AEGIS CAPITAL CORP

Biotechnology
Raghuram Selvaraju, Ph.D.
(646) 502-2464
rselvaraju@aegiscap.com

Yi Chen, Ph.D.
(646) 502-2463
ychen@aegiscap.com

Initiating Coverage

June 12, 2012

Key Metrics

SGYP - NASDAQ	$4.66
Pricing Date	Jun 11 2012
Price Target	$25.00
52-Week Range	$7.08 - $1.86
Shares Outstanding (mm)	64.3
Market Capitalization ($mm)	$299.6
3-Mo Average Daily Volume	242,377
Institutional Ownership	NA
Debt/Total Capital	NM
ROE	NM
Book Value/Share	$0.06
Price/Book	77.7x
Dividend Yield	NM
LTM EBITDA Margin	NM

EPS ($) FY: December

	2011A	Prior 2012E	Curr. 2012E	Prior 2013E	Curr. 2013E
1Q-Mar	(0.04)	--	(0.13)A	--	(0.15)E
2Q-Jun	(0.05)	--	(0.16)E	--	(0.15)E
3Q-Sep	(0.01)	--	(0.18)E	--	(0.17)E
4Q-Dec	(0.12)	--	(0.21)E	--	(0.20)E
FY	(0.30)	--	(0.69)E	--	(0.68)E
P/E	NM		NM		NM

Company Description:

Synergy Pharmaceuticals, Inc., an emerging biopharmaceutical company, develops drugs to treat gastrointestinal (GI) disorders and diseases. It is developing plecanatide (SP-304), a guanylyl cyclase C (GC-C) receptor agonist, to treat GI disorders, primarily chronic constipation and IBS-C. The firm is headquartered in New York, New York; the company's web site is www.synergypharma.com.

Synergy Pharmaceuticals, Inc.

Rating: Buy

Cracking Chronic Constipation

Investment Highlights:

- **Initiating Coverage.** We are initiating coverage of Synergy Pharmaceuticals with a Buy rating and a 12-month price target of $25 per share. We believe Synergy represents a unique investment opportunity in the gastrointestinal (GI) disorders space, targeting a major unmet medical need with a novel, safe, and effective drug.
- **Plecanatide Potential.** Synergy's lead compound, plecanatide (SP-304), is a peptide analog of an endogenous human hormone that controls fluid secretion in the small intestine. As such, it works through a localized mechanism and is not systemically absorbed, making it very safe. In a Phase 2a trial, Synergy's lead drug provided substantial relief to individuals with chronic constipation over a 14-day period. The agent was exceptionally well-tolerated, with no serious adverse events noted and no incidence of diarrhea. In our view, this gives plecanatide an advantage over another agent currently under review at the FDA that shares the same mechanism of action, linaclotide. Plecanatide is in a Phase 2/3 trial in chronic idiopathic constipation (CIC), slated to complete enrollment in July of this year and report top-line data in October.
- **Significant Market Opportunity.** The market for chronic constipation (CC) and constipation-predominant irritable bowel syndrome (IBS-C) is substantial, with >100mm people suffering from these disorders in the U.S., Europe, and Japan. Roughly 8mm individuals in the U.S. alone seek treatment for constipation-related disorders every year. Existing therapies are either palliative or marginally effective, with substantial side effects. This could create a large opportunity for firms like Synergy, since plecanatide is based on a naturally-occurring hormone called uroguanylin and utilizes an evolutionarily-derived mechanism of action.
- **Attractive Valuation.** Synergy's current market cap of $300mm does not adequately value the potential of plecanatide and the firm's platform technology, in our view. We derive our 12-month price target using a risk-adjusted Net Present Value (rNPV) approach, which assumes launch of the drug in 2016 and peak sales of roughly $4.1bn in 2021, the last year prior to U.S. patent expiry. This methodology ascribes a $1.9bn total enterprise value to Synergy, resulting in a price objective of $25 per share, assuming roughly 80mm shares outstanding in mid-2013. We also note that linaclotide, which is closely related to plecanatide and which has already demonstrated positive Phase 3 data, is currently valued at a level approaching $3bn based on the market cap of Ironwood Pharmaceuticals, the originator of this agent.

