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Life Sciences -- Biotechnology

Synergy Pharmaceuticals

Initiating at BUY, $7 target: Fast follower into the GC-C market

BUY

SGYP : NASDAQ : US$3.67

TARGET PRICE: US$7.00

Inside

Investment recommendation

Initiating at BUY with $7 target on unmet need in severe chronic constipation and plecanatide's potential superior tolerability. We see clear unmet need for the large proportion of chronic constipation patients non-responsive to current therapies and the smaller proportion that experience severe diarrhea with linaclotide (Linzess). Compared to recently approved Linzess (Forest/Ironwood), plecanatide may have better tolerability, with no diarrhea signal seen in Phase 2a. Data from the Phase 2b/3 trial is due by YE12, and if safety continues to be clean we expect wide use in severe chronic constipation, noting the market for severe idiopathic constipation may be limited.

Investment highlights

- **Chronic constipation (CC) is highly prevalent with unmet need in severe patients.** CC is estimated to affect up to 15% of the US population. While most patients with CC do not seek prescriptions, CC still leads to ~2.5M physician visits per year. Of patients with severe disease who failed prior OTC treatments, ~70% are unsatisfied with current treatment options.
- **Plecanatide safety/tolerability so far is superior to first-in-class GC-C receptor Linzess (linaclotide, Forest/Ironwood).** GC-C receptor agonists mimic the endogenous gut hormone uroguanylin to stimulate fluid secretion into the intestine. Linzess was the 1st GC-C agonist approved by FDA, and launch is expected in Q4/12. Plecanatide has shown similar efficacy to Linzess in a Phase 2a trial. Unlike Linzess, which has a diarrhea warning included in the label, no diarrhea was reported in the plecanatide arms of the Phase 2a trial.
- **Phase 2b/3 trial ongoing; we expect positive data by year-end 2012.** The trial, designed as a pivotal trial, enrolled ~880 patients and will evaluate plecanatide over 12 weeks. If Phase 3 efficacy is comparable and safety profiles continue to be favorable, we see plecanatide as potentially superior to Linzess, especially for patients that have issues with GI-related tolerability. If approved, we would expect fairly rapid uptake: Linzess' launch will have established disease and treatment class awareness that Synergy would be able to take advantage of.

Company statistics

Shares Out (M):	65.8
Market Cap (M):	US$242
52-week Range:	US$3.17 - 7.08

Price chart

Earnings summary

FYE Dec		2011A	2012E	2013E
Revenue:		0.0	0.0	0.0
EPS:		(0.30)	(0.60)	(0.59)
Revenue:	Q1	0.0	0.0A	-
	Q2	0.0	0.0A	-
	Q3	0.0	0.0	-
	Q4	0.0	0.0	-
Total		0.0	0.0	0.0
EPS:	Q1	(0.08)	(0.13)A	-
	Q2	(0.10)	(0.17)A	-
	Q3	(0.01)	(0.15)	-
	Q4	(0.12)	(0.15)	-
Total		(0.30)	(0.60)	(0.59)

Company description

Synergy Pharmaceuticals is a developmental stage biopharmaceutical company that focuses on the development of drugs to treat gastrointestinal disorders. Synergy's lead investigational drug, plecanatide, is an analogue of urogyanylin, a natural hormone, and activates GC-C receptors that increase the flow of water into the intestine. Plecanatide is currently being tested in a Phase 2b/3 trial in patients with chronic constipation, with top-line data due by the end of 2012.

Figure 1: SGYP pipeline

Drug/Program	Disease	Licensing/ Partnership	Preclinical	Phase 1	Phase 2	Phase 3	Post-Marketing
plecanatide (GC-C agonist)	Chronic Constipation	Wholly owned					
plecanatide (GC-C agonist)	IBS-C	Wholly owned					
sp-333 (GC-C agonist)	Ulcerative colitis	Wholly owned					
FV-100 (oral anti-viral)	Shingles	Wholly owned					

Source: Company reports and Canaccord Genuity estimates

INVESTMENT THESIS

We believe Synergy's plecanatide could become an important treatment option for chronic idiopathic constipation and IBS-C

We think plecanatide, Synergy's Phase 2/3 guanylin/uroguanylin analogue, could become a very important treatment option for chronic idiopathic constipation (CIC) and likely constipation predominant IBS (IBS-C). We believe the drug's structure (imparting improved stability), mechanistic rationale and early Phase 1 and 2 data suggest that the drug has meaningful clinical activity and excellent safety. Based on biological rationale, we think the drug should be equally efficacious and safe in IBS-C.

Mechanism rationale and early clinical data suggest plecanatide could have a different drug profile from Linzess, the first approved GCC agonist

Plecanatide is a very close analogue of the natural gut hormones guanylin and uroguanylin, which work through the activation of the GC-C receptor, which increases intracellular cGMP and results in fluid secretion into the lumen of the gut. The single peptide substitution confers increased stability and a longer half-life at body temperatures compared to the natural hormone. Linzess, while also resembling guanylin/uroguanylin, more closely resembles heat stable toxins secreted by gut bacteria that can cause infectious diarrhea. Linzess causes a stronger than natural signal at the GC-C receptor which may be the cause of the relatively high (15-20%) diarrhea rate associated with the drug. We think that since plecanatide results in more natural signaling at the GC-C receptor, it would be associated with significantly less diarrhea although we do acknowledge that this could simultaneously result in more moderate efficacy.

We think plecanatide could be an important treatment option for CIC patients who cannot or are unwilling to tolerate Linzess' treatment-associated diarrhea

We believe there is a significant proportion of CIC patients that cannot tolerate the GI symptoms associated with Linzess therapy. We note that ~16% of patients in the Linzess Phase 3 trials reported diarrhea, with another 5-10% reporting other GI side effects such as bloating and abdominal pain. Further, ~5% of patients dropped out of the Phase 3 trials due to diarrhea, and about 26% of patients dropped out of the open-label extension study due to diarrhea. We think these patients represent a meaningful proportion of overall CIC and IBS-C patients that want a more tolerable treatment even if it has slightly less efficacy than Linzess. We think plecanatide has a good chance of providing this treatment profile.

We also think plecanatide could become an important treatment option for IBS-C patients for the same reason as for CIC patients

We think Linzess showed similar efficacy between its Phase 3 program in CIC and IBS-C and has shown proof of concept for GC-C agonists in IBS-C. In fact, Linzess showed optically slightly better efficacy than in CIC as well a statistically significant dose response that was not shown in the CIC Phase 3 program. As such, we think CIC may be the harder of the two related conditions to treat. Further, we note that while abdominal pain is a large part of IBS-C's constellation of symptoms, it is also a GI side effect that is sometimes associated with Linzess. Should plecanatide prove to have better GI

tolerability, this drug could prove to have a preferable tolerability profile among IBS-C patients, especially during disease episodes without severe constipation.

Together, CIC and IBS-C likely represent such a large market opportunity that even a 10-15% market share could result in blockbuster plecanatide sales.

While the estimates for prevalence of functional constipation vary greatly, the mean estimate across studies for chronic idiopathic constipation is acknowledged to be about 15%. The condition is more prevalent in the elderly, so the overall US prevalence is growing as the population ages. Even though only about ~10% of CIC patients experience symptoms problematic enough to seek treatment, this still represents over 3 million patients seeking an effective drug therapy. We do not think a safe, effective long-term treatment exists for the majority of these patients today, resulting in a significant unmet medical need that could drive plecanatide sales, which we estimated could reach ~$400MM at peak for each CIC and IBS-C, using modest 12% penetration assumption of those patients seeking treatment.

Figure 2: SGYP upcoming catalysts

Expected date	Drug/Program	Item	Impact
YE2012	Plecanatide in CC	Top-line data from Ph2/3 trial in CC	+++
Q4/12	Plecanatide in IBS-C	Initation of Phase2b trial in IBS-C	+
H1/13	SP-333 in ulcerative colitis	Initation of Phase 1 MAD study in hea	+
Q2/12	Plecanatide in CC	Expected intiation of Ph3 in CC	+

Source: Company reports and Canaccord Genuity estimates

INVESTMENT RISKS

Clinical risk – Plecanatide's Phase 2/3 trial may not show statistical significance in CIC clinical measures

Plecanatide showed trends in improvement in many measure of CIC symptoms, including patient reported outcomes in its Phase 2a. Data, however, did not reach statistical significance, nor did it show clear dose-dependent activity in functional outcomes and measures. However, we note that patient numbers in this trial were very small, with less than 20 patients per dose group, which led to very poor statistical powering.

Clinical risk – Plecanatide's Phase 2/3 trial may not show a magnitude of clinical benefit or sufficiently improved safety to represent an improved therapy compared to Linzess

Linzess' Phase 3 trials showed clear statistically significant clinical benefit in all of its primary and secondary endpoints. The drug resulted in a mean increase of 1.5 complete spontaneous bowel movements (CSBMs) and a ~35% rate in CIC and IBS-C patients. Should plecanatide ultimately show a smaller than 1.0 placebo adjusted benefit in CSBMs or less than a 30% responder rate, or a higher rate of GI symptoms, clinicians and patients may deem the drug to be therapeutically inferior to Linzess, adversely impacting its chance of both regulatory and commercial success.

Regulatory risk – FDA may require Synergy to conduct two additional Phase 3 clinical trials in CIC to secure approval for that indication

Synergy has indicated that plecanatide's current Phase 2/3 trial is adequately powered to show statistical significance in the primary endpoint, which is also one of Linzess' registrational primary endpoints. However the standalone trial, which has close to 900 patients, is still smaller than the full Linzess CIC clinical program which had about 1600 patients total. As such, we think it likely that FDA will ask for another formal Phase 3 trial in CIC and note that there may be a chance that they may be unsatisfied with the design of the current Phase 2/3 trial and may require a second formal Phase 3 trial as well. We think this may only be the case should the Ph2/3 be statistically weak.

Commercial risk – Linzess will represent an establish and potentially entrenched for CIC and IBS-C when plecanatide may be approved

Ironwood and US partner Forest are currently planning to commercially launch Linzess in December 2012, and pre-launch marketing activities are already underway. We think this may give Linzess close to a three-year commercial head-start on plecanatide. During this time, we think clinicians will develop significant treatment experience and prescribing familiarity and/or comfort with the drug. We also think Linzess will have accumulated a meaningful market share by this point, and many may be averse to switching therapies. However, we believe that there will still be a significant proportion of patients that are treatment naïve or dissatisfied with Linzess treatment due to its side effect profile. We think these patients will provide enough market opportunity for plecanatide to meet our current market estimates.

Financing risk – Synergy may choose to raise cash to fund plecanatide and other pipeline clinical and regulatory development through an equity offering or other methods

We believe Synergy has close to 18 months of operating cash on its balance sheet, which should fund the company through upcoming Phase 2/3 plecanatide CIC data. However, this operating capital is unlikely to last through another plecanatide Phase 3 CIC trial or fund complete Phase 3 development of plecanatide for IBS-C.

VALUATION

We have built our valuation of Synergy Pharmaceuticals using a probability-weighted NPV model of peak sales.

Potential upside to valuation

We see the following as potential drivers of upside to our model:

- **Strong-than-expected clinical efficacy data from plecanatide's Phase 2/3 and Phase 3 trials.** Based in mechanistic rationale, we think that plecanatide may have milder (yet still clinically meaningful) benefit in CIC and IBS-C than Linzess. Should clinical data suggest that plecanatide has as good if not better clinical data than Linzess, plecanatide could become the best-in-class GC-C therapy, achieve greater market penetration and peak sales than we are estimating, driving additional value.

- **Partner-driven fast commercial uptake and higher-than-expected peak market penetration.** Should Synergy strike a commercial partnership for plecanatide with a strong commercial partner, the drug could become the market leader for this drug class given the promotion-sensitivity of the primary care market care. This could raise peak sales beyond our estimates and also drive upside to our current valuation, even with partnership economics.

Potential downside to valuation

As with all companies in commercial and clinical development, there always exists the risk of failed or inconclusive clinical trials, slower-than-expected commercial launch or lower-than-expected peak sales, which would lead to downward pressure on the stock.

REVENUE MODEL AND VALUATION

Figure 3: Plecanatide market and revenue model

US - Tedizolid in ABSSSI													
		2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
US Population (M)	1%	314.7	317.9	321.0	324.2	327.5	330.8	334.1	337.4	340.8	344.2	347.6	351.1
Functional Constipation													
Patients w/ Functional Constipatio	12%	37.76	38.14	38.52	38.91	39.30	39.69	40.09	40.49	40.89	41.30	41.72	42.13
Patients seeking Rx treatment	10%	3.78	3.81	3.85	3.89	3.93	3.97	4.01	4.05	4.09	4.13	4.17	4.21
plecanatide market share				*0.00%*	*0.00%*	*0.50%*	*1.00%*	*3.00%*	*6.00%*	*8.00%*	*9.00%*	*10.00%*	*11.00%*
CC patients on plecanatide				-	-	19,649	39,691	120,265	242,935	327,152	371,727	417,160	463,465
Cost per day	5%			$ 3.60	$ 3.78	$ 3.97	$ 4.17	$ 4.38	$ 4.59	$ 4.82	$ 5.07	$ 5.32	$ 5.58
Annual days on treatment				150	150	150	150	150	150	150	150	150	150
Revenue per patient				$ 540.00	$ 567.00	$ 595.35	$ 625.12	$ 656.37	$ 689.19	$ 723.65	$ 759.83	$ 797.83	$ 837.72
Total US Revenue				**$ -**	**$ -**	**$ 11.70**	**$ 24.81**	**$ 78.94**	**$ 167.43**	**$ 236.74**	**$ 282.45**	**$ 332.82**	**$ 388.25**
IBS-C													
Patients w/ IBS-C	5%	15.74	15.89	16.05	16.21	16.37	16.54	16.70	16.87	17.04	17.21	17.38	17.56
Patients seeking Rx treatment	22%	3.46	3.50	3.53	3.57	3.60	3.64	3.67	3.71	3.75	3.79	3.82	3.86
plecanatide market share				*0.00%*	*0.00%*	*0.50%*	*1.00%*	*3.00%*	*6.00%*	*8.00%*	*9.00%*	*10.00%*	*11.00%*
CC patients on plecanatide				-	-	18,012	36,384	110,243	222,690	299,889	340,749	382,397	424,843
Cost per day	5%			$ 3.60	$ 3.78	$ 3.97	$ 4.17	$ 4.38	$ 4.59	$ 4.82	$ 5.07	$ 5.32	$ 5.58
Annual days on treatment				175	175	175	175	175	175	175	175	175	175
Revenue per patient				$ 630.00	$ 661.50	$ 694.58	$ 729.30	$ 765.77	$ 804.06	$ 844.26	$ 886.47	$ 930.80	$ 977.34
Total US Revenue				**$ -**	**$ -**	**$ 12.51**	**$ 26.53**	**$ 84.42**	**$ 179.06**	**$ 253.18**	**$ 302.07**	**$ 355.93**	**$ 415.21**

Source: Canaccord Genuity estimates

Figure 4: SGYP valuation

Drug name	Indication	Status	Launch	Years to Launch	Years to Launch plus 7	Success	Sales (US$m)	Probability weighted Peak Sales (US$m)	Royalty	Profitability	Probability weighted Peak Profit (US$m)	Discount Factor	NPV (US$)
US - Plecanatide	CC	Phase 3	2016	3	10	45%	282.5	127.1	100%	75%	95.33	6.48	3.24
US - Plecanatide	IBS-C	Phase 2	2016	3	10	45%	302.1	135.9	100%	75%	101.95	6.48	3.46
												Less debt:	0.00
										Total			**6.70**

Source: Company reports and Canaccord Genuity estimates

RECOMMENDATION

We see Synergy's GC-C agonist plecanatide as a promising new treatment for chronic idiopathic constipation as well as IBS-C. We think the drug will show clinically meaningful efficacy in both conditions with potentially greater tolerability than Linzess, the first GC-C agonist to market. We think the drug's mechanism, however, suggests that this increase in tolerability may come at the expense of slightly decreased clinical activity compared to Linzess.

We think plecanatide's current Phase 2/3 trial in CIC will yield positive statistically significant efficacy data by year-end 2012 along with very good tolerability. We believe Synergy will then hold a successful end-of-Phase 2 meeting with FDA in Q1/13 and receive clarity on additional required Phase 3 development. Should the current Phase 2/3 yield strongly significant data, we think there is a good chance that Synergy may only need to conduct only one additional Phase 3 trial. We would expect Synergy to start this trial in mid-2013 with data in H2/14, file in early 2015 and be approved in early 2016.

Should plecanatide prove to have our predicted therapeutic profile, we anticipate the drug to reach about 12% peak market penetration amongst the ~10% of chronic constipation patient that seek prescription therapy. We also believe it could capture about 12% peak market share of the 22% of IBS-C patients that seek prescription therapies. We strongly believe this market share will be driven by patient demand for a more tolerable long-term CIC and IBS-C therapy, even if it has slightly less functional benefit. We believe each of these markets represents peak market sales of about $400MM. We expect that sales for both indications will start in 2016 with the CIC approval, although IBS-C sales at this point would be off-label although likely supported by Phase 2 or even Phase 3 data. We would expect formal IBS-C approval to come in 2017 or early 2018.

COMPANY OVERVIEW

Synergy Pharmaceuticals is focused on the development of drugs to treat gastrointestinal disorders and diseases. Its current platform is focused on drug candidates based on the endogenous human hormone uroguanylin, which regulates fluid and inflammation in the digestive system. Its lead product candidate is plecanatide, a uroguanylin analogue guanylyl cyclase C (GC-C) receptor agonist. In a Phase 2a study in patients with chronic idiopathic constipation (CIC), plecanatide was shown to be minimally absorbed, effective and safe, with no detectable plasma concentrations and no SAEs reported at any dose. Importantly, no patients receiving plecanatide experienced diarrhea at any point during the study. Plecanatide showed positive trends in efficacy, increasing the number of bowel movements/week and improving stool consistency, key endpoints for approvability. Plecanatide is currently in a Phase 2b/3 trial in chronic idiopathic constipation with data due by the end of 2012. Synergy is also developing a second generation GC-C agonist, SP-333 in ulcerative colitis. Synergy plans to initiate Phase 1 trials before year-end 2012.

CHRONIC CONSTIPATION

Chronic constipation (CC) is characterized by infrequent bowel movements and difficult passage of stools. Chronic constipation can generally be divided into two categories, functional constipation or constipation dominant irritable bowel syndrome (IBS-C). IBC-C is characterized by chronic abdominal pain, discomfort, bloating, and constipation. Functional constipation is roughly defined as constipation without IBS associated symptoms (i.e., the high degree of abdominal pain). Both IBS-C and idiopathic chronic constipation are characterized by symptoms in the absence of tissue abnormalities or physical/mechanical pathology that could be responsible for reduced GI motility or bowel movements.

While not life-threatening, CC can have significant negative effects on a patient's quality of life. Generally, constipation from any cause is a result of dehydration of the fecal matter, as a result of intestinal osmotic imbalances or decreased intestinal motility (and resulting increases in colonic transit time).

CC and IBS are among the most common functional gastrointestinal disorders (FGIDs), with prevalence estimates ranging from 2% to 28% for CC and 3% to 20% for IBS, with an average of 15% – resulting in an estimated 10 million people in the US suffering from the disease. The prevalence of constipation tends to be higher in women than in men; the prevalence is 2.2 times higher in females. Additionally, the prevalence also tends to be higher in non-white populations.

Rome III diagnostic criteria for chronic constipation

The standardized diagnostic criteria for chronic constipation are known as the Rome III criteria, published in 2006, which were developed by the Rome Foundation to classify functional gastrointestinal disorders whose symptoms cannot be explained by the presence of structural or tissue abnormality The diagnostic criteria for IBS-C include abdominal discomfort or pain associated with two or more of the conditions listed in Figure 5 at least 25% of the time, as well as the absence of an inflammatory, anatomic,

metabolic, or neoplastic process that could explain the symptoms. The criteria for functional constipation (Figure 5) require that a patient has had two of the six listed symptoms, in addition to infrequent loose stools and insufficient criteria for IBS-C. The criteria must be fulfilled for the most recent three concurrent months, with symptom onset at least six months prior to diagnosis.

Figure 5: Rome III diagnostic criteria for chronic constipation and the Bristol Stool Form Scale

- Symptoms ≥3 mo; onset ≥6 mo prior to diagnosis

Functional Constipation	IBS-C
• Must include ≥2 of the following: – Straining* – Lumpy or hard stools* – Sensation of incomplete evacuation* – Sensation of anorectal obstruction/blockage* – Manual maneuvers to facilitate defecation (eg, digital evacuation, support of the pelvic floor)* – <3 defecations/wk • Loose stool rarely present w/o use of laxatives • Insufficient criteria for IBS-C	• IBS: Recurrent abdominal pain/discomfort ≥3 d/mo for the past 3 mo, associated with ≥2 of the following: – Improvement with defecation – Onset associated with change in stool frequency – Onset associated with change in stool form • IBS is subtyped by predominant stool pattern – IBS-C: hard or lumpy stools† ≥25% of defecations; loose or watery stools‡ <25% of defecations§

*≥25% of defecations. †Bristol Stool Form Scale 1–2: separate, hard lumps like nuts (difficult to pass); or lumpy, sausage-shaped stool. ‡Bristol Stool Form Scale 6–7: fluffy pieces of stool with ragged edges; mushy stool; or watery w/out solid pieces (entirely liquid). §In the absence of use of antidiarrheals or laxatives.

TABLE 1

The Bristol Stool Form Scale

Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on its surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cut edges (passed easily)
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces; entirely liquid

LEWIS SJ, HEATON KW. STOOL FORM SCALE AS A USEFUL GUIDE TO INTESTINAL TRANSIT TIME. SCAND J GASTROENTEROL 1997; 32:920–924.
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Source: www.romecriteria.org; Foxx-Orenstein et al. 2008

Current treatment landscape

Patients with chronic constipations are often first advised to increase their fluid intake and the fiber content of their diet, as well as increase physical activity. These lifestyle changes do not reliably result in satisfactory improvements. Current suggested drug treatment options for constipation start with laxatives which work to increase the flow of fluid into the intestinal lumen or to speed intestinal transit (directly or indirectly).

First line therapy is generally bulk laxatives (fiber supplements) in combination with increased exercise and water intake. Bulk laxatives are soluble or insoluble fibers that retain water and therefore help to increase the water content, and thus consistency, of the stool. Fiber, however, is associated with well known side effects such as bloating/distension, abdominal discomfort or cramps and excessive gas production. While some patients may benefit from the use of these agents, there is little evidence (via randomized controlled trial or otherwise) that shows their long-term efficacy.

Patients with persistent functional constipation or IBS-C often move from bulk laxatives to osmotic laxatives, molecules that are either not absorbed or are poorly absorbed, and thus draw water into the lumen via an osmotic gradient. This class of laxative can cause side effects including bloating, diarrhea, electrolyte disturbances, volume overload, or dehydration. As such, their use is somewhat limited, and they are generally not used in patients with renal insufficiency or cardiac abnormalities.

Stimulant or irritant laxatives are usually used when bulk and osmotic laxatives fail. These agents alter intestinal motility and intestinal fluid secretion, and work relatively quickly (can elicit a bowel movement 2 to 8 hours after dosing). The use of this class of laxative is less prevalent and generally is only used for short periods of time when needed due to concerns of colon damage or injuring or desensitizing the enteric nervous system of the gut. While these fears are not based on solid clinical evidence, the idea does limit the use of this drug class in practice nonetheless. Additionally, these agents can cause electrolyte imbalances and high volume watery diarrhea when overused. As such, these agents are generally reserved for patients with severe constipation and used for short periods of time.

Figure 6: Commonly used laxatives

Table 3. Medications Commonly Used for Constipation.

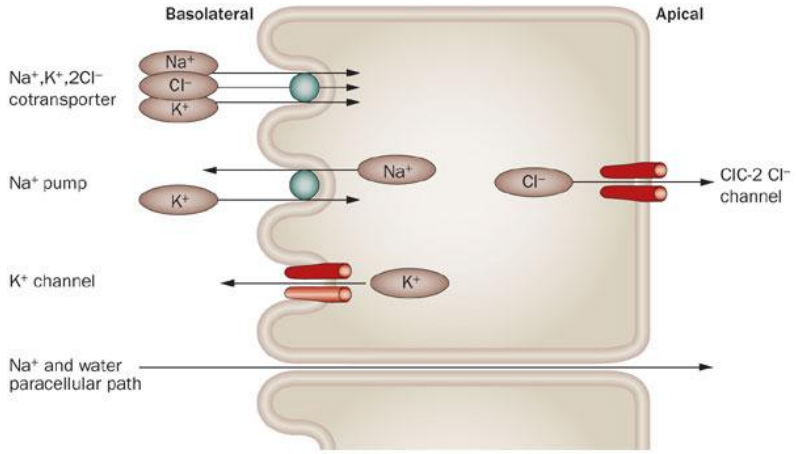
Medication	Maximal Recommended Dose	Comments
Bulk laxative		Increases colonic residue, stimulating peristalsis
Psyllium (Metamucil, Perdiem, Fiberall)	Titrate up to –20 g	Natural fiber that undergoes bacterial degradation, which may contribute to bloating and flatus; should be taken with plenty of water to avoid intestinal obstruction; allergic reactions such as anaphylaxis and asthma are rare
Methylcellulose (Citrucel)	Titrate up to –20 g	Semisynthetic cellulose fiber that is relatively resistant to colonic bacterial degradation
Polycarbophil (Fibercon, Equalactin, Konsyl)	Titrate up to –20 g	Synthetic fiber of polymer of acrylic acid, resistant to bacterial degradation
Osmotic laxative		Draws water into the intestines along osmotic gradient
Saline laxatives		
Magnesium hydroxide (Phillips' Milk of Magnesia)	15–30 ml once or twice a day	A small percentage of magnesium is actively absorbed in the small intestines; hypermagnesemia can occur in patients with renal failure and in children
Magnesium citrate (Evac-Q-Mag)	150–300 ml as needed	
Sodium phosphate (Fleet Enema, Fleet Phospho-Soda, Visicol)	10–25 ml with 12 oz (360 ml) of water as needed	Hyperphosphatemia can occur in patients with renal insufficiency; commonly used for bowel preparation before colonoscopy
Poorly absorbed sugar		
Lactulose (Cephulac, Chronulac, Duphalac)	15–30 ml once or twice a day	Synthetic disaccharide consisting of galactose and fructose linked by bond resistant to disaccharidases; not absorbed by the small intestine; undergoes bacterial fermentation in the colon with formation of short-chain fatty acids; gas and bloating are common side effects
Sugar alcohols		
Sorbitol (Cystosol)	15–30 ml once or twice a day	Poorly absorbed by intestine; undergoes bacterial fermentation
Mannitol		
Polyethylene glycol and electrolytes (Colyte, GoLYTELY, NuLYTELY)	17–36 g once or twice a day	Organic polymers that are poorly absorbed and not metabolized by colonic bacteria and may therefore cause less bloating and cramping than other poorly absorbed sugars[40]; can be mixed with noncarbonated beverages
Polyethylene glycol 3350 (Miralax)	17–36 g once or twice a day	Does not include electrolytes and is packaged for more regular use
Stimulant laxative		Stimulates intestinal motility or secretion
Anthraquinones		Converted by colonic bacteria to their active form; may cause melanosis coli, a benign condition that is usually reversible within 12 months after the cessation of laxative use; no definitive association between anthraquinones and colon cancer or myenteric nerve damage has been established
Cascara sagrada (Colamin, Sagrada-lax)	325 mg (or 5 ml) daily	
Senna (Senokot, Ex-Lax)	187 mg daily	
Castor oil (Purge, Neoloid, Emulsoil)	15–30 ml daily	Hydrolyzed by lipase in the small intestine to ricinoleic acid, which inhibits intestinal water absorption, increases mucosal permeability, and stimulates motor function through the release of neurotransmitters from mucosal enterochromaffin cells; cramping and severe diarrhea are common
Diphenylmethane derivatives		
Bisacodyl (Dulcolax, Correctol)	5–10 mg every night	Hydrolyzed by endogenous esterases; stimulates secretion and motility of small intestine and colon
Sodium picosulfate (Lubrilax, Sur-lax)	5–15 mg every night	Hydrolized to its active form by colonic bacterial enzymes; affects only the colon
Stool softener		
Docusate sodium (Colace, Regulax SS, Surfak)	100 mg twice a day	Ionic detergents soften stool by allowing water to interact more effectively with solid stool; modest fluid secretion; efficacy for treatment is not well established
Mineral oil (Fleet Mineral Oil)	5–15 ml orally every night	An emollient providing lubrication for the passage of stool; long-term use can cause malabsorption of fat-soluble vitamins and anal seepage; lipoid pneumonia can occur in patients predisposed to aspiration of liquids

Source: Lembo and Camilleri, 2003

Newer agents that are used to treat functional constipation and IBS-C include lubiprostone (Amitiza, Sucampo/Takeda) and the recently approved linaclotide (Linzess, Forest Labs/Ironwood).

Lubiprostone (Amitiza, Sucampo/Takeda). Lubiprostone, an osmotic agent, was first approved by the FDA in 2008 and will go off patent in 2014. It is a locally acting agonist of the chloride channel subtype 2 (ClC-2), which is found on the apical membrane of intestinal epithelial cells. Lubiprostone increases Cl- ion flow (and water) into the luminal space without altering the sodium and potassium concentrations in the serum. The drug is minimally absorbed, with serum concentrations below the limit of detection.

Figure 7: Lubiprostone activates ClC-2 causing increased fluid secretion and water transfer



Source: http://www.nature.com/nrgastro/journal/v6/n5/fig_tab/nrgastro.2009.62_F1.html

Lubiprostone was evaluated in two randomized, controlled, double-blind trials in patients with chronic idiopathic constipation. In both studies it was shown to increase the frequency of spontaneous bowel movements (SBMs) within the first 24 hours after first dose and to significantly improve symptoms of constipation compared to placebo. It was also evaluated in three open-label, long-term clinical safety studies. These studies showed that lubiprostone decreased symptoms of constipation throughout treatment periods of 6 to 12 months.

Figure 8: Spontaneous bowel movement frequency rates – Amitiza vs. placebo

Trial	Study Arm	Baseline *Mean ± SD Median*	Week 1 *Mean ± SD Median*	Week 2 *Mean ± SD Median*	Week 3 *Mean ± SD Median*	Week 4 *Mean ± SD Median*	Week 1 Change from Baseline *Mean ± SD Median*	Week 4 Change from Baseline *Mean ± SD Median*
Study 1	Placebo	1.6 ± 1.3 1.5	3.5 ± 2.3 3.0	3.2 ± 2.5 3.0	2.8 ± 2.2 2.0	2.9 ± 2.4 2.3	1.9 ± 2.2 1.5	1.3 ± 2.5 1.0
	AMITIZA™	1.4 ± 0.8 1.5	5.7 ± 4.4 5.0	5.1 ± 4.1 4.0	5.3 ± 4.9 5.0	5.3 ± 4.7 4.0	4.3 ± 4.3 3.5	3.9 ± 4.6 3.0
Study 2	Placebo	1.5 ± 0.8 1.5	4.0 ± 2.7 3.5	3.6 ± 2.7 3.0	3.4 ± 2.8 3.0	3.5 ± 2.9 3.0	2.5 ± 2.6 1.5	1.9 ± 2.7 1.5
	AMITIZA™	1.3 ± 0.9 1.5	5.9 ± 4.0 5.0	5.0 ± 4.2 4.0	5.6 ± 4.6 5.0	5.4 ± 4.8 4.3	4.6 ± 4.1 3.8	4.1 ± 4.8 3.0

The above frequency rates are calculated as 7 times (number of SBMs) / (number of days observed for that week).

Source: www.accessdata.gov – Amitiza label

Nausea was the most commonly reported adverse event, with 31% of patients reporting nausea, 3.4% reporting severe nausea, and 8.7% of study participants discontinuing treatment due to nausea. This seemed to be dose dependent, and was less pronounced when the drug was dosed with food. In the longer-term studies, lubiprostone did not appear to place patients at increased risk of nausea. High rates of nausea appear to be the main tolerability issue with Amitiza treatment and continue to limit its use. The second most common side effect was diarrhea, which occurred in 13.2% of study patients, with a 2.2% discontinuation rate. The incidence of diarrhea did not appear to be dose dependent. Notably, no SAEs related to electrolyte imbalance were reported in any of the late-stage clinical trials, and no changes in serum electrolyte levels were seen while patients were receiving lubiprostone.

Amitiza had net sales of $226M in 2011, short of the $800M that Sucampo/Takeda had forecasted at the start of commercialization.

Resolor (prucalopride, J&J). Prucalopride is approved in the EU and Canada for the treatment of chronic constipation. Ex-US, Resolor is marketed by J&J, and Shire acquired the rights to market prucalopride in the US in January 2012. In the US, prucalopride is currently in two Phase 3 trials: one for pediatric constipation and one in constipated adult men.

Prucalopride is a selective 5-HT_4 receptor agonist that stimulates high-amplitude contractions to increase intestinal motility. Prucalopride is highly selective and thus far has shown favorable safety and tolerability profiles.

Figure 9: Summary of prucalopride in EU registration trials

Reference	Study design (No. of patients)	Outcomes (2 mg and 4 mg prucalopride *versus* placebo)
[Camilleri *et al.* 2008b]	12 weeks (620)	No. of patients achieving
	Prucalopride 2 mg or 4 mg daily *versus* placebo	1. ≥ 3 SCBMs/week: 30.9% and 28.4% *versus* 12% 2. An increase of ≥ 1 SCBM/week: 47.3% and 46.6% *versus* 25.8%
[Quigley *et al.* 2009]	12 weeks (641)	No. of patients achieving:
	Prucalopride 2 mg or 4 mgdaily *versus* placebo	1. ≥ 3 SCBMs/week: 23.9% and 23.5% *versus* 12.1% 2. An increase of ≥ 1 SCBM/week: 42.6% and 46.6% *versus* 27.5%
[Tack *et al.* 2009]	12 weeks (713)	No. of patients achieving:
	Prucalopride 2 mg or 4 mgdaily *versus* placebo	1. ≥ 3 SCBMs/week: 19.5% and 23.6% *versus* 9.6% 2. An increase of ≥ 1 SCBM/week: 38.1% and 44.1% *versus* 20.9%

Source: Quigley 2012

Resolor was approved in the EU on the basis of three randomized, controlled, double-blind trials that enrolled patients with chronic constipation. Duration of treatment was 12 weeks, and the primary endpoint was the proportion of patients having three or more CSBMs per week, averaged over the 12 weeks of treatment. In all three trials, treatment with Resolor resulted in a significant increase in the proportion of patients achieving at least three SCBMs per week as compared to placebo. Response rates in the 2mg dose ranged from 19.5% to 31%, in the 4mg dose from 24% to 28%, and in the placebo group from 9.6% to 12%.

Propulsid (cisapride) and Zelnorm (tegaserod). First generation 5-HT_4 agonists Propulsid and Zelnorm were originally approved in 1993 and 2002, respectively. By binding to 5-

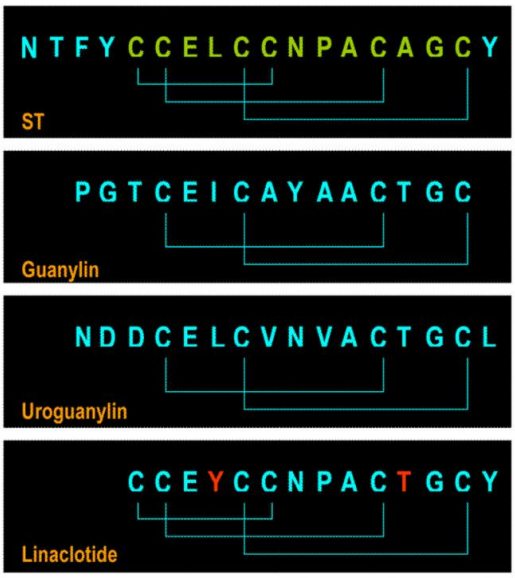
HT_4 receptors in the GI tract, these drugs stimulate intestinal motility. Both were subsequently removed from the market, Propulsid in 2000 and Zelnorm in 2007, due to concerns about the high risk of cardiovascular events compared to placebo. The cardiac effect was hypothesized to be caused by off target actions, as both of these drugs were less selective, activating off target receptors including 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2B} and hERG. In 1999, Propulsid generated sales of $950M (though it was also used to treat upper GI disorders). In 2006, Zelnorm had US sales of $488M.

Linaclotide (Linzess, Ironwood/Forest) – blazing the trail for GC-C drugs.

Linaclotide is a novel peptide agonist of guanylate cyclase type C (GC-C). GC-C is selectively expressed on the apical surface of intestinal mucosa cells from the duodenum to the rectum. The drug was approved by the FDA in August 30, 2012 for both IBS-C and chronic idiopathic constipation, and Forest and Ironwood intend to launch the drug in Q4/12. Linzess is covered by a composition of matter patent that expires in 2025.

Linaclotide is a substituted analog of bacterial heat stable enterotoxins (ST), which are in turn analogs of endogenous hormones guanylin and uroguanylin. As compared to the endogenous hormones, linaclotide's structure preserves the three disulfide bonds that are present in the ST structure, which stabilizes the molecule (enhance potency). Linaclotide is 8 times more potent than the endogenous hormones.

Figure 10: Sequence of linaclotide compared to ST and endogenous hormones

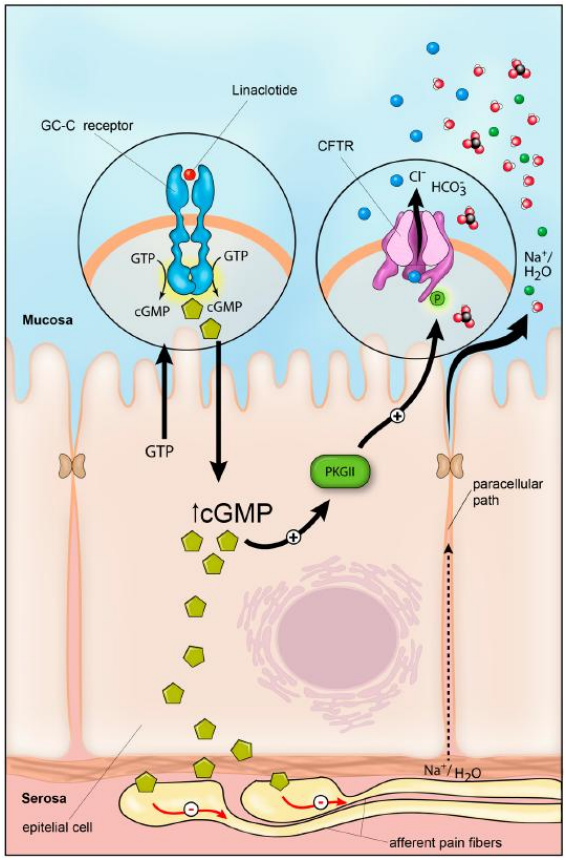


Source: Bharucha and Waldman, 2010

Linaclotide mimics the activity of endogenous hormones guanylin and uroguanylin, binding to the GC-C, which activates the intracellular catalytic domain, converting GTP to cyclic guanosine monophosphate (cGMP). cGMP then induces downstream effectors that phosphorylate (activate) the cystic fibrosis transmembrane conductance receptor (CFTR). CFTR is a Cl- ion channel that, when activated, increases the flow of Cl- ions (and water) into the luminal space, accelerating transit. Linaclotide is minimally absorbed, with

plasma concentrations of both it and its active metabolite below the limit of quantification after 145mcg and 290 mcg doses.

Figure 11: Regulation of intestinal secretion by GC-C



Source: Lacy et al. 2012

Linaclotide IBS-C clinical development and data

Linaclotide was evaluated in two randomized, controlled, double-blind trials in adults with IBS-C. All patients met Rome II criteria for IBS. In both trials, the proportion of patients who were responders to linaclotide was statistically significantly higher than placebo. Improvements from baseline in abdominal pain and CSBM frequency was seen over 12 weeks of treatment, reaching maximum at 6-9 weeks. Active arm patients had on average 1.5 more CSBMs per week in both trials.

Figure 12: Efficacy responder rates in the two-placebo controlled IBS-C at least 9 out of the 12 weeks

	Trial 1			Trial 2		
	LINZESS 290 mcg (N=405)	Placebo (N=395)	Treatment Difference [95% CI]	LINZESS 290 mcg (N=401)	Placebo (N=403)	Treatment Difference [95% CI]
Combined Responder* (Abdominal Pain and CSBM Responder)	12.1%	5.1%	7.0% [3.2%, 10.9%]	12.7%	3.0%	9.7% [6.1%, 13.4%]
Abdominal Pain Responder* (≥ 30% Abdominal Pain Reduction)	34.3%	27.1%	7.2% [0.9%, 13.6%]	38.9%	19.6%	19.3% [13.2%, 25.4%]
CSBM Responder* (≥ 3 CSBMs and Increase ≥1 CSBM from Baseline)	19.5%	6.3%	13.2% [8.6%, 17.7%]	18.0%	5.0%	13.0% [8.7%, 17.3%]
* Primary Endpoints Note: Analyses based on first 12 weeks of treatment for both Trials 1 and 2 CI =Confidence Interval						

Source: www.accessdata.gov – Linzess label

Patients treated with linaclotide also had significant improvements across secondary endpoints, including changes in bowel symptoms, stool consistency, straining severity, bloating and abdominal discomfort. The effect of linaclotide in these symptoms of constipation were observed within the first 24 hours and sustained through 16 weeks.

The most common adverse event in IBS-C trials was diarrhea, with 20% of linaclotide patients experiencing diarrhea compared to 3% of placebo patients. 2% of linaclotide patients reported severe diarrhea, and 5% of patients discontinued treatment due to diarrhea vs. less than 1% of placebo patients. Abdominal pain was the second most frequent AE experienced by 7% of linaclotide patients and 5% of placebo patients. When considering all AEs, 9% of linaclotide patients and 3% of placebo patients discontinued from the study due to adverse events.

Figure 13: AEs reported in at least 2% of linaclotide patients at an incidence greater than placebo patients in IBS-C trials

Adverse Reactions	LINZESS 290 mcg [N=807] %	Placebo [N=798] %
Gastrointestinal		
Diarrhea	20	3
Abdominal pain[a]	7	5
Flatulence	4	2
Abdominal distension	2	1
Infections and Infestations		
Viral Gastroenteritis	3	1
Nervous System Disorders		
Headache	4	3

a: "Abdominal pain" term includes abdominal pain, upper abdominal pain, and lower abdominal pain.

Source: www.accessdata.gov – Linzess label

Linaclotide CIC clinical development and data

Linaclotide was evaluated in two randomized, controlled, double-blind trials in adult patients with chronic idiopathic constipation. All patients met the modified Rome II criteria for functional constipation. In both trials, the proportion of patients who were responders was statistically significantly greater than with placebo. On average, patients receiving linaclotide had greater improvements in stool frequency and stool consistency, having on average 1.5 more CSBMs than placebo at week 12.

Figure 14: Efficacy responder rates in the two-placebo controlled CIC trials: at least 9 out of the 12 weeks

	Trial 3			Trial 4		
	LINZESS 145 mcg (N=217)	Placebo (N=209)	Treatment Difference [95% CI]	LINZESS 145 mcg (N=213)	Placebo (N=215)	Treatment Difference [95% CI]
CSBM Overall Responder (≥ 3 CSBMs and Increase ≥ 1 CSBM from Baseline)	20.3%	3.3%	16.9% [11.0%, 22.8%]	15.5%	5.6%	9.9% [4.2%, 15.7%]
*Primary Endpoint CI=Confidence Interval						

Source: www.accessdata.gov – Linzess label

The most common adverse event in CIC trials was diarrhea, with 16% of linaclotide patients experiencing diarrhea compared to 5% of placebo patients. 2% of linaclotide patients reported severe diarrhea, and 5% of patients discontinued treatment due to diarrhea vs. less than 1% of placebo patients. When considering all AEs, 8% of linaclotide patients and 4% of placebo patients discontinued from the study due to adverse events.

Figure 15: AEs reported in at least 2% of linaclotide patients at an incidence greater than placebo patients in IBS-C trials

Adverse Reactions	LINZESS 145 mcg [N=430] %	Placebo [N=423] %
Gastrointestinal		
Diarrhea	16	5
Abdominal pain[a]	7	6
Flatulence	6	5
Abdominal distension	3	2
Infections and Infestations		
Upper respiratory tract infection	5	4
Sinusitis	3	2

a: "Abdominal pain" term includes the abdominal pain, upper abdominal pain, and lower abdominal pain

Source: www.accessdata.gov – Linzess label

While the results of theses trial were statistically significant, we note that a minority of treated patients met the primary end points in each of the trials. Additionally, it has not been established that linaclotide will be more effective than osmotic laxatives, which work through a similar osmotic mechanism of action.

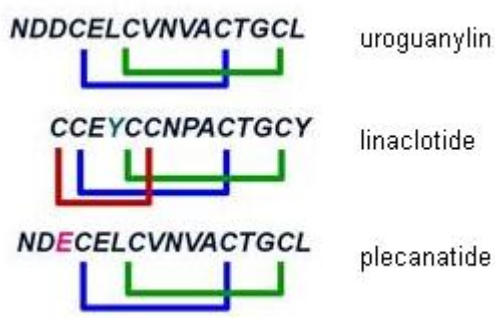
PLECANATIDE

Background

Plecanatide, like linaclotide, is a GC-C agonist. Unlike linaclotide with its heat-stable bacterial enterotoxin analog (with a closer resemblance to ST toxins than endogenous gut hormones), plecanatide is nearly structurally identical to the endogenous uroguanylin hormone except for an extra methylene at the third amino-acid position (Asp(D)→Glu(E)). This substitution allows for the formation of an additional hydrogen bond that stabilizes plecanatide in its bioactive formation. As a result, plecanatide is 8 times more potent than endogenous uroguanylin. Unlike linaclotide (and ST toxins in general), it does not cause increased signaling and potential overstimulation when bound to the GC-C receptor.

Given the identical target, plecanatide has the same mechanism as linaclotide, working through the CFTR receptor to create an osmotic gradient and draw water into the luminal space. However, we think mechanism and binding characteristic may allow plecanatide to have a more physiological normal impact on gut motility, resulting in a better side-effect profile and improved tolerability. Specifically, we think plecanatide could prove to have reduced rates of diarrhea, bloating and distension than linaclotide. Should plecanatide show equal efficacy to linaclotide, we think this drug could easily become the best-in-class GC-C drug and market leader for treatment. Should plecanatide's efficacy prove to be more moderate than plecanatide, we still think there could be an excellent market opportunity for the drug. We believe there may be a number of patients that cannot tolerate linaclotide's diarrhea side effects or would prefer a milder treatment with better tolerability, especially for maintenance therapy.

Figure 16: Structure of Uroguanylin, linaclotide and plecanatide



Source: SGYP company presentation

Phase 2a trial

Plecanatide was evaluated in a phase 2a dose-escalation trial in patients with chronic idiopathic constipation (CIC). A total of 80 patients were enrolled in the study, which evaluated 4 doses of plecanatide vs. placebo (3:1 randomized per dose group). Patients were administered one daily dose of plecanatide for 14 days, and a safety review was

conducted after the completion of each cohort. Patients enrolled met the ROME III diagnostic criteria for chronic constipation.

Figure 17: GI related adverse event summary with relationship to treatment

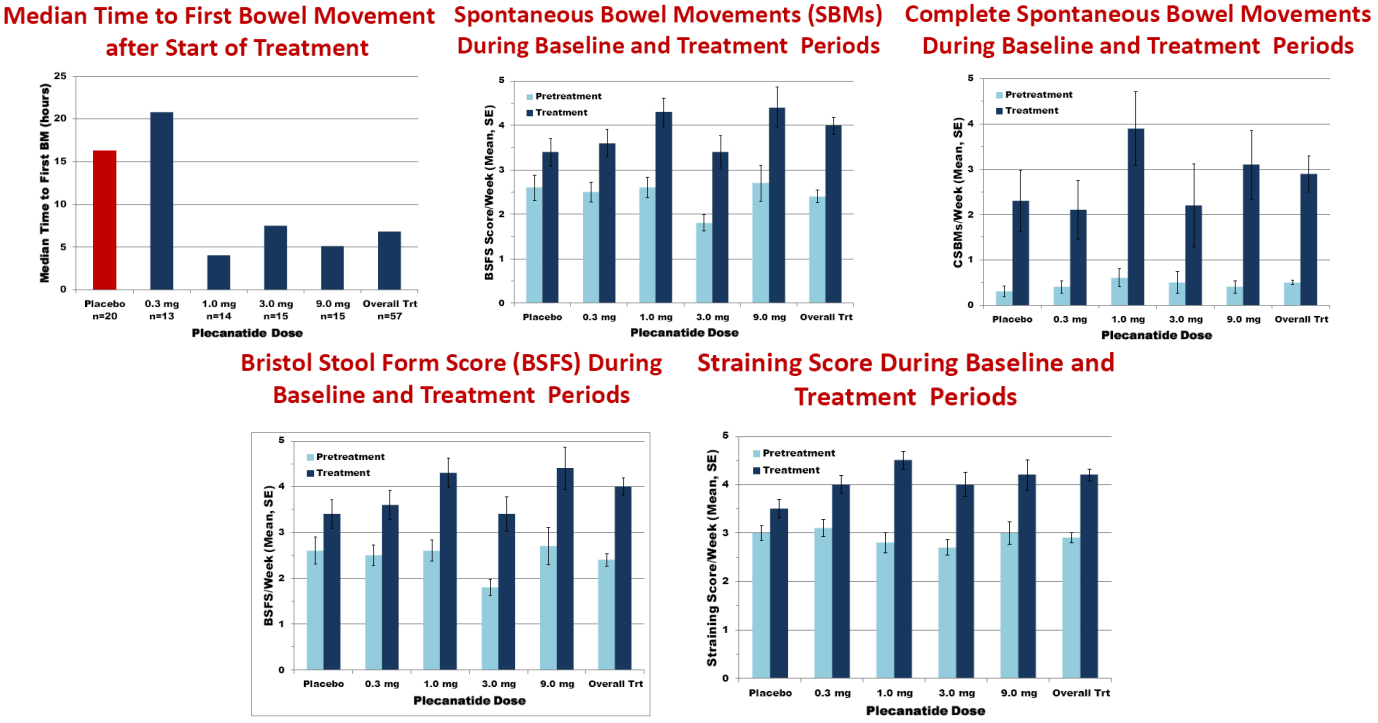
AE	Placebo	0.3 mg	1.0 mg	3.0 mg	9.0 mg
Ab Cramping	1 (5.0%)	0	0	0	0
Ab Pain	1 (5.0%)	0	0	0	0
Bloating	0	0	0	0	1 (6.7%)
Diarrhea	1 (5.0%)	0	0	0	0
Flatulence	2 (10.0%)	0	0	0	0
Nausea	0	1 (7.1%)	0	0	
Upset Stomach	0	0	0	1 (6.7%)	0

Ab = Abdominal

Source: Shailubhai et al. 2011 – ACG

This trial showed that plecanatide was generally safe and well tolerated, with no SAEs reported in subjects receiving plecanatide. 8.6% of plecanatide patients experienced GI-AEs as compared to 10% of placebo patients. Importantly, there were no reports of diarrhea in patients receiving plecanatide. GI symptoms were limited to bloating, nausea and upset stomach. As expected, there was no detectable absorption of plecanatide (serum levels below the lower limit of quantification).

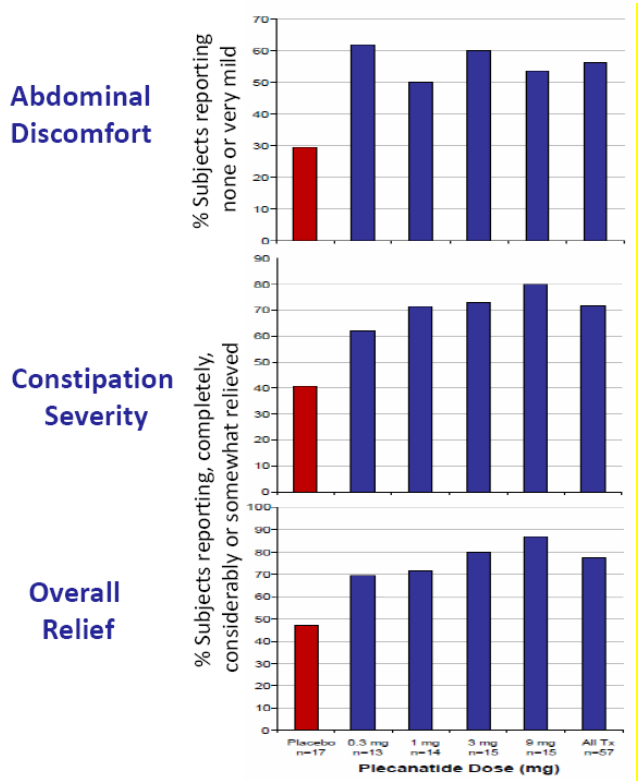
Figure 18: Efficacy results from Ph2a trial



Source: Shailubhai et al. 2011 – ACG

While this trial was not powered to show efficacy, all plecanatide groups showed a significant decrease in time to first bowel movement – 50% of patients in the plecanatide arm achieved first bowel movement within 7 hours first dose, compared to 17 hours in the placebo arm. The drug also showed consistent trends in increasing stool frequency, both CSBM and SBM, and plecanatide improved stool consistency, reduced straining and reduced abdominal discomfort.

Figure 19: Global Assessment scores after treatment

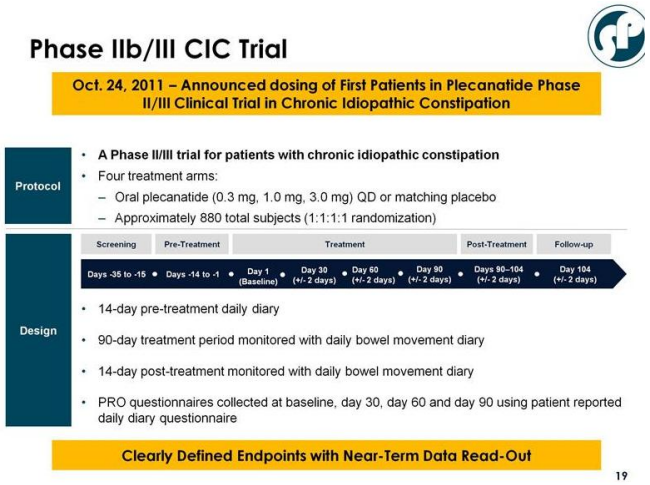


Source: Shailubhai et al. 2011 – ACG

Ongoing Phase 2b/3 trial of plecanatide in CIC

On the basis of the Phase 2a CIC trial, Synergy moved plecanatide forward into a phase 2b/3 repeat, oral dose ranging trial in CIC, which meets all the requirements for a registration trial. The 12-week trial enrolled ~880 patients who met modified Rome III criteria. Patients were monitored for inclusion/exclusion criteria during a two-week pre-treatment screening during which patients were required to call in and report bowel movement as they occur (BM diary). Additionally, they were required to call at least once daily to complete a patient diary of questions on their constipation symptoms (symptom diary). This same reporting protocol was used during treatment period of the trial.

Figure 20: Ph2b/3 trial design



Source: SGYP company presentation

Patients who successfully complete the pre-treatment period were equally randomized to placebo, 0.3, 1.0 and 3.0 mg once per day. In addition to the call-ins and BM and symptom diaries, patients are seen every four weeks during the treatment phase. Patients will have a two-week post-treatment period without drug, followed by an end-of-study visit.

The trial is powered to detect a 10% difference in overall CSBM responders between each dose and placebo. A weekly responder is defined as three or more CSBMs and an increase of at least one from baseline; monthly responders are those that are weekly responders for at least three of four weeks in a month; and an overall responder must achieve monthly responses for two of the three months of the trial, with one of the months being the last treatment period. The trial will evaluate secondary endpoints including SBMs, straining and stool consistency, and abdominal discomfort. It will also evaluate the safety of plecanatide and the impact of the drug on the quality of life and constipation symptoms using proprietary PRO questionnaires.

Figure 21: Ph 2b/3 trial design details

NCT ID	NCT01429987
Design	Randomized, Controlled, double blind
Condition	Chronic Idiopathic constipation
Number of patients	~880
Duration of treatment	12 weeks
Dosing	plecanatide .3mg QD plecanatide 1.0mg QD plecanatide 3.0mg QD placebo QD
Key inclusion criteria	• Modified Rome III criteria for functional chronic idiopathic constipation for at least 3 months with symptom onset for at least 6 months. ○ Note: For this trial, patients with manual maneuvers required for >25% of defecations not be eligible • Less than 3 CSBMs per week at baseline and during pretreatment
Key exclusion criteria	• No use of supplemental fiber, laxatives, prescription/nonprescription medications, herbal or dietary supplements for constipation during screening, pre-treatment, treatment and 2-week post-treatment periods • Loose stool (mushy) or watery (Bristol: 6/7) stool in absence of laxative or prohibited medicine for > 25% of BMs during 3 months prior to screening visit OR during the 14 day treatment period • Rome III criteria for Irritable Bowel Syndrome (IBS-C)

Primary endpoint	• **Complete Spontaneous Bowel Movement (CSBM) in 12 weeks**
	  ○ 10% difference in Overall CSBM responders between each dose of plecanatide and placebo. A
	  ▪ complete spontaneous bowel movement occurs 24 hours away from laxative use and the patient reports a feeling of complete evacuation.
	  ▪ A weekly responder will have 3 or more CSBMs and an increase of at least one CSBM from baseline.
	  ▪ A monthly responder achieves this for 3 of the 4 weeks in a month.
	  ○ An overall responder must achieve this in 2 of the 3 months of treatment with one month being the latest treatment period.

Secondary Endpoint **Data Timing**	• Reduction in straining/abdominal symptoms (e.g.) pain, discomfort bloating over 12 Weeks ○ via patient reported outcome (PRO) measures • Improvement in the hardness of stool • the frequency of spontaneous movements • reduction in time to first bowel movement. To monitor and report • all treatment emergent adverse events • Top-line data due Q4/2012

Source: clinicaltrials.gov

Additional Indications

Synergy also plans to initiate a Phase 2b trial of plecanatide in IBS-C patients. The protocol has been successfully reviewed by the FDA and aligns with guidance regarding trials in IBS-C trials. The trial will enroll ~350 patients, and the trial is expected to begin before year-end 2012.

Competitive landscape

We think there are several competitors that will provide significant challenges to a prucalopride launch, including the widely available and inexpensive laxatives, as well as linaclotide, which will likely have been on the market for several years before prucalopride. In addition, there are several treatments for functional constipation and IBS-C in late stage clinical trials.

Figure 22: Key competitors in late stage clinical trials

Drug	MOA	Developer	Phase	Data Expected	Comments
prucalopride	(5-HT_4) receptor agonist	Shire/Movetis	Phase 3	Q2/13	Approved in EU (Resolor); currently in 2 US Ph3s, in pediatric and male CC patients
elobixibat	IBAT inhibitor	Ferring/Albireo	Phase 3 ready	n/a	Successfully completed Ph2, licensed by Ferring in July 2012
YKP10811	(5-HT_4) receptor agonist	SK biopharmaceuticals	Phase 2	Q2/13	Shown to be safe in Ph1 healthy volunteer trial
TU-100 (daikenchuto)	likely (5-HT_4) receptor mediated	Tsumura USA	Phase 2	Q4/12	is a traditional Japanese medicine; a mixture of extract powders from dried Japanese pepper, processed ginger, ginseng radix, and maltose powder
RDX5791	NHE3 inhibitor	AstraZeneca/Ardelyx	Phase 2 ready	n/a	Successfully completed Ph2a, licensed by AZN in Oct 2013

Source: clinical trials.gov, company websites

The most advanced is prucalopride, which is currently in two Phase 3 trials: one for pediatric constipation and one in constipated adult men. Prucalopride is approved in the EU and Canada for the treatment of chronic constipation. Ex-US Resolor is marketed by J&J, and Shire acquired the rights to market prucalopride in the US in January 2012.

Prucalopride is a selective 5-HT_4 receptor agonist that stimulates high-amplitude contractions to increase intestinal motility. Previous members of the 5-HT_4agonist class, including tegaserod and cisapride, were both withdrawn from the market due to the risk of adverse cardiovascular events. These agents were less selective, however, and it is largely believed that cardiovascular issues were a result of off-target activity with other receptors including 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2B} and hERG. Prucalopride, on the other hand, is highly selective and thus far has shown favorable safety and tolerability profiles.

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Phase 3 ready elobixibat is a first-in-class compound that partially inhibits the Ileal Bile Acid transporter (IBAT), which modulates the enterohepatic circulation of bile acids which increases colonic fluid secretion and motility. In Phase 2 trials, elobixibat demonstrated clinically meaningful and statistically significant improvement in constipation and IBS-C symptoms such as bowel movement frequency, straining, stool consistency, and bloating. Additionally, the studies provided evidence that the drug may have a cholesterol-lowering effect.

Additional compounds that are in Phase 2 development include: 5-HT_4 receptor agonist YKP108111, the traditional Japanese medicine daikenchuto that also likely works the t5-HT_4 receptor, and RDX5791 that is a selective inhibitor of NHE3, a sodium transporter on the surface of intestinal epithelia.

Should any of these drugs make it to market, they would provide additional competition to prucalopride.

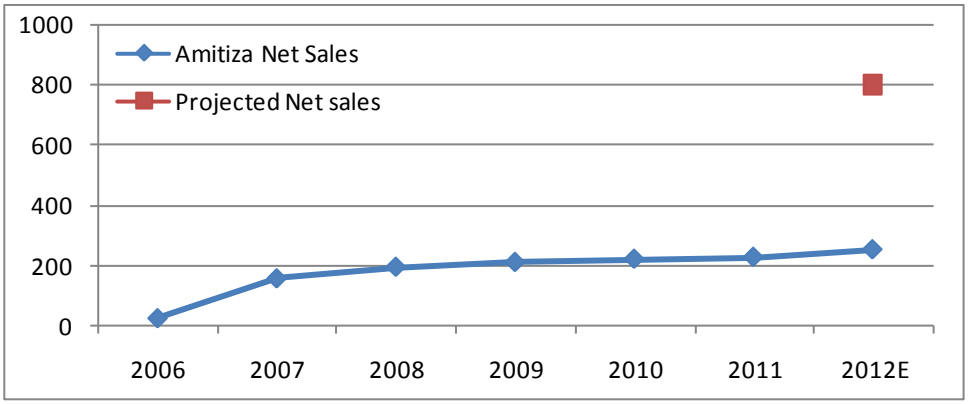
Market opportunity

CC and IBS are among the most common functional gastrointestinal disorders (FGIDs), with prevalence estimates ranging from 2% to 28% for CC and 3% to 20% for IBS, with an average of 15%. The prevalence of constipation tends to be higher in women than in men; the prevalence is 2.2 times higher in females. Additionally, the prevalence also tends to be higher in non-white populations.

Amitiza (lubiprostone) was approved in 2006, though sales have been lackluster. In their 2011 10-k, Sucampo notes disappointment in the launch, blaming their commercial partner Takeda for lack of best effort, resulting in low patient and doctor awareness and

unacceptable sales. Amitiza had net sales of $226M in 2011, short of the $800M that the company had forecasted at the start of commercialization. While these disappointing sales may partially be a result of poor commercialization effort, we think they also reflect demand. Given the widespread availability of inexpensive treatment options, we think the market opportunity for branded, prescription constipation treatments may be limited

Figure 24: Amitiza net sales since launch



Source: Sucampo company reports

OTHER AREAS OF DEVELOPMENT

FV-100 for shingles

In August 2012, Synergy acquired the rights to FV-100 from Bristol-Meyers Squibb, which acquired the drug in its 2012 acquisition of Inhibitex. FV-100 is a novel oral anti-herpes Zoster nuceleoside analog being developed for the treatment of shingles. Shingles is the adult reactivation of the varicella zoster (aka chickenpox) virus and the most common neurological disease in the US. 80% of cases occur in patients over 40, and incidence in the US is rising steeply with the aging of the overall population.

The estimated herpes zoster reactivation/recurrence rate is currently estimated to be about 6.2%. Treating these patients may represent a >$500MM market opportunity, which current market research estimated is driven by 2.5-3.5M antiviral prescriptions. We think the shingles treatment market has the potential to reach $1B or more given current drugs are suboptimal, off-label generics. There is a particular need for drugs that have the potential to prevent post-herpetic neuralgia (PHN). PHN is a complication of shingles where viral damage to the nerves results in lingering neuropathic pain. PHN eventually develops in 15-25% of shingles patients. Synergy believes that there is a significant market opportunity for a new chemical entity therapy that could reduce incidence of PHN by 25% or more.

FV-100 clinical data to date

The drug was evaluated in a Phase 2a, double-blind study compared to active control valacyclovir. The trial enrolled 350 patients >50 years old who had shingles associated pain and presented to the clinic within 72 hours of first lesion appearance. Randomization was equal across three arms: 200 mg FV-100 administered once daily for

seven days; 400 mg FV-100 administered once daily for seven days; or 1,000 mg valacyclovir administered three times per day for seven days. The primary efficacy analysis was conducted on the modified intent-to-treat population, which included all intent-to-treat subjects but excluded subjects whose lesions were PCR (-) for varicella zoster virus and PCR (+) for herpes simplex virus.

The primary composite endpoint of the study was reduction in the burden of illness over the first 30 days post-infection (BOI_{30AUC}). This endpoint measures the reduction in severity and duration of shingles-associated acute pain. Patients receiving 200mg and 400mg doses of FV-100 had 3% and 7% improvements in the primary endpoint, respectively. In the key BOI_{90AUC} secondary endpoint, FV-100 patients experienced a 4% and 14% reduction on the 200mg and 400mg doses, respectively, compared to active control. Additionally, the incidence of post-herpetic neuralgia (PHN) was lower in FV-100 treated patients, and no difference in time to lesion healing was observed between treatment groups.

Figure 25: Efficacy summary in mITT population

	Primary Endpoint	Key Secondary Pain Endpoints	
Cohort (N)	Least Squares Mean $BOI_{30\ days\ AUC}$ ± S.E.	Least Squares Mean $BOI_{90days\ AUC}$ ± S.E.	Incidence of PHN (%)
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
3000 mg valacyclovir (N=109)	117.96 ± 6.25	229.59 ± 19.55	20.2

Source: Inhibitex company report

FV-100 was well tolerated at both doses, with the frequency of AEs being similar across all arms. In the 400 mg FV-100 dose group, the most common adverse events were headache (13%) and nausea (9%) while the most common adverse events in the valacyclovir arm were nausea (6%) and upper abdominal pain (5%).

Figure 26: Adverse event summary

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: Inhibitex company report

SP-333 for bowel diseases

Synergy is also developing SP-333, a second generation GC-C receptor analog in ulcerative colitis and irritable bowel diseases. In pre-clinical studies oral doses of SP-333 down regulated inflammatory cytokines, such as IL-4, IL-5, IL-17, IL-23 and TNF-alpha.

The company filed an IND for the compound in September and plans to begin a Phase 1 trial in healthy volunteers before year end 2012. The Phase 1 trial will be a single dose, dose escalation trial in approximately 40 patients, after which the company plans to start trials in patients with ulcerative colitis.

INTELLECTUAL PROPERTY

Synergy owns several patents that cover plecanatide, including two composition of matter patents. The first patent was issued in 2006 and expires in March 2023, and the second patent was issued on September 21, 2010 and expires in June 2022. Both of these patents may be eligible for patent term extensions.

Synergy has also filed for additional patent applications to broaden IP protection for their uroguanylin receptor agonists.

Figure 27: Key patents covering plecanatide

Patent Number	Title	Issue Date	Expiration	Synopsis
7041786	Guanylate cyclase receptor agonists for the treatment of tissue inflammation and carcinogenesis	May 9, 2006	March 25, 2023	Composition of matter
7799897	Guanylate cyclase receptor agonists for the treatment of tissue inflammation and carcinogenesis (continuation)	September 21, 2010	June 9, 2022	Continuation of the '786 patent

Source: Company reports, www.uspto.gov

FINANCIALS

Our forecast financial model is built on the assumption that plecanatide will be approved in early 2016 for the treatment of chronic idiopathic constipation with supportive data in IBS-C which should drive off-label sales starting 2016. We believe Synergy will likely secure formal IBS-C approval in late 2017 or early 2018.

Our current valuation assumes that Synergy will choose to self-commercialize plecanatide, focusing its commercial efforts on gastroenterologists. We believe this could be the most efficient, leveraged marketing strategy for this drug given clinicians' current perception of the drug as a third-line treatment for chronic constipation and IBS-C. We do acknowledge that limited promotion to specialists, rather than targeting primary care physicians as well, will limit the drug's peak sales.

In this scenario on which we base our valuation, plecanatide would see good uptake in the US CIC and IBS-C market. We expect the drug to be priced around ~$540 net per year of treatment. We anticipate about $400M peak annual US sales for both CIC and IBS-C for total peak sales of ~$800M.

In order to promote to the primary care market and maximize peak drug sales, Synergy would have to partner the drug, reducing its economics. However, an alternate market model and valuation that we have developed that would capture this partnership scenario value also suggests an identical $8/share value. In this scenario a strong partner would increase the percentage of CIC patients seeking prescription therapy as well as the peak market share of plecanatide in both CIC and IBS-C.

At the end of June 2012, Synergy had $45million in cash. We think this represents almost 18 months of cash on hand. We think it is likely that the current cash balance will last through completion of the current Phase 2/3 trial but not likely through the completion of plecanatide's required second trial in CIC or additional development in IBS-C.

MANAGEMENT TEAM

The synergy management team has a strong history of research and development. President and Chief Executive Officer Dr. Gary Jacob joined Synergy in 1999 as Chief Scientific Officer, a position he held until 2003. He became Chairman of Synergy in 2003 and has held his current position since July 2008. From 1990 to 1998, Dr, Jacob held various positions at Monsanto, including the Director of Functional Genomics and Director of Glycobiology at GD Searle Pharmaceuticals (which was acquired by Monsanto in 1985).

Dr. Kunwar Shailubhai joined Synergy in 2001 as VP, Drug Discovery, served as SVP, Drug Discovery from 2003 to 2008, and became Chief Scientific Officer in 2008. From 1993-2000, Dr. Shailubhai worked at Monsanto, serving as the Group Leader of the cancer chemoprevention group.

Synergy's CMO is Dr. Gail Comer, who joined the company in 2012. Prior to joining Synergy, Dr. Comer was Senior Director of the BioTherapeutics Research Unit at Pfizer.

She has also served as medical research leader in Gastroenterology at Wyeth and medical director at Abbott Laboratories.

Bernard Denoyer is Synergy's SVP, Finance and Secretary, a position he has held since 2008. Prior to joining Synergy, he served as Senior Financial Officer and Secretary of Callisto Pharmaceuticals, where he started in 2004. From 2001 to 2003, he served as an independent consultant, providing interim CFO services to emerging technology companies. From 1994 to 2000, Mr. Denoyer served as Chief Financial Officer and Senior Vice President at META Group, Inc, and from 1990 to 1993 he served as VP, Finance of Environetics, Inc. a pharmaceutical water diagnostic business.

Dr. Laura Barrow joined Synergy in 2011 as SVP, Clinical Operations. Prior to joining Synergy, she served as Worldwide Head of Clinical and Regulatory Standard Operating Procedures at Pfizer. Before Pfizer, she spent 17 years in project management and organizational effectiveness at Bristol Meyers Squibb, and seven years in clinical research at Hoffman La-Roche.

Synergy's VP and Senior Director of Product Development is Dr. Stephen Comiskey, who joined the company in 2008. Prior to joining Synergy, Dr. Comiskey served as Director of Product Development at Nucleonics, Inc. and at Orapharma, Inc., and Group Leader at Aventis and American Home Products (Wyeth).

Figure 28: Key SGYP management

Name	Title	Experience Prior to SGYP	Joined SGYP in:
Gary S. Jacob, PhD	President & Chief Executive Officer	Callisto Monsanto	1999
Kunwar Shailubhai, PhD, MBA	Chief Scientific Officer	Callisto Monsanto	2001
Gail M. Comer, MD	Chief Medical Officer	Pfizer Abbott Labs	2012
Bernard F. Denoyer, CPA, MBA	Senior Vice President, Finance	Callisto META Group, Inc. Environetics, Inc.	2008
Laura Barrow, PharmD	Senior Vice President, Clinical Operations	Pfizer Bristol-Myers Squibb Hoffmann-La Roche	2011
Stephen Comiskey, PhD	Vice President, Product Development	Nucleonics, Inc. Orapharma, Inc. Aventis Wyeth	2008

Source: Company website

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Figure 29: SGYP P&L

	2011A	Q1/12A	Q2/12A	Q3/12E	Q4/12E	2012E	2013E	2014E	2015E
Revenues	**-**	**-**	**-**	**-**	**-**	**-**	**-**		**-**
Cost of sales	-	-	-	-	-	-	-	-	-
Gross Profit	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Research and Development	13.4	5.3	7.6	8.0	9.0	30.0	38.0	40.0	40.0
General and Administrative	6.7	1.7	1.9	2.0	2.0	7.6	9.4	12.0	13.0
Total operating expense	**20.2**	**7.1**	**9.5**	**10.0**	**11.0**	**37.6**	**47.4**	**52.0**	**53.0**
Operating income	**(20.2)**	**(7.1)**	**(9.5)**	**(10.0)**	**(11.0)**	**(37.6)**	**(47.4)**	**(52.0)**	**(53.0)**
Interest and investment Income	0.1	0.0	0.0	0.0	0.0	0.2	0.2	-	-
Interest Expense	(0.0)	-	-	-	-	-	-	-	-
Other Income	0.4	-	0.3	-	-	0.3	-	-	-
Change in fair value of derivative instruments - w arrants	5.3	0.0	(1.3)	-	-	(1.3)	-		
Total other income (expense)	**5.7**	**0.0**	**(1.0)**	**0.0**	**0.0**	**(0.9)**	**0.2**	**-**	**-**
Pre-tax income	**(14.5)**	**(7.0)**	**(10.6)**	**(10.0)**	**(11.0)**	**(38.5)**	**(47.2)**	**(52.0)**	**(53.0)**
Income tax expense (benefit)	-	-	-	-	-	-	-	-	-
Net Income	**(14.5)**	**(7.0)**	**(10.6)**	**(10.0)**	**(11.0)**	**(38.5)**	**(47.2)**	**(52.0)**	**(53.0)**
Basic EPS	**(0.30)**	**(0.13)**	**(0.17)**	**(0.15)**	**(0.15)**	**(0.60)**	**(0.59)**	**(0.59)**	**(0.59)**
Diluted EPS	**(0.30)**	**(0.13)**	**(0.17)**	**(0.15)**	**(0.15)**	**(0.60)**	**(0.59)**	**(0.59)**	**(0.59)**
Basic shares outstanding	**47.6**	**54.3**	**60.4**	**66.5**	**75.5**	**64.2**	**80.2**	**88.1**	**89.8**
Diluted shares outstanding	**47.6**	**54.3**	**60.4**	**66.5**	**75.5**	**64.2**	**80.2**	**88.1**	**89.8**

Source: Company reports and Canaccord Genuity estimates

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(as of 1 October 2012)

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Speculative Buy	63	6.7%	50.8%
Hold	267	28.2%	13.9%
Sell	34	3.6%	5.9%
	947*	100.0%	

*Total includes stocks that are Under Review

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