	103.5	110.7	118.5	126.8	135.7	145.2	155.3
R&D	3.7	9.6	13.4	5.3	7.6	8.3	8.0	29.3	60.0	75.0	86.3	90.6	95.1	99.8	104.8	110.1	115.6	121.4	127.4
Operating Income (Loss)	(8.2)	(16.1)	(20.2)	(7.1)	(9.5)	(10.3)	(10.1)	(37.0)	(69.3)	(88.0)	(102.3)	(136.9)	(76.5)	60.4	224.6	372.2	486.5	570.3	641.5
Interest Income	0.1	0.1	0.1	0.0	0.0	0.1	0.1	0.2	0.1	0.2	0.2	0.2	0.1	0.3	1.0	2.3	4.0	6.0	8.2
Interest expense	-	-	(0.0)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other income		0.5	0.4	-	0.3														
Change in fair value of derivatives-warrants		0.3	5.3	0.0	(1.3)	(1.3)	(1.3)	(3.9)	(3.9)	(3.9)	(3.9)	(3.9)	(3.9)	(3.9)	(3.9)	(3.9)	(3.9)	(3.9)	(3.9)
Pre-tax Income	(8.1)	(15.2)	(14.5)	(7.0)	(10.6)	(11.6)	(11.4)	(40.8)	(73.2)	(91.8)	(106.0)	(140.7)	(80.3)	56.7	221.6	370.5	486.5	572.3	645.8
Tax Rate	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	38.0%	38.0%	38.0%	38.0%	38.0%	38.0%
Tax	-	-	-	-	-	-	-	-	-	-	-	-	-	21.5	84.2	140.8	184.9	217.5	245.4
Net income (Loss)	(8.1)	(15.2)	(14.5)	(7.0)	(10.6)	(11.6)	(11.4)	(40.8)	(73.2)	(91.8)	(106.0)	(140.7)	(80.3)	35.1	137.4	229.7	301.6	354.8	400.4
Diluted Shares	36.64	44.9	47.6	54.3	60.4	65.8	65.8	61.6	83.0	95.0	103.0	109.0	109.0	109.0	109.0	109.0	109.0	109.0	109.0
EPS	($0.22)	($0.34)	($0.30)	($0.13)	($0.17)	($0.18)	($0.17)	($0.65)	($0.88)	($0.97)	($1.03)	($1.29)	($0.74)	$0.32	$1.26	$2.11	$2.77	$3.26	$3.67

Consensus Revs	0.00	0.00	0.00	0.00	0.0	74.9	174.0
Consensus EPS	($0.15)	($0.15)	($0.59)	(0.55)	(0.71)	0.01	0.83

Margin Analysis	2009	2010	2011	1Q:12A	2Q:12A	3Q:12E	4Q:12E	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Gross Margin											NM	90.0%	90.6%	91.2%	91.8%	92.4%	93.0%	93.6%	94.2%
COGS											NM	10.0%	9.4%	8.8%	8.2%	7.6%	7.0%	6.4%	5.8%
SG&A											NM	185.7%	76.8%	37.3%	24.3%	19.2%	17.1%	16.2%	15.8%
R&D											NM	186.8%	70.5%	33.6%	21.5%	16.7%	14.6%	13.6%	13.0%
Operating Margin											NM	-282.5%	-56.7%	20.3%	46.0%	56.5%	61.3%	63.8%	65.4%
Net Income Margin											NM	-290.3%	-59.6%	11.8%	28.2%	34.9%	38.0%	39.7%	40.8%
Growth (Y/Y)	2009	2010	2011	1Q:12A	2Q:12A	3Q:12E	4Q:12E	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Net Sales													180%	122%	65%	36%	21%	13%	10%
COGS													161%	106%	53%	25%	11%	3%	-1%
Gross Profit													180%	122%	65%	36%	21%	13%	10%
SG&A		47%	3%	-9%	26%	81%	-5%	15%	20%	40%	23%	463%	15%	7%	7%	7%	7%	7%	7%
R&D		156%	40%	261%	224%	114%	40%	118%	105%	25%	15%	5%	5%	5%	5%	5%	5%	5%	5%
Operating Income (Loss)		97%	25%	109%	146%	107%	27%	84%	87%	27%	16%	34%	-44%	179%	272%	66%	31%	17%	12%
Interest Income		45%	-17%	61%	141%	194%	129%	128%	-56%	89%	18%	-13%	-51%	206%	286%	127%	75%	50%	37%
Pre-tax Income		87%	-5%	90%	132%	1883%	102%	182%	80%	25%	15%	33%	-43%	171%	291%	67%	31%	18%	13%
Tax															291%	67%	31%	18%	13%
Net income (Loss)		-87%	5%	-90%	-132%	-1883%	-102%	-182%	-280%	-225%	-215%	-233%	-157%	-56%	291%	67%	31%	18%	13%
EPS		-253%	-190%	-261%	-279%	-1526%	-249%	-315%	-35%	-10%	-7%	-25%	43%	144%	291%	67%	31%	18%	13%

Source: Company reports, Cantor Fitzgerald estimates, and Thomson Reuters Consensus

Exhibit 16: Synergy Risk-Adjusted Sales Estimates (dollars in millions)

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Plecanatide U.S.	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$48.5	$134.8	$256.7	$393.2	$508.2	$600.5	$686.2	$776.0
Growth									*178%*	*90%*	*53%*	*29%*	*18%*	*14%*	*13%*
Plecanatide EU	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$40.4	$76.6	$116.6	$141.2	$146.0	$141.8
Growth											*89%*	*52%*	*21%*	*3%*	*-3%*
Plecanatide Japan	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$18.1	$34.3	$51.6	$61.7	$63.4
Growth												*90%*	*50%*	*20%*	*3%*
SP-333	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Growth															
FV-100	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Growth															
Total Product Sales	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$48.5	$134.8	$297.1	$487.9	$659.1	$793.3	$894.0	$981.2
Growth									*178%*	*120%*	*64%*	*35%*	*20%*	*13%*	*10%*

Source: Company reports and Cantor Fitzgerald estimates

Exhibit 17: Synergy Balance Sheet Estimates (dollars in millions)

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Assets																
Current assets																
Cash and cash equivalents	0.2	7.2	1.7	13.2	5.3	81.4	139.5	134.0	94.5	21.2	66.5	215.9	459.0	775.7	1,148.4	1,570.8
Available for sale securities	0.0	0.0	0.0	0.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Note receivable	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Prepaid expenses and other current assets	0.0	1.1	1.0	1.1	1.3	1.5	1.8	2.2	2.6	3.2	3.8	4.6	5.5	6.6	7.9	9.5
Total current assets	**0.9**	**8.2**	**2.7**	**14.3**	**26.6**	**103.0**	**161.3**	**156.2**	**117.1**	**44.4**	**90.3**	**240.5**	**484.5**	**802.3**	**1,176.3**	**1,600.3**
PP&E	0.0	0.0	0.0	0.0	0.2	0.4	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0	2.2	2.4
Security deposits	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Due from majority shareholder	0.0	1.0	1.7	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total assets	**0.9**	**9.2**	**4.4**	**15.9**	**28.4**	**105.0**	**163.5**	**158.6**	**119.7**	**47.2**	**93.4**	**243.7**	**487.9**	**806.0**	**1,180.2**	**1,604.4**
Liabilities and Stockholders' Equity																
Current liabilities																
Accounts payable	2.0	1.3	3.0	1.4	1.5	1.6	1.6	1.7	1.6	2.8	5.8	8.9	11.1	12.3	12.7	12.6
Accrued expenses	0.1	0.4	2.1	1.3	4.7	6.1	7.9	10.2	13.3	17.3	22.5	29.2	38.0	49.4	64.2	83.5
Total current liabilities	**2.1**	**1.7**	**5.0**	**2.7**	**6.1**	**7.6**	**9.5**	**12.0**	**14.9**	**20.1**	**28.3**	**38.1**	**49.1**	**61.8**	**77.0**	**96.2**
Derivative instruments, at estimated fair value-warrants	**0.0**	**0.0**	**3.5**	**3.3**	**3.8**	**4.3**	**4.8**	**5.4**	**6.1**	**6.8**	**7.7**	**8.5**	**9.5**	**10.6**	**11.8**	**13.1**
Total Liabilities	**2.1**	**1.7**	**8.5**	**6.1**	**9.9**	**11.9**	**14.4**	**17.4**	**21.0**	**27.0**	**36.0**	**46.7**	**58.7**	**72.4**	**88.7**	**109.3**
Stockholders' Equity																
Common stock	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Preferred stock	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Additional paid-in capital	30.6	47.4	51.0	79.4	128.8	276.6	424.5	522.5	620.7	622.5	624.6	626.8	629.3	632.0	635.0	638.3
Deficit accumulated during development stage	(31.8)	(39.9)	(55.1)	(69.6)	(110.4)	(183.5)	(275.3)	(381.3)	(522.0)	(602.3)	(567.2)	(429.8)	(200.0)	101.6	456.4	856.8
Total stockholders' equity	**(1.2)**	**7.5**	**(4.1)**	**9.8**	**18.4**	**93.1**	**149.2**	**141.2**	**98.7**	**20.2**	**57.4**	**197.1**	**429.2**	**733.6**	**1,091.4**	**1,495.1**
Total liabilities and stockholders' equity	**0.9**	**9.2**	**4.4**	**15.9**	**28.4**	**105.0**	**163.5**	**158.6**	**119.7**	**47.2**	**93.4**	**243.7**	**487.9**	**806.0**	**1,180.2**	**1,604.4**

Source: Company reports and Cantor Fitzgerald estimates

Exhibit 18: Synergy Statement of Cash Flows (dollars in millions)

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Operating Cash Flow																
Net income (loss)	(31.76)	(8.13)	(15.22)	(14.47)	(40.75)	(73.15)	(91.77)	(105.99)	(140.71)	(80.31)	35.15	137.41	229.72	301.64	354.84	400.39
Depreciation	0.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Stock-based compensation	0.38	1.05	0.71	0.82	1.15	1.27	1.39	1.53	1.68	1.85	2.04	2.24	2.47	2.71	2.99	3.28
Purchased in-process R&D	28.16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Change in fair value of derivative instruments-warrants	0.00	0.00	(0.30)	(5.26)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Working Capital	**1.34**	**(1.42)**	**3.35**	**(2.33)**	**3.18**	**1.21**	**1.58**	**2.07**	**2.52**	**4.65**	**7.54**	**9.06**	**10.09**	**11.50**	**13.87**	**17.61**
Net cash provided by operating activities	**(1.88)**	**(8.49)**	**(11.45)**	**(21.23)**	**(35.43)**	**(69.68)**	**(87.80)**	**(101.40)**	**(135.51)**	**(72.81)**	**45.73**	**149.70**	**243.28**	**316.86**	**372.70**	**422.29**
Cash flows from investing activities																
Net cash paid on Exchange Transaction	(0.16)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Loans from (to) related parties	(0.69)	(0.28)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Purchase of available for sale securities	0.00	0.00	0.00	0.00	(20.00)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
PP&E	(0.01)	0.00	(0.70)	0.13	(1.20)	(1.20)	(1.20)	(1.20)	(1.20)	(1.20)	(1.20)	(1.20)	(1.20)	(1.20)	(1.20)	(1.20)
Net cash used in investing activities	**(0.86)**	**(0.28)**	**(0.702)**	**0.13**	**(21.20)**	**(1.20)**	**(1.20)**	**(1.20)**	**(1.20)**	**(1.20)**	**(1.20)**	**(1.20)**	**(1.20)**	**(1.20)**	**(1.20)**	**(1.20)**
Cash flows from financing activities																
Proceeds from Private Placement	3.03	15.97	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Fees and expenses	(0.07)	(0.26)	(0.47)	(2.15)	(3.50)	(3.50)	(3.50)	(3.50)	(3.50)	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Proceeds from sale of common stock	0.00	0.00	7.18	34.37	51.75	150.00	150.00	100.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Proceeds from exercise of warrants	0.00	0.00	0.00	0.42	0.46	0.50	0.55	0.61	0.67	0.74	0.81	0.89	0.98	1.08	1.18	1.30
Net cash used in financing activities	**2.95**	**15.71**	**6.71**	**32.64**	**48.71**	**147.00**	**147.05**	**97.11**	**97.17**	**0.74**	**0.81**	**0.89**	**0.98**	**1.08**	**1.18**	**1.30**
Net increase (decrease) in cash and cash equivalents	**0.21**	**6.94**	**(5.45)**	**11.54**	**(7.92)**	**76.12**	**58.05**	**(5.49)**	**(39.54)**	**(73.27)**	**45.34**	**149.39**	**243.06**	**316.74**	**372.68**	**422.39**
Cash at the beginning of the year	0.00	0.22	7.15	1.71	13.24	5.33	81.45	139.50	134.01	94.47	21.20	66.53	215.93	458.98	775.72	1,148.40
Cash at the end of the year	**0.22**	**7.15**	**1.7**	**13.2**	**5.33**	**81.45**	**139.50**	**134.01**	**94.47**	**21.20**	**66.53**	**215.93**	**458.98**	**775.72**	**1,148.40**	**1,570.80**

Source: Company reports and Cantor Fitzgerald estimates

Exhibit 19: Companies Mentioned

Company Name	Exchange	Ticker	Rating
Albireo	Private	N/A	NC
BRISTOL-MYERS SQUIBB COMPANY	NEW YORK STOCK EXCHANGE, INC.	BMY	NC
Ferring Pharmaceuticals	Private	N/A	NC
FOREST LABORATORIES, INC.	NEW YORK STOCK EXCHANGE, INC.	FRX	BUY
IRONWOOD PHARMACEUTICALS, INC.	NASDAQ	IRWD	SELL
SALIX PHARMACEUTICALS, LTD.	NASDAQ	SLXP	BUY
SHIRE PLC	NASDAQ	SHPGY	NC
SUCAMPO PHARMACEUTICALS, INC.	NASDAQ	SCMP	NC

APPENDIX

Johnston JM et. al, Complete Spontaneous Bowel Movement Frequency as a Primary Outcome Measure in Patients with Chronic Constipation and Healthy Volunteers Treated with Linaclotide. Poster 628 presented at American College of Gastroenterology 2007.

Shailubhai, K et. al, A Phase IIa Randomized, Double Blind, Placebo-Controlled, 14-Day Repeat, Oral, Range-Finding Study to Assess the Safety, Pharmacokinetic and Pharmacodynamic Effects of Plecanatide (SP-304) in Patients with Chronic Idiopathic Constipation (Protocol No. SP-SP304201-09). Poster 762 presented at the American College of Gastroenterology, 2010.

#628

MICROBIA

Complete Spontaneous Bowel Movement Frequency as a Primary Outcome Measure in Patients with Chronic Constipation and Healthy Volunteers Treated with Linaclotide

Jeffrey M. Johnston, M.D., James E. MacDougall, Ph.D., Bernard J. Lavins, M.D. and Caroline B. Kurtz, Ph.D.
Microbia, Inc., Cambridge, MA USA

www.microbia.com

1. Background

- Chronic constipation (CC) is a common functional gastrointestinal disorder characterized by multiple symptoms including infrequent stools, hard/lumpy stools, difficulty with stool passage, bloating and a sense of incomplete evacuation of bowels[1,2]. The Rome diagnostic criteria for functional constipation, commonly used as a guide for clinical trial enrollment, require the presence of 2 or more of the following symptoms for at least 25% of defecations: straining, lumpy/hard stools, a sense of incomplete evacuation, a sensation of anorectal obstruction/blockage, manual maneuvers to facilitate defecation, and fewer than 3 defecations per week.
- Although clinicians tend to focus on the absolute frequency of bowel movements, only 13% of patients report stool frequency of less than 3 SBMs per week as their most bothersome symptom[3].
- Patient reported outcomes (PRO's) reflecting broader and, potentially, more complex concepts of the patient's constipation may more fully measure the patient's disease status and response to intervention and, as such, may offer a more clinically meaningful outcome to follow a patient's status in clinical practice as well as to assess outcome in CC clinical trials[4].
- Although a minority of CC patients report stool frequency as their most bothersome symptom, the majority of patients report that their SBM's are associated with a sense of incomplete evacuation[5]. Complete SBM (CSBM, an SBM associated with a sense of complete evacuation) may therefore integrate the objective, quantitative sign of stool frequency with the subjective, qualitative symptom of complete defecation.

2. Aims

- To compare attributes of CSBM and SBM as a primary outcome measure, including absolute and change from baseline frequency as well as responder analyses of these endpoints.
- To compare the correlations of change in CSBM with SBM to improvement in other bowel habits and global PRO measures.

3. Methods

Data from 2 studies of oral linaclotide, a single-center Phase 1 study in healthy volunteers (n=48)[6] and a multicenter Phase 2 study in patients with CC (n=42)[7], were evaluated in this post-hoc analysis. Both were randomized, double-blind, placebo-controlled, multiple-repeat-dose studies of once-daily, orally administered linaclotide in males and females.

Table 1: Linaclotide Studies Used in Post-hoc CSBM Analyses

Study Type	Study Endpoints	Dose Groups (entered/ completed)	Duration of Study Periods	Diagnostic Inclusion Criteria
Ph 1	Safety PK GI PD	Linaclotide: 30 µg – 8/8 100 µg – 8/8 300 µg – 8/8 1000 µg – 8/8 Placebo - 16/16	Pre – 7 days Tmt – 7 days Post – 7 days	Healthy Volunteers Age 18 – 65 yrs BM > 3/wk BSFS = 2-5
Ph 2	Safety Bowel Habits PROs	Linaclotide: 100 µg – 12/10 300 µg – 10/9 1000 µg – 10/10 Placebo – 10/9	Pre – 7 days Tmt – 14 days Post – 7 days	Rome II criteria Age 18 – 65 yrs ≤ 3 SBMs per wk

Linaclotide is a first-in-class peptide that agonizes guanylate cyclase-C receptors on the luminal membrane of intestinal enterocytes resulting in elevation of intracellular cGMP, which in turn activates ion channels to increase chloride and bicarbonate efflux into the intestinal lumen with concomitant fluid secretion[8].

Daily bowel habits were analyzed daily in both studies and included:

- SBM and CSBM frequency
- Stool consistency using the 7-point Bristol Stool Form Scale (1=hard stool; 7=water stool)
- Straining using the 7-point Ease-of-Passage Scale (1=manual disimpaction/enema needed; 7=incontinent)

The CC study also evaluated the following global PROs:

- Daily abdominal discomfort using a 7-point Likert-type scale (0=none; 6=very severe)
- Weekly severity of constipation using a 7-point Likert-type scale (0=none; 6=very severe)
- Weekly relief of symptoms using a 7-point balanced scale (0=completely relieved; 3=unchanged; 6=significantly worse)

Treatment effects of linaclotide doses were compared with placebo using analysis of covariance with the corresponding pre-treatment value as the covariate and treatment as a fixed effect, and Pearson's correlation coefficients of all outcome measures (change from baseline) were derived.

4. Results

Figure 1: Ph1 and Ph2 Baseline SBMs and CSBMs

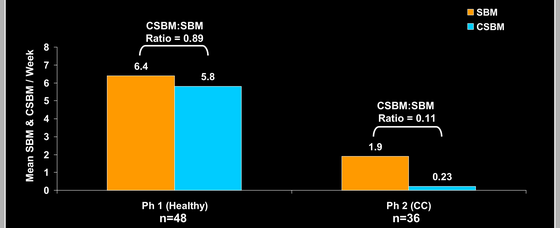


Table 2: Ph 1 CSBM:SBM Ratio

CSBM:SBM Ratio	Placebo n=16	30 µg n=8	100 µg n=8	300 µg n=8	1000 µg n=8
Mean (StdDev)					
Pre-Treatment	0.89 (0.214)	1.00 (0.00)	0.71 (0.373)	0.85 (0.184)	1.00 (0.00)
Treatment	0.85 (0.252)	1.00 (0.00)	0.66 (0.407)	0.77 (0.258)	1.00 (0.00)
Change	-0.04 (0.223)	0.00 (0.00)	-0.04 (0.321)	-0.08 (0.117)	0.00 (0.00)

Table 3: Ph 2 CSBM:SBM Ratio

CSBM:SBM Ratio	Placebo n=9	100 µg n=10	300 µg n=7	1000 µg n=10
Mean (StdDev)				
Pre-Treatment	0.17 (0.354)	0.05 (0.158)	0.10 (0.252)	0.12 (0.249)
Treatment	0.29 (0.317)	0.26 (0.299)	0.42 (0.296)	0.45 (0.343)
Change	0.12 (0.398)	0.21 (0.379)	0.33 (0.270)	0.33 (0.465)

Figure 2: Ph 2 Change from Baseline in SBMs and CSBMs

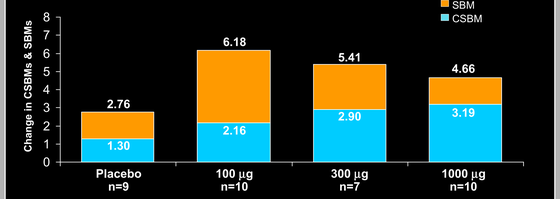


Figure 3: Ph 2 SBM Stool Frequency Responder Definition (% of patients with ≥ 3 SBM/wk + change from baseline of ≥ 1 SBM/wk)

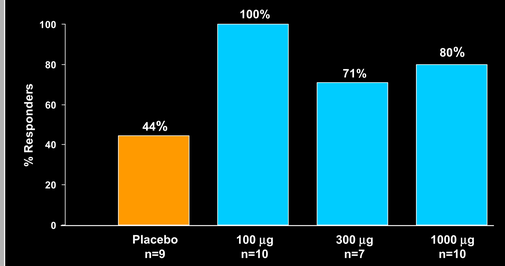


Figure 4: Ph 2 CSBM Stool Frequency Responder Definition (% of patients with ≥ 3 CSBM/wk + change from baseline of ≥ 1 CSBM/wk)

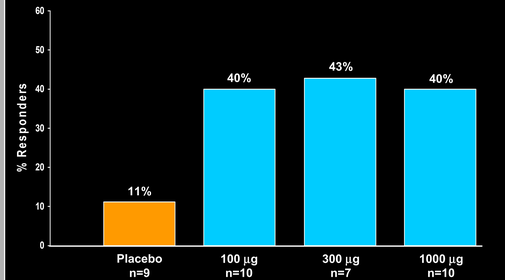


Table 4: Ph 2 Correlations Among Efficacy Endpoints (Change from Baseline)

Efficacy Endpoints (N=36)	CSBM	SBM	BSFS (Consistency)	Ease of Passage (Straining)	Abdominal Discomfort[a]	Severity of Constipation[a]	Overall Relief[a]
CSBM	1.000	0.700	0.699	0.720	-0.581	-0.712	-0.696
SBM		1.000	0.473	0.421	-0.418	-0.488	-0.445
BSFS (Consistency)			1.000	0.824	-0.628	-0.642	-0.663
Ease of Passage (Straining)				1.000	-0.587	-0.606	-0.649
Abdominal Discomfort[a]					1.000	0.465	0.451
Severity of Constipation[a]						1.000	0.818
Overall Relief[a]							1.000

[a] denotes parameters where a decrease from baseline indicates improvement
Note: p-value < 0.05 for all correlations

5. Conclusions

- These data indicate that for CC, compared to SBM, CSBM responder analysis demonstrates a lower placebo response rate (11% vs 44%) and a higher treatment effect relative to placebo (~4-fold vs ~2-fold increase).
- CC patients reported that very few SBMs were associated with complete evacuation at baseline (11% in this CC study). As the dose of linaclotide increased, the proportion of SBMs that were CSBMs increased, suggesting that the predominate effect observed at the low dose, increased stool frequency, was augmented by completeness of evacuation at higher linaclotide doses.
- CSBM had a consistently higher correlation compared with SBM to other bowel habits and PROs (|r|= ~0.7 vs ~0.45). BSFS also demonstrated very strong correlations with all other outcome measures except for SBMs.
- Additionally, these data indicate that the mean CSBM frequency for healthy subjects was approximately 1 per day, essentially the same as the mean SBM frequency (6.4 vs 5.8 per week during the pre-treatment baseline period), and that CSBM:SBM ratio was essentially unaffected by linaclotide administration.

These data support the integrative aspect of CSBM, incorporating components of an objective bowel habit sign (i.e., stool frequency) and a qualitative PRO (i.e., feeling of complete evacuation of stool from the bowels) and suggest that CSBM may represent the preferred primary endpoint for clinical trials of new treatments for CC, as well as a simple robust measurement for clinical practice.

6. References

1. Longstreth at al. Gastroenterology 2006;130: 1480-1491
2. Johanson et al. Aliment Pharmacol Ther 2007; 25:500-608
3. Pare et al. Am J Gastroenterol 2001; 96:3130-3137
4. FDA Guidance for Industry; PRO Measures Feb 2006
5. Stewart et al. Am J Gastroenterol 1999;94:3530-3540
6. Kurtz et al. Gastroenterology 2006; 130:A26
7. Johnston et al. ACG Scientific Meeting, Oct 2006 (late-breaking submission)
8. Bryant et al. Gastroenterology 2005; 128:A464

P762

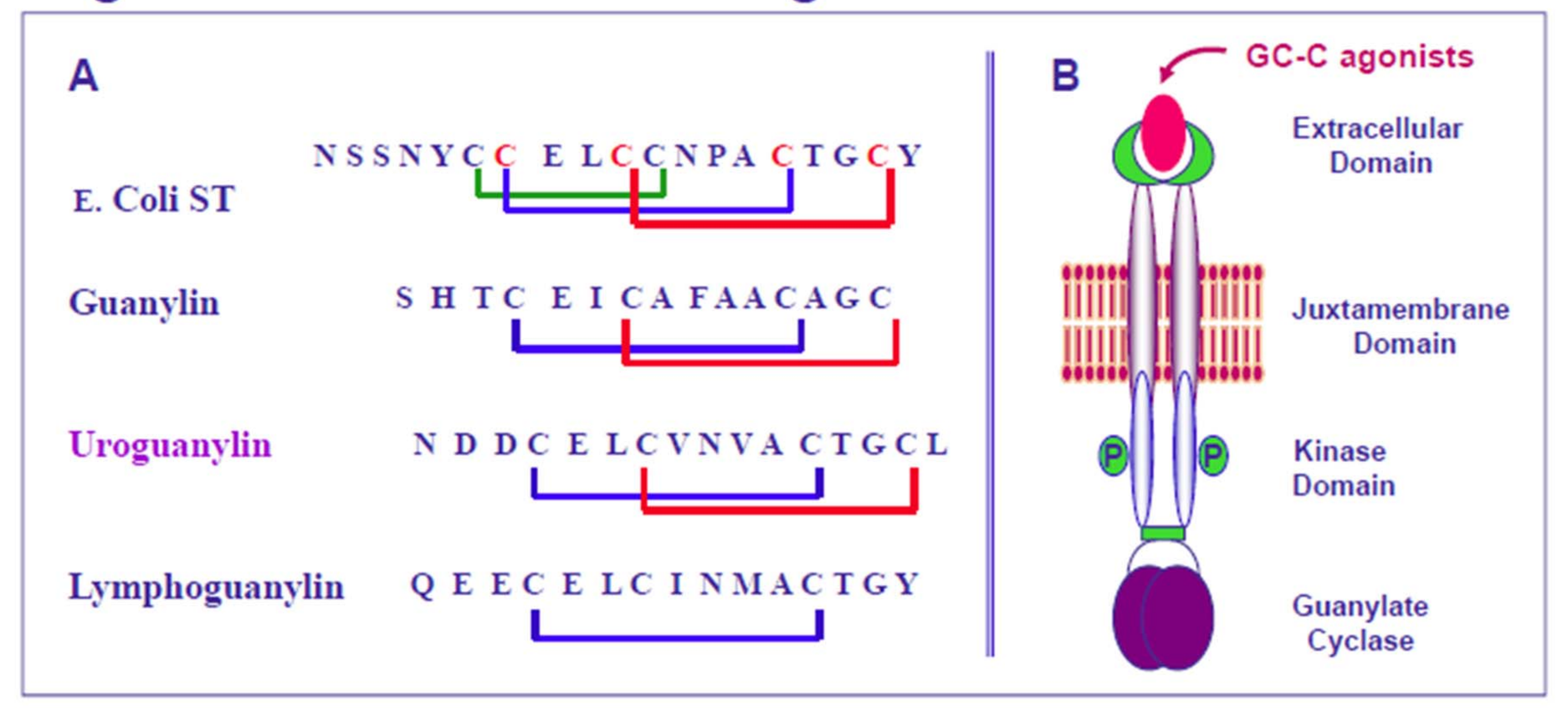
A Phase IIa Randomized, Double Blind, Placebo-Controlled, 14-Day Repeat, Oral, Range-Finding Study to Assess the Safety, Pharmacokinetic and Pharmacodynamic Effects of Plecanatide (SP-304) in Patients with Chronic Idiopathic Constipation (Protocol No. SP-SP304201-09)

K. Shailubhai, C. Talluto, S. Comiskey, J. Foss, R. Feng, A. Joslyn, and G. Jacob
Synergy Pharmaceuticals, Inc., New York, NY

Background

Uroguanylin (UG) and guanylin (GN) are physiological agonists of the guanylate cyclase-C (GC-C) receptor. Activation of the GC-C receptor stimulates intracellular synthesis of cyclic GMP, resulting in activation of the cystic fibrosis transmembrane conductance regulator (CFTR). Activation of CFTR results in augmented flow of fluid and bicarbonate into the intestinal lumen. Optimum volume of fluid secretion in the proximal intestine is critical for normal bowel movement and also for complete defecation. Thus, oral treatment with a GC-C agonist is expected to promote spontaneous bowel movement (SBM), reduce abdominal discomfort and bloating. Plecanatide (SP-304) is an analog of UG that appears to mimic the physiological functions of UG in the GI tract. T84 cell assays have also demonstrated that plecanatide has an 8-fold higher binding affinity to GC-C receptors than UG. This trial was designed to evaluate the safety and to explore the efficacy of plecanatide in chronic constipation (CC) patients.

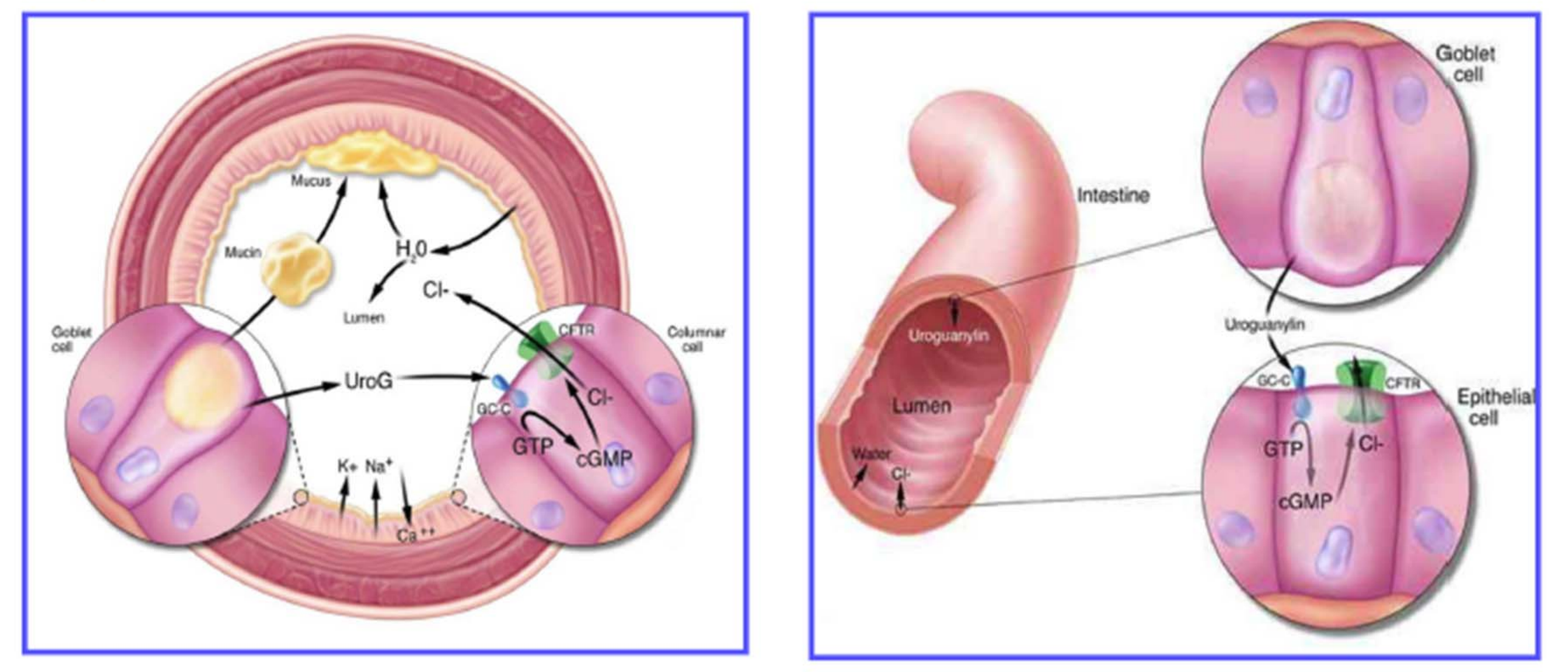
Fig. 1: Known mammalian agonists GC-C



Uroguanylin and *E. coli* enterotoxin ST peptide bind to the same GC-C receptors and follow the same mechanism of action. Thus, ST peptide exploits the same GC-C signaling that causes diarrhea. GC-C receptors are transmembrane glycoproteins that are expressed on the luminal side of the GI mucosa. Binding of GC-C agonist to the extracellular domain of the GC-C receptor leads to activation of the guanylate cyclase domain located on the cytoplasmic side.

Fig 2: Mechanism of action of GC-C agonists in the GI tract

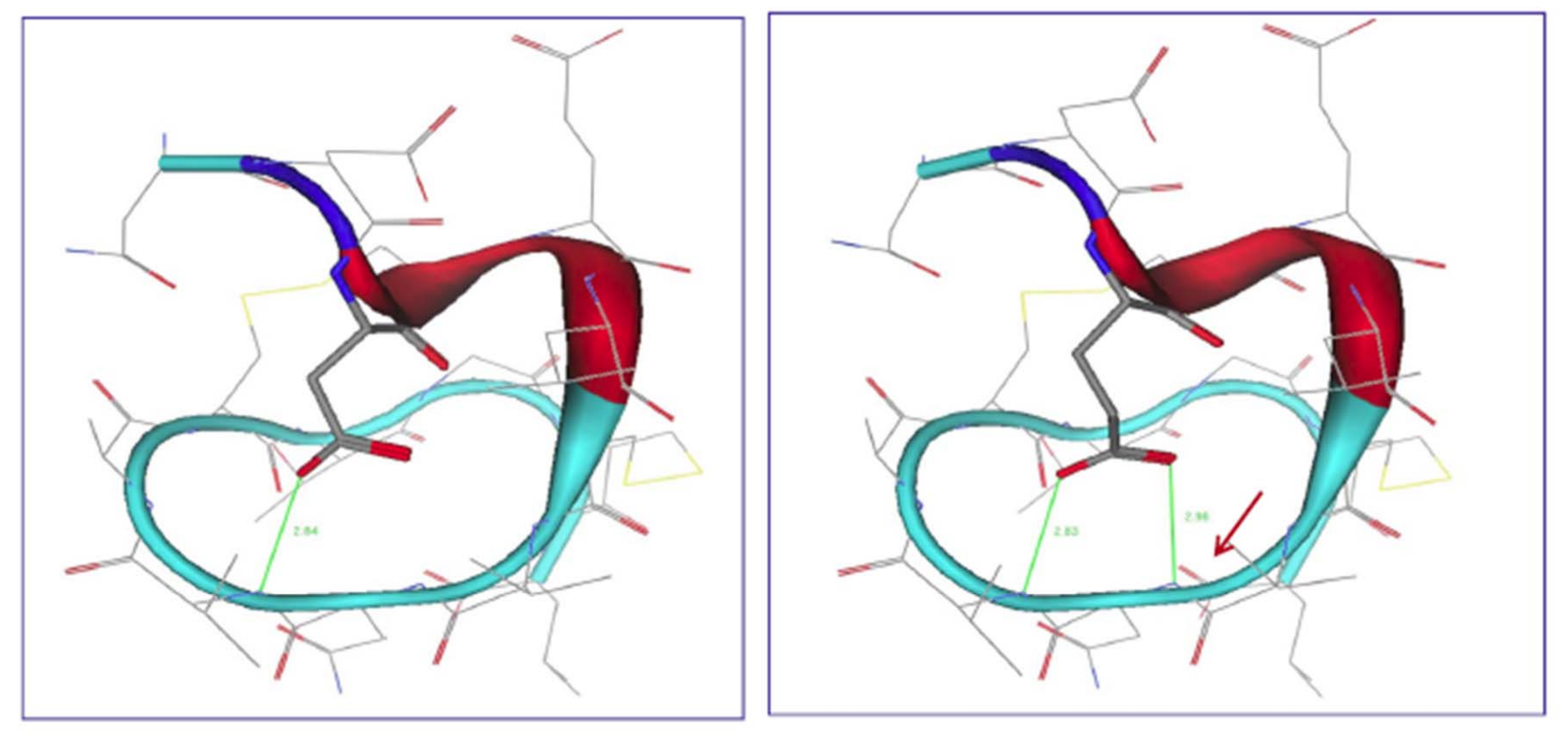
Binding of GC-C agonists to their receptors located in the GI lumen stimulates fluid, chloride and bicarbonate secretions. Optimal volume of fluid secretion in the proximal intestine is essential for normal bowel movement. Reduced volume of fluid secretion may cause chronic constipation and other GI disorders. By contrast, excessive fluid secretion may lead to diarrhea.



Cross section of intestine — GC-C signaling in the intestine

Background (continued)

Fig.3: Plecanatide is a superior analog of the natural GI hormone uroguanylin



Objectives

Primary Objective:

- To evaluate the safety of plecanatide for 14 days in patients with CC

Secondary Objectives:

- To assess the pharmacokinetic profile after the first daily dose of plecanatide and prior to and after the last dose of plecanatide
- To assess the time to first bowel movement after first daily dose of plecanatide as compared with placebo
- To assess changes in bowel habits over time (frequency, completeness of evacuation, stool consistency, straining and abdominal discomfort) during daily dosing with plecanatide or placebo

Methods

- This was a Phase IIa, randomized, double-blind, placebo-controlled, 14-day repeat, oral, dose-ranging study
- There were four dose cohorts in this trial:
  - Plecanatide (0.3 mg, 1.0 mg, 3.0 mg or 9.0 mg) and matching placebo
  - 3:1 randomization (plecanatide:matching placebo)
  - 20 subjects per dose cohort (15 plecanatide:5 matching placebo)
- Subjects took one daily dose in the morning for 14 days
- After each cohort was completed, a safety review was conducted prior to initiating the next cohort

Methods (continued)

Study Design

Screening	Pre-Treatment	Treatment		Follow-Up
		Week 1	Week 2	
Days -28 to -14	Days -14 to -1	Days 1 to 7 (+/- 1 Day)	Days 8 to 14	Day 21 (+/- 3 Days)

Primary Subject Selection Criteria:

- Meet modified ROME III criteria for CC
- Colonoscopy within past 5 years with no significant finding
- Good health as determined by physical examination, medical history, vital signs, ECG, clinical chemistry, hematology, urinalysis, drug screen and serology assessments
- During 14-day pre-treatment period, subjects must report < 6 SBM and < 3 CSBM in each pre-treatment week

Statistical Analysis:

- Primary endpoints for the safety evaluation were summarized by descriptive statistics for the patients that received at least one dose of plecanatide or placebo (safety population)
- The secondary assessments for pharmacodynamic activity were summarized by descriptive statistics for the patients that received at least 5 doses of either plecanatide or placebo and had corresponding diary data for daily bowel habits (per protocol population)
  - Time to first bowel movement after first daily dose
  - Stool frequency (spontaneous bowel movements, SBMs)
  - Completeness of evacuation (complete spontaneous bowel movements, CSBMs)
  - Stool consistency (Bristol stool form scale, BSFS)
  - Straining (7-category scale)
  - Abdominal Discomfort (6-category scale)

Results - Demographics

Table 1: Summary of Subject Demographics

	Placebo	0.3 mg	1.0 mg	3.0 mg	9.0 mg
Age*	47.7 (14.6)	51.1 (11.9)	50.5 (10.6)	48.5 (16.1)	47.3 (12.7)
Gender					
Female	18 (90%)	12 (85.7%)	14 (100%)	13 (86.7%)	12 (80%)
Male	2 (10%)	2 (14.3%)	0 (0%)	2 (13.3%)	3 (20%)
Race					
Caucasian	17 (85%)	13 (92.9%)	12 (85.7%)	14 (93.3%)	12 (80%)
African Am	1 (5%)	0	1 (7.1%)	0	2 (13.3%)
Asian Am	1 (5%)	1 (7.1%)	1 (7.1%)	0	1 (6.7%)
Am Indian	1 (5%)	0	0	0	0
Other	0	0	0	1 (6.7%)	0

* Mean (SD)
Am = American

Results - Safety

- No detectable systemic absorption of plecanatide (assay sensitivity > 10 ng/mL)
- No serious adverse events (SAE) reported in subjects receiving plecanatide
- No deaths reported in this study
- % subjects who reported AEs considered related to treatment
  - Placebo 10% (2/20)
  - Plecanatide 17.2% (10/58)
- % subjects who reported GI-related AEs
  - Placebo 10% (2/20)
  - Plecanatide 8.6% (5/58)
- Majority of adverse events (AE) were mild / moderate and transient in nature
- No diarrhea reported for any subject receiving plecanatide
  - 1 subject on placebo discontinued from the study due to diarrhea

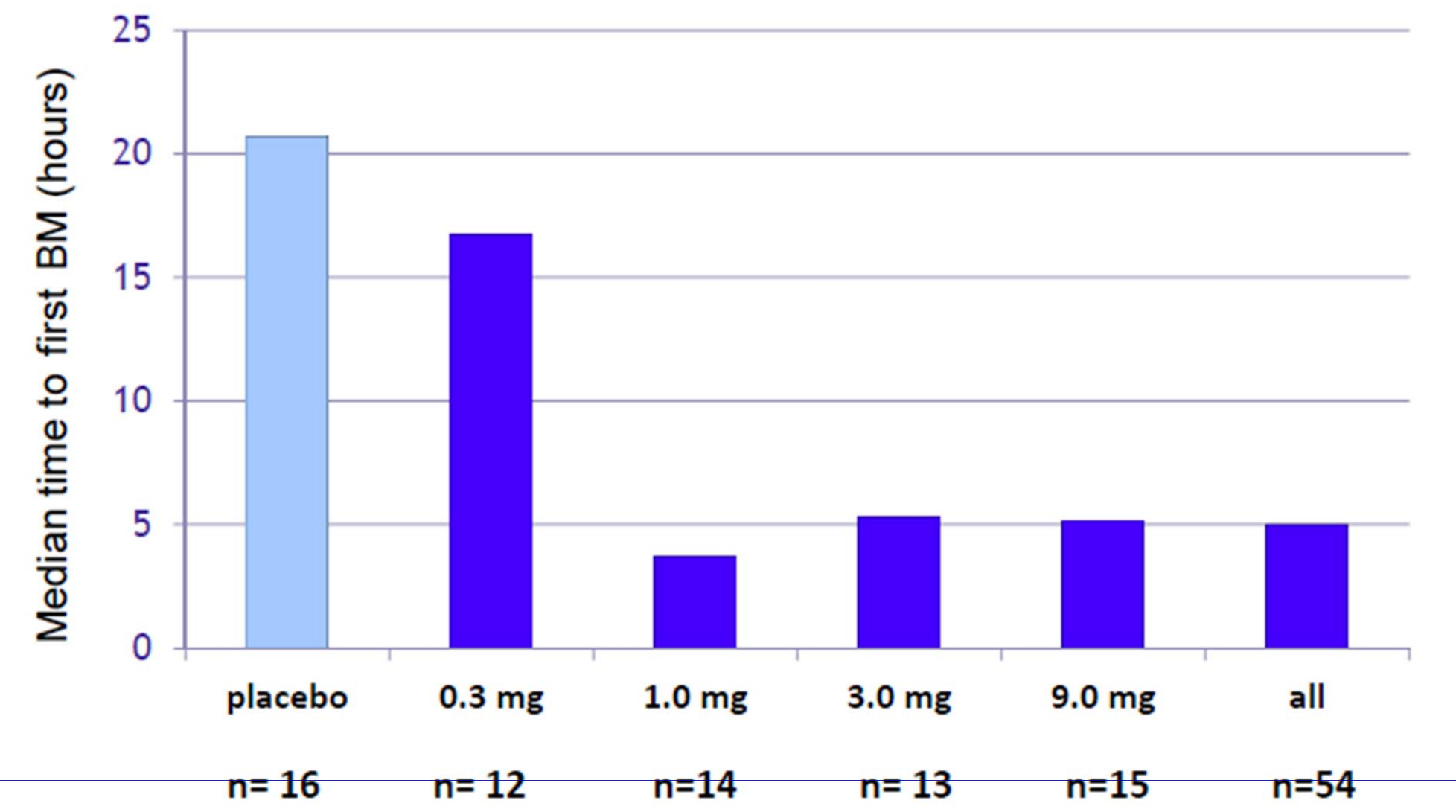
Table 2: GI-Related Adverse Event Summary with Relationship to Treatment

AE	Placebo n=20	0.3 mg n=14	1.0 mg n=14	3.0 mg n=15	9.0 mg n=15
Ab Cramping	1 (5.0%)	0	0	0	0
Ab Pain	1 (5.0%)	0	0	0	0
Bloating	0	0	0	0	1 (6.7%)
Diarrhea	1 (5.0%)	0	0	0	0
Flatulence	2 (10.0%)	0	0	0	0
Nausea	0	1 (7.1%)	0	0	1 (6.7%)
Tingling/mouth	0	0	0	1 (6.7%)	0

Ab = Abdominal

Results - Efficacy

Figure 4: Plecanatide reduces the time to first bowel movement Median reduction in time to first BM (hours)



Results – Efficacy (con't)

Figure 5: Change from Baseline in Spontaneous Bowel Movements (SBM) after 14-Days of Treatment (Per Protocol Population)

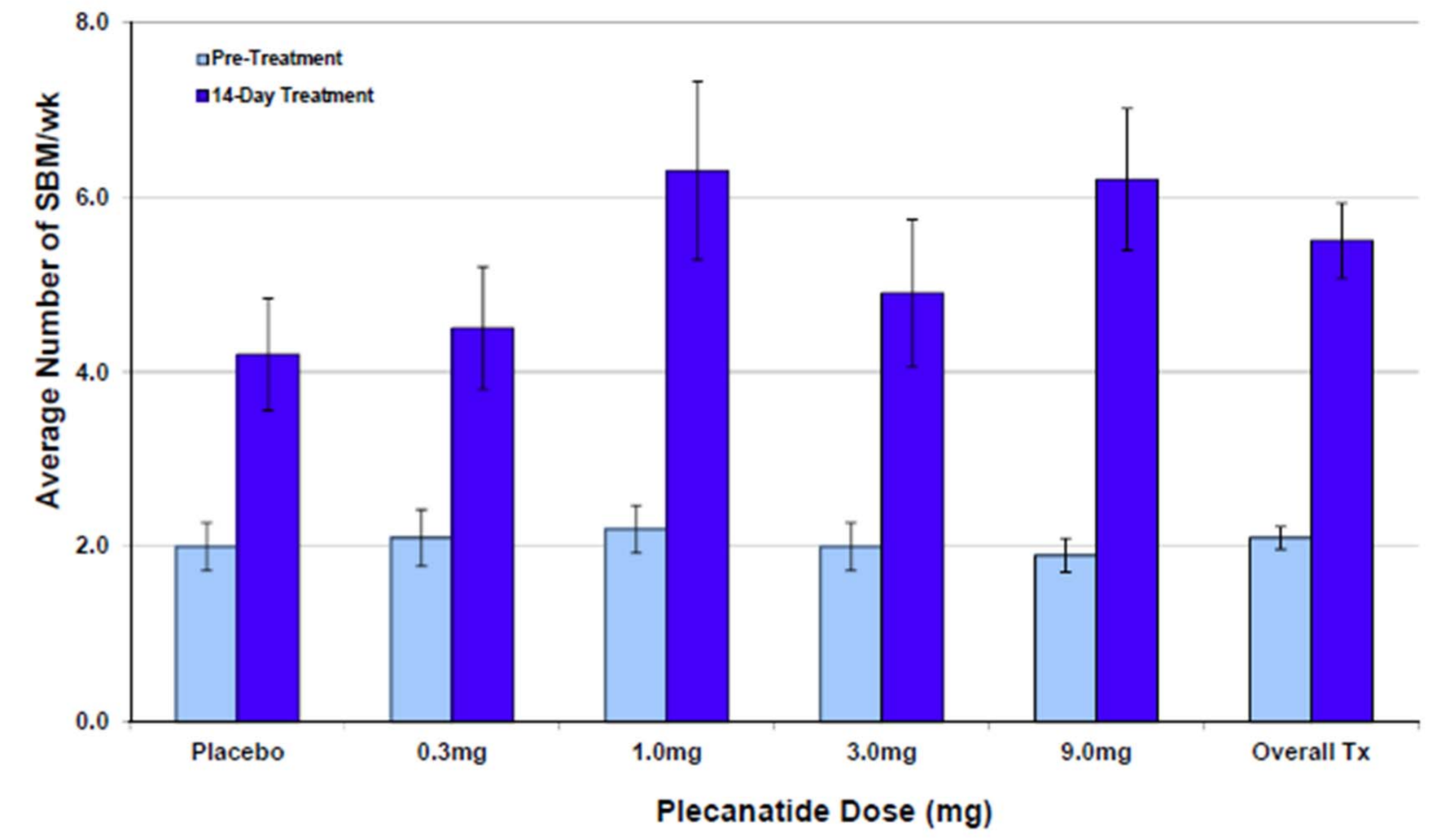


Figure 6: Change from Baseline in Complete Spontaneous Bowel Movements (CSBM) after 14-Days of Treatment (Per Protocol Population)

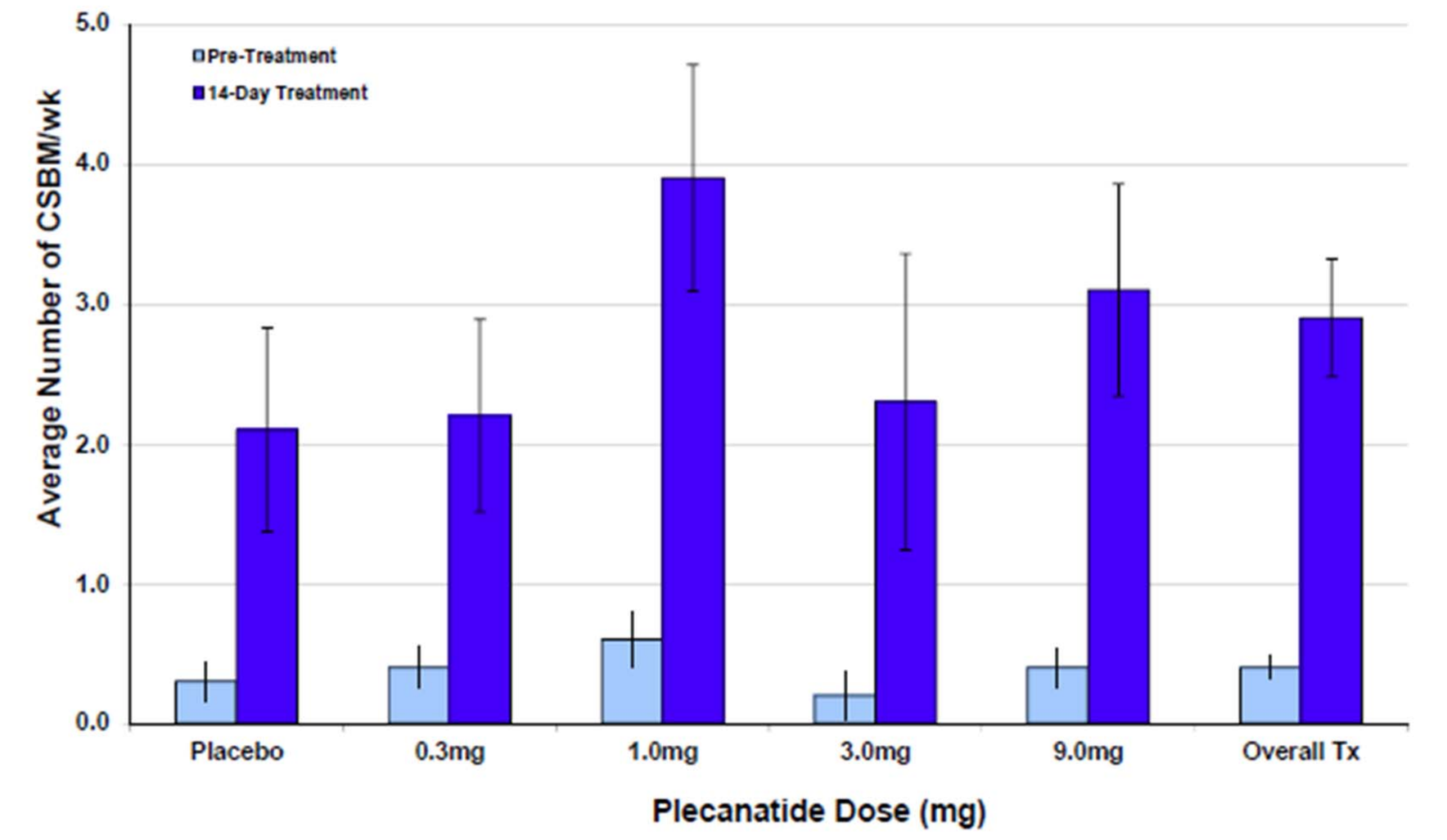
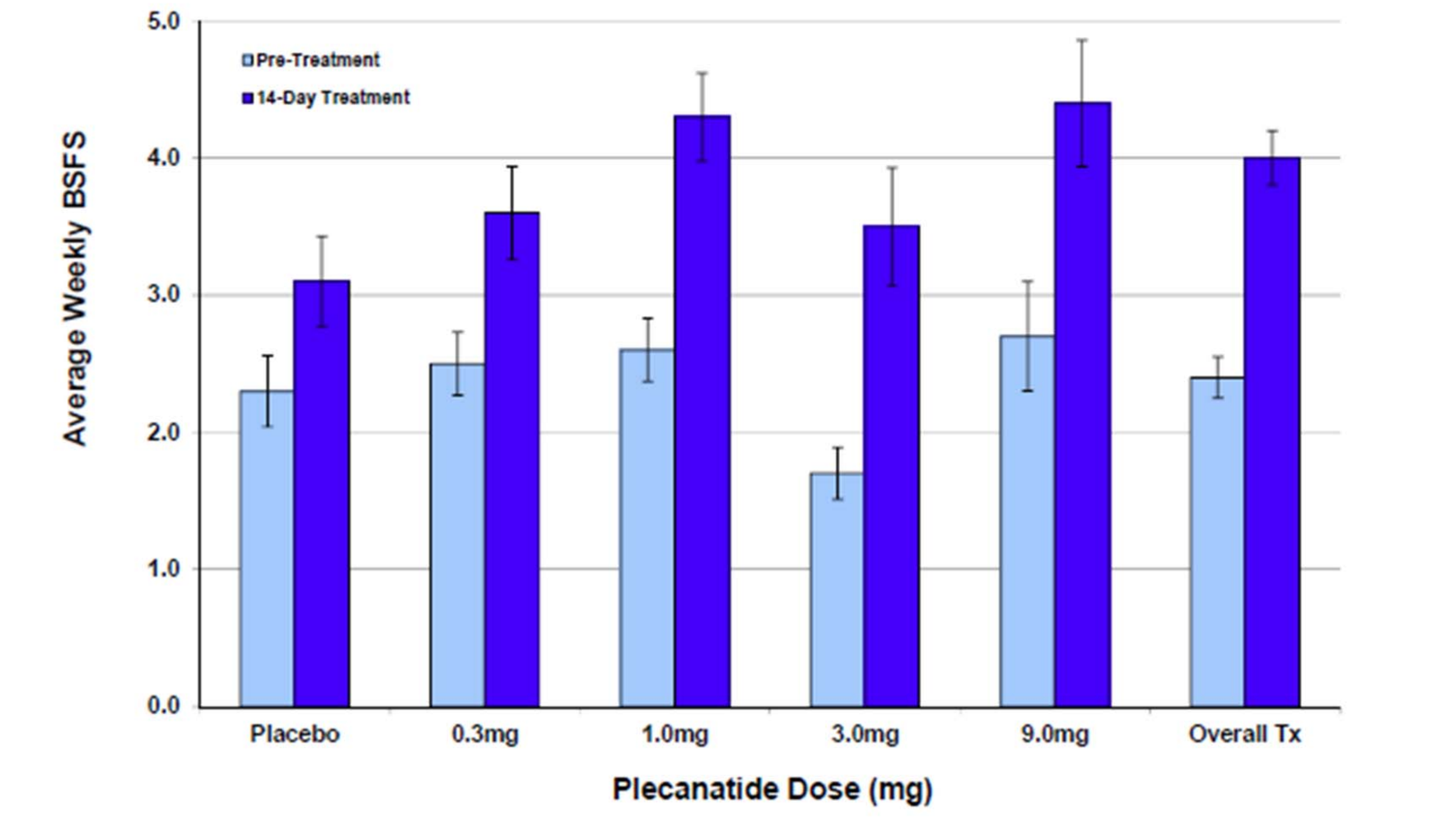


Figure 7: Change from Baseline in Bristol Stool Form Score (BSFS) after 14-Days of Treatment (Per Protocol Population)



Results – Efficacy (con't)

Figure 8: Change from Baseline in Straining Scores after 14-Days of Treatment (Per Protocol Population)

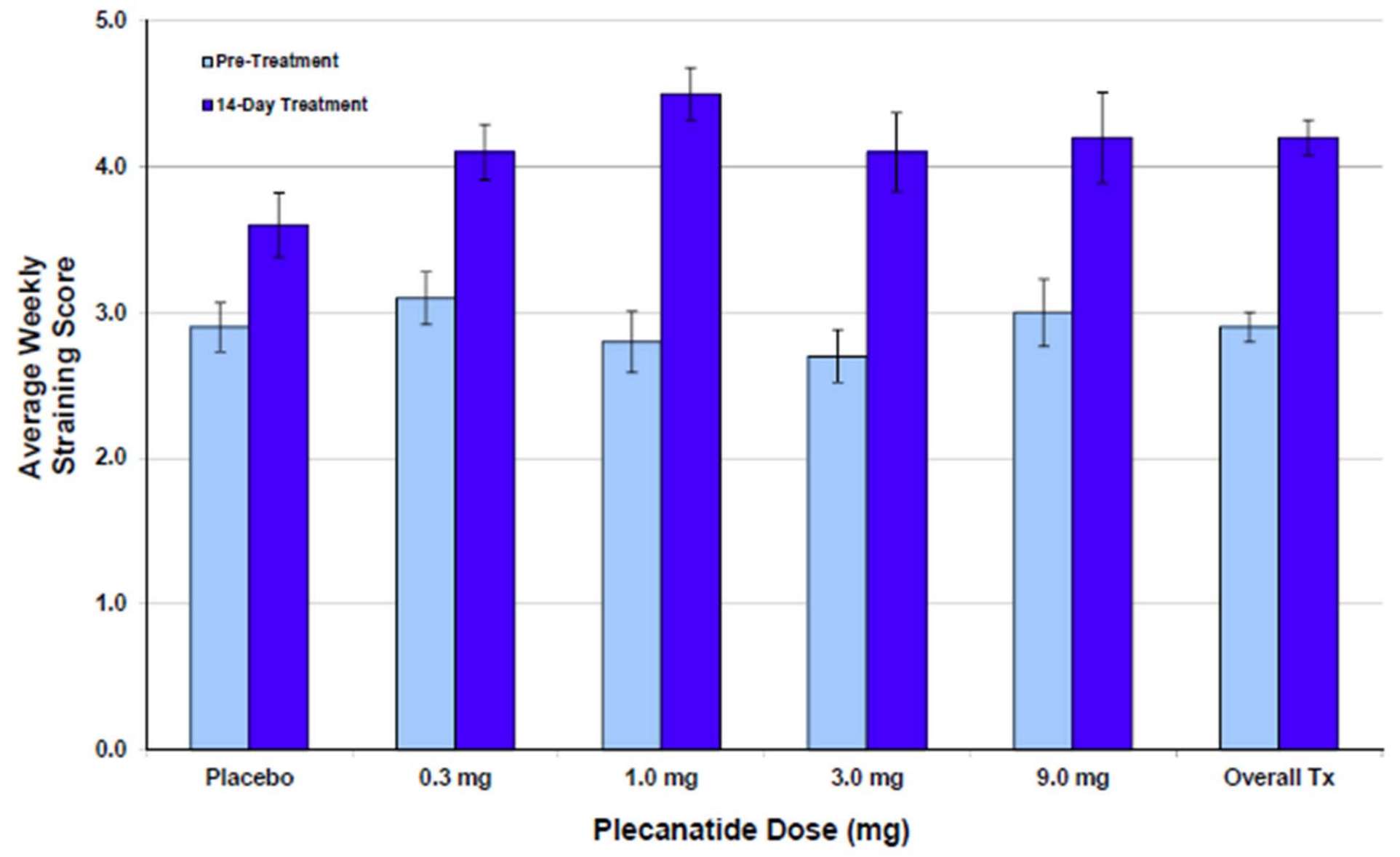
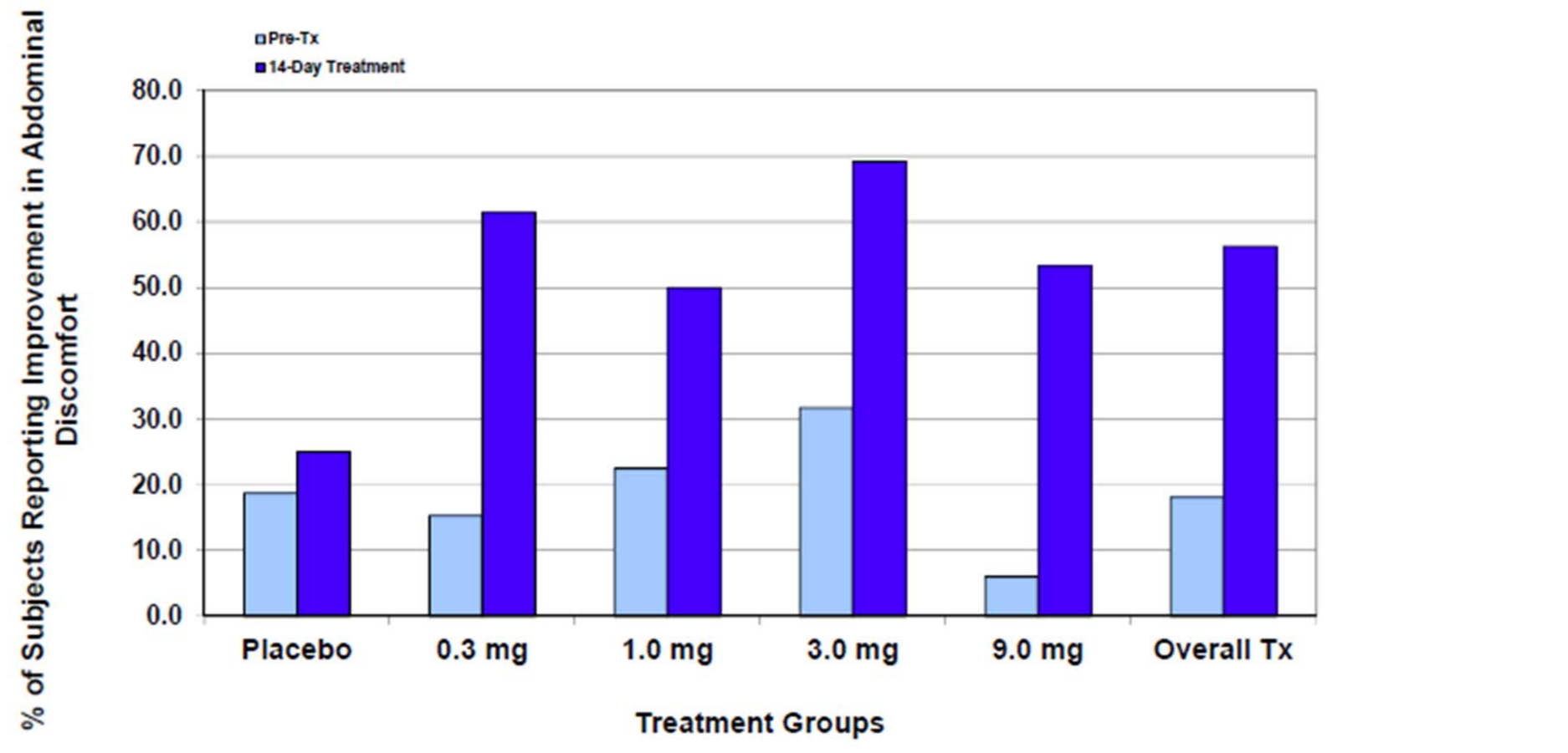


Figure 9: Percent of Subjects Reporting Improvements in Abdominal Discomfort Scores after 14-Days of Treatment (Per Protocol Population)



Conclusions

- There was no detectable systemic absorption of plecanatide at any dose up to 9 mg (assay sensitivity: 10 ng/mL)
- The safety profile demonstrated minimal adverse events
- No SAEs reported in subjects receiving plecanatide
- No reports of diarrhea in subjects who received plecanatide
- All plecanatide groups reported a significant decrease in time to first bowel movement
- Plecanatide demonstrated increases in stool frequency (SBM and CSBM)
- Plecanatide improved stool consistency, reduced straining and reduced abdominal discomfort

Disclosures Appendix

Analyst Certification

The analyst primarily responsible for this research report, and whose name appears on the front cover, certifies that: (i) all of the views expressed in this research report accurately reflects his or her personal views about any and all of the subject securities or issuers featured in this report; and (ii) no part of any of the research analyst's compensation was, is, or will be, directly or indirectly related to the specific recommendations or views expressed by the research analyst in this report.

Legal Disclosures

Lead or Co-manager: Cantor Fitzgerald and/or its affiliates, has acted as lead or co-manager in a public offering of equity and/or debt securities for Synergy Pharmaceuticals, Inc. within the last 12 months

Investment banking (last 12 months): Cantor Fitzgerald and/or its affiliates has received compensation for investment banking services in the last 12 months from Synergy Pharmaceuticals, Inc..

Investment banking (next 3 months): Cantor Fitzgerald and/or its affiliates, expect to receive, or intend to seek, compensation for investment banking services within the next three months from all of the companies referenced within this report.

Cantor Fitzgerald and/or its affiliates is a market maker in Synergy Pharmaceuticals, Inc..

Lead or Co-manager: Cantor Fitzgerald and/or its affiliates, has not acted as lead or co-manager in a public offering of equity and/or debt securities for Forest Laboratories, Inc. within the last 12 months

Cantor Fitzgerald and/or its affiliates has not received compensation for investment banking services in the last 12 months from Forest Laboratories, Inc..

Cantor Fitzgerald and/or its affiliates is a market maker in Forest Laboratories, Inc..

Lead or Co-manager: Cantor Fitzgerald and/or its affiliates, has not acted as lead or co-manager in a public offering of equity and/or debt securities for Ironwood Pharmaceuticals, Inc. within the last 12 months

Cantor Fitzgerald and/or its affiliates has not received compensation for investment banking services in the last 12 months from Ironwood Pharmaceuticals, Inc..

Cantor Fitzgerald and/or its affiliates is a market maker in Ironwood Pharmaceuticals, Inc..

Lead or Co-manager: Cantor Fitzgerald and/or its affiliates, has not acted as lead or co-manager in a public offering of equity and/or debt securities for Salix Pharmaceuticals, Ltd. within the last 12 months

Cantor Fitzgerald and/or its affiliates has not received compensation for investment banking services in the last 12 months from Salix Pharmaceuticals, Ltd..

Cantor Fitzgerald and/or its affiliates is a market maker in Salix Pharmaceuticals, Ltd..

Cantor Fitzgerald's rating system

BUY: We have a positive outlook on the stock based on our expected 12 month return relative to its risk. The expected return is based on our view of the company and industry fundamentals, catalysts, and valuation. We recommend investors add to their position.
HOLD: We have a neutral outlook on the stock based on our expected 12 month return relative to its risk. The expected return is based on our view of the company and industry fundamentals, catalysts, and valuation.
SELL: We have a negative outlook on the stock based on our expected 12 month return relative to its risk. The expected return is based on our view of the company and industry fundamentals, catalysts, and valuation. We recommend investors reduce their position.
NC: Not Covered. Cantor Fitzgerald does not provide an investment opinion or does not provide research coverage on this stock.

Prior to September 12, 2006, Cantor Fitzgerald had the below ratings:
BUY - denotes stocks that we expect will provide a total return (price appreciation plus yield) of 15% or more over a 12-month period. a BUY rated stock is expected to outperform the total average return of analyst's industry coverage universe on a risk adjusted basis.
HOLD - denotes stocks that we suggest will provide a total return or total negative return of up to 15% over 12-month period. A HOLD rated stock is expected to perform in-line with the total average return of the analyst's industry coverage universe on a risk adjusted basis.
SELL - denotes stocks that we expect to provide a total negative return of more than 15% over a 12 month period. A SELL rated stock is expected to underperform the total average return of the analyst's industry coverage universe on a risk adjusted basis.
NC - Not Covered. Cantor Fitzgerald does not provide research coverage on this company.

Other Disclosures

This report is for informational purposes only and is based on publicly available data believed to be reliable, but no representation is made that such data are accurate or complete. Opinions and projections contained herein reflect our opinion as of the date of this report and are subject to change. Pursuant to Cantor Fitzgerald's policy, the author of this report does not own shares in any company he/she covers.

Additional material for UK investors

This material is approved for distribution in the United Kingdom by Cantor Fitzgerald Europe, regulated by the Financial Services Authority (FSA). While we believe this information and the materials upon which this information was based is accurate, except for any obligations under the rules of

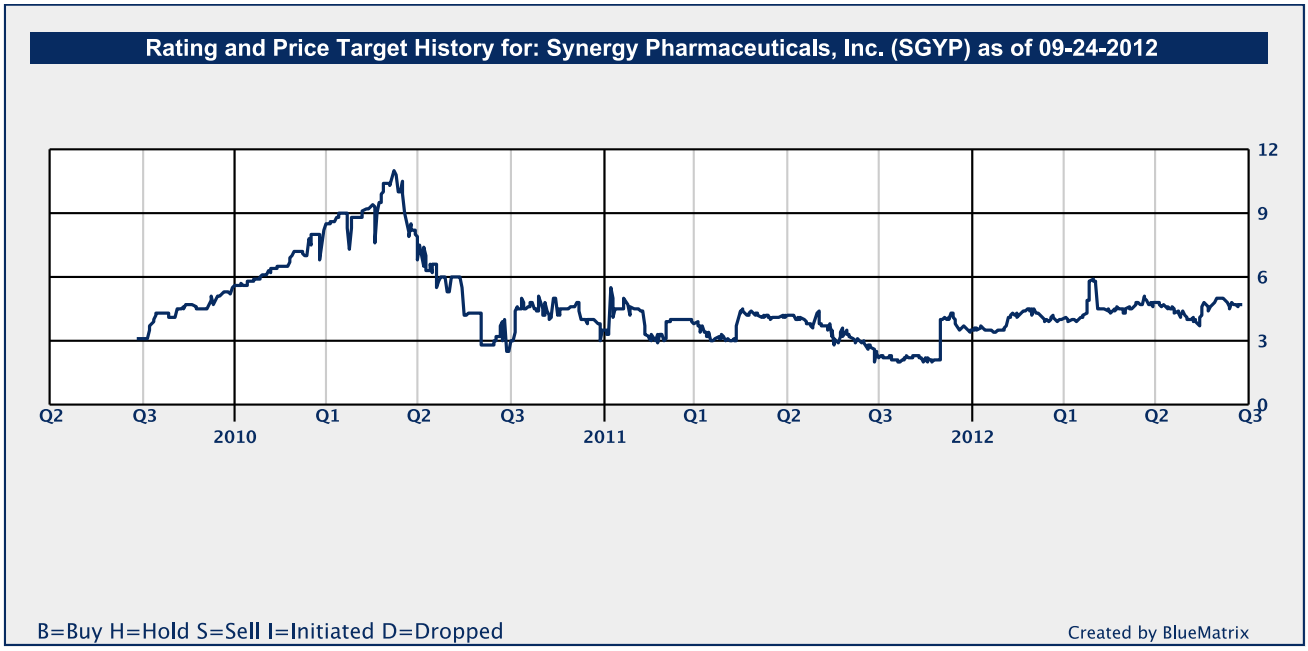
the FSA, we do not guarantee its accuracy. This material is only intended for use by professionals or institutional investors who fall within articles 19 or 49 of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2001 and not the general investing public. None of the investments or investment services mentioned or described herein are available to other persons in the U.K and in particular are not available to "private customers" as defined by the rules of the FSA.

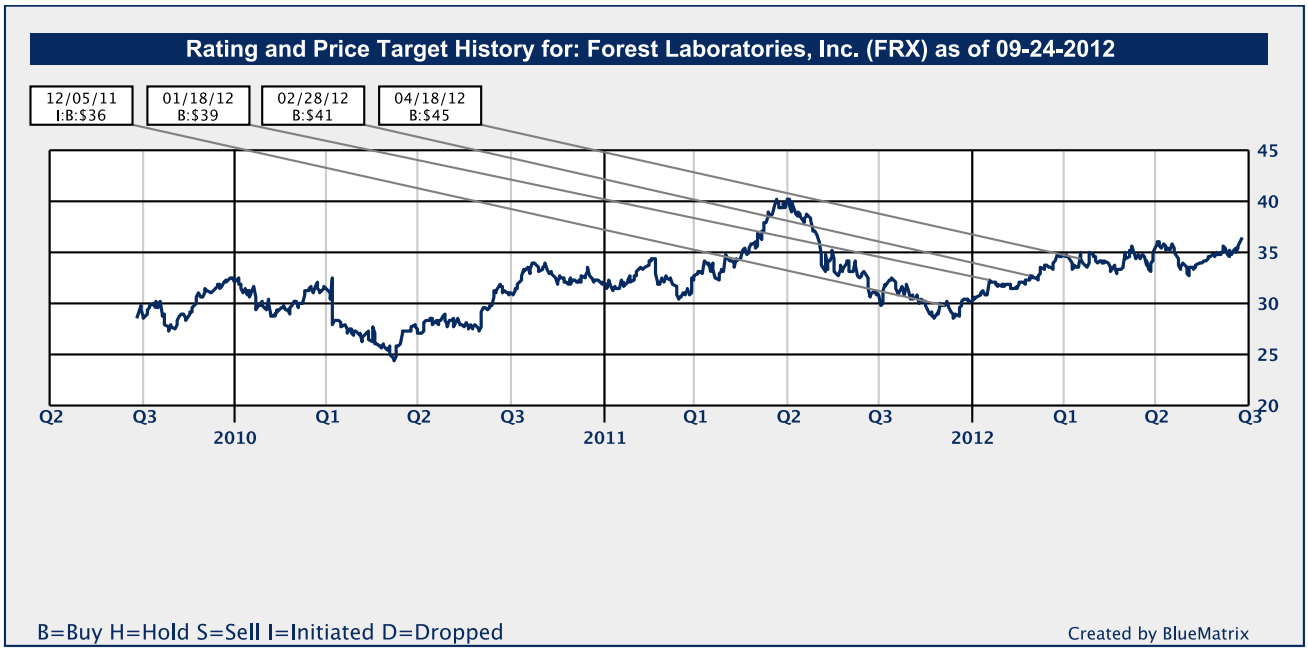
Disclosure for Canadian Institutional Investors

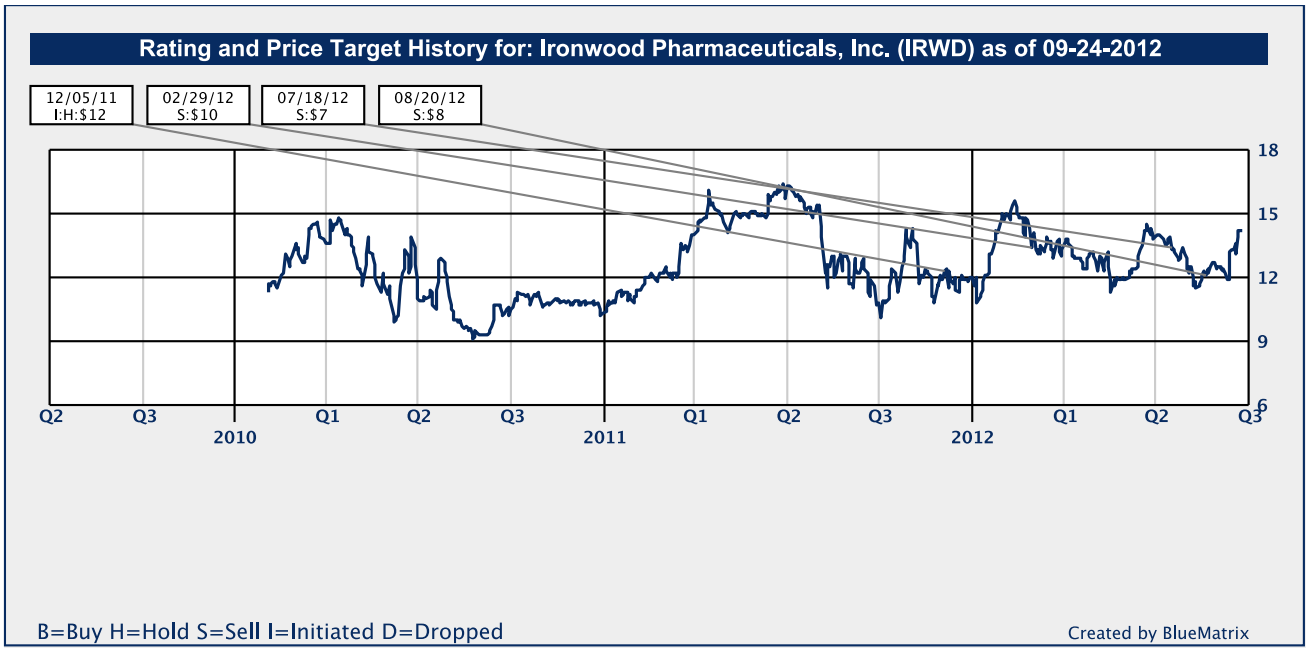
This research report was prepared by analysts of Cantor Fitzgerald & Co. and not by Cantor Fitzgerald Canada Corporation. As a result this report has not been prepared subject to Canadian Disclosure requirements. Cantor Fitzgerald Canada Corporation itself does not issue research reports but may distribute research reports prepared by its affiliates.

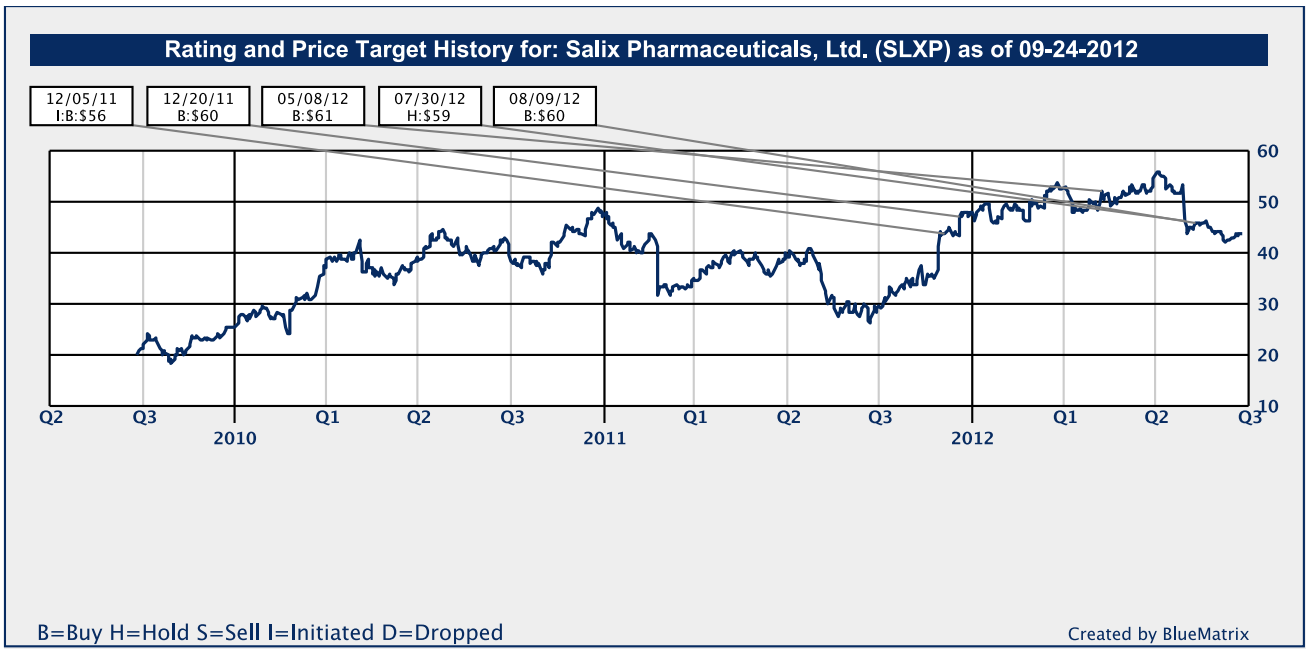
Risks

The financial instruments discussed in this report may not be suitable for all investors and investors must make their own investment decisions based on their specific investment objectives. Past performance should not be taken as an indication or guarantee of future performance. The price, value of and income from, any of the financial instruments featured in this report can rise as well as fall and be affected by changes in economic, financial and political factors. If a financial instrument is denominated in a currency other than the investor's currency, a change in exchange rates may adversely affect the price or value of, or income derived from, the financial instrument, and such investors effectively assume currency risk. In addition, investors in securities such as ADRs, whose value is affected by the currency of the home market of the underlying security, effectively assume currency risk.









Distribution of Ratings/Investment Banking Services (IB) as of 09/25/12

Cantor

Rating	Count	Percent	IB Serv./Past 12 Mos. Count	IB Serv./Past 12 Mos. Percent
BUY [B]	79	51.30	13	16.46
HOLD [H]	64	41.56	3	4.69
SELL [S]	11	7.14	0	0.00