The Disclosure section may be found on pages 48 - 49 of this report.

Investment Thesis

Synergy Pharmaceuticals is an emerging biotechnology firm focused on the development of a novel class of peptide drugs to treat gastrointestinal disorders. The company has already released positive data from a Phase 2a study with its lead molecule, plecanatide, and is currently running a Phase 2/3 trial with this agent in chronic idiopathic constipation (CIC), with data expected in late 2012. Plecanatide has significant advantages, in our view, over another drug candidate in this class, linaclotide, which has completed Phase 3 trials in chronic constipation and irritable bowel syndrome. We believe plecanatide could potentially be a best-in-class molecule.

We are initiating coverage of Synergy Pharmaceuticals (SGYP) with a Buy / High Risk rating and a 12-month price target of $25 per share, which assumes a total firm value of $1.9 billion and 80 million shares outstanding as of mid-2013.

Investment Positives

We Believe Plecanatide is a Substantially Risk-Mitigated Asset Targeting a Massive Commercial Opportunity. Over 100 million people worldwide are estimated to suffer from constipation-predominant irritable bowel syndrome (IBS-C) or chronic constipation (CC). Roughly 20 million sufferers of these severe diseases are estimated to be located in the U.S., Japan, and Europe. In the U.S. alone, approximately 15% of the total population of the country is estimated to suffer from some form of IBS-C or CC. Nearly 10 million people seek treatment every year in the U.S. for these conditions. In our view, Synergy's lead drug candidate, plecanatide, is a substantially risk-mitigated asset, as this drug has already demonstrated proof-of-concept efficacy in a Phase 2a study and shown exemplary safety, with no incidence of diarrhea as a significant adverse event. In addition, we note that linaclotide, a closely related compound that shares a mechanism of action with plecanatide, has demonstrated positive efficacy results in four Phase 3 trials, spanning both IBS-C and CC. Linaclotide – developed by Ironwood Pharmaceuticals – is the subject of three high-profile corporate partnerships with Forest Laboratories in the U.S., Astellas in Asia, and Almirall S.A. in Europe.

Established Pharmaceutical Firms Have An Appetite for GI Market Assets. While the specialty pharmaceuticals firms have been the primary heavy bettors in the GI market in recent years (rather than the large-cap pharmaceutical companies), the deals that have been signed are highly lucrative for the licensors, even when involving only specific geographies. We would cite two specific examples: the €428mm acquisition of Movetis by Shire Pharmaceuticals, in August 2010, which provided Shire with the rights to Resolor, a treatment for chronic constipation in women that is only marketed in Europe, and the deals that Ironwood signed with Forest Labs, Astellas, and Almirall for region-specific rights to linaclotide. While Resolor was already being marketed when Movetis was acquired by Shire, the deals that Ironwood signed on linaclotide were inked when the product was still in mid-stage clinical development and had not completed pivotal development. Pre-commercial milestones alone that are due Ironwood on linaclotide as a result of the three signed deals total $240mm, with substantial royalties on future sales of the drug. We calculate that the total implied net present value of linaclotide, given Ironwood's current enterprise value, is in excess of $3.5bn. In our opinion, the market opportunity for plecanatide and its follow-on compound, SP-333, along with the similarities between Synergy's platform and linaclotide, make Synergy an attractive licensing partner or acquisition prospect.

Differentiated Product Profile. Thus far, plecanatide has demonstrated an exemplary safety profile. This is to be expected, given the fact that it is derived from uroguanylin, which is an endogenous human peptide produced in the GI tract with a specific and well-

characterized mechanism of action involving agonism of the guanylate cyclase C (GC-C) receptor. Unlike linaclotide, which has similarity to the native human uroguanylin sequence but is actually derived from a bacterial peptide, plecanatide has structural homology to the human hormone and binds in an analogous fashion to the GC-C receptor. This confers a more beneficial safety profile to plecanatide and also provides substantial confidence that the activity profile of the drug is likely to be either as good as, or better than, that seen with linaclotide.

Investment Risks

Financial Outlook and History of Unprofitable Operations. Synergy has incurred operating losses since inception and, in our view, may not achieve profitability for several years. Although the firm has been able to obtain capital in order to fund its operations, it is not known whether Synergy will be able to continue this practice or be able to obtain other types of financing to meet its operating needs. We estimate that the company will probably need to raise additional funds within the next 12 – 18 months to support the completion of pivotal clinical development for plecanatide and advance SP-333, which is assumed in our financial models. Given these factors, potential investors should recognize that, in our opinion, shares of Synergy Pharmaceuticals are subject to above-average risk and may experience excessive price volatility.

Clinical Development Risk. While plecanatide has thus far demonstrated encouraging efficacy data and a positive safety profile, we note that the drug has yet to complete the final stage of clinical development – pivotal Phase 3 trials – and that hitherto-unforeseen safety issues could emerge during this final stage of testing. In addition, we note that an efficacy signal seen in a small data set could potentially evaporate in a larger patient population. Synergy's second pipeline candidate, SP-333, has yet to enter human testing. Safety issues could emerge in preclinical toxicology or safety tests that might preclude further development of SP-333. Accordingly, we believe that substantial development risk remains for both plecanatide and SP-333.

FDA Unpredictability. New therapeutics development is a multi-year process that requires human clinical trials prior to FDA approval. The agency may require additional clinical data from Synergy prior to granting approval for plecanatide, including information from pivotal trials that have yet to be designed or initiated. The company may not be able to enroll patients in these studies at the desired rate, which could delay submission of a regulatory filing on plecanatide petitioning for approval of the drug. Also, review times at the FDA may prove longer than originally expected. The agency could potentially require head-to-head trials between plecanatide and linaclotide, if linaclotide is already approved once plecanatide enters the final stages of clinical development. Such trials would likely require significant expense and might not conclusively demonstrate an advantage for plecanatide versus linaclotide.

Over-Specialization. Although plecanatide has demonstrated impressive safety and efficacy in clinical testing thus far, it remains the only clinical-stage asset that Synergy is currently developing. Should the continued advancement of plecanatide through to commercialization be compromised, the overall prospects of the company would be adversely impacted to a significant extent. While Synergy does have a platform, this technology is materially dependent upon the outlook for the GC-C receptor agonist sub-class, and any adverse clinical data seen with any molecules of this class might have a considerable negative impact on the outlook for the firm, particularly its ability to attain profitability or attract interest from an acquirer.

Potential Dependency on Partners to Provide Enhanced Market Penetration. If Synergy elects to partner plecanatide and/or SP-333, the potential licensee would likely be responsible for the commercialization of the drug. Market penetration would therefore

be dependent on the licensee's commitment to timely clinical development, as well as the product rollout. While we believe an established pharmaceutical firm might contribute meaningfully to the commercial optimization of drugs like plecanatide and SP-333, lack of commitment from a licensee could also potentially hinder Synergy's ability to realize favorable economics from the partnering of its core assets.

Competitive Landscape. If Synergy's products do reach the market, they will likely face competitors with greater financial resources and larger organizations for marketing, sales, distribution, and service. Many of the company's competitors offer broader product lines and may extend price discounts as a competitive tactic. In the GI tract market, specifically with regard to the treatment of constipation, major competitors include Sucampo Pharmaceuticals (SCMP/NASDAQ; Not Rated) and its partner Takeda Pharmaceuticals (TKPHF.PK/Other OTC; Not Rated) with Amitiza (lubiprostone), which has been launched in the U.S.; Forest Laboratories, Almirall, Astellas, and Ironwood Pharmaceuticals with linaclotide, which is under review at the U.S. FDA for both chronic constipation and constipation-predominant irritable bowel syndrome (IBS-C) and which is under review in Europe for IBS-C alone; and Shire Pharmaceuticals with Resolor (prucalopride), which is currently marketed only in Switzerland, the UK and a few other countries (not reimbursed in Germany) to treat chronic constipation in women. In our view, the most significant direct plecanatide competitor is linaclotide, which is about 24 – 36 months ahead in development. It is also possible that new treatment modalities for constipation-predominant irritable bowel syndrome and/or chronic constipation could emerge over the course of the next several years. Such approaches could include application of kappa (κ) opioid receptor agonists, such as fedotozine and asimadoline; use of probiotics, such as the bacterial organisms *Lactobacillus acidophilus* (*L. acidophilus*) and *bifidobacterium lactis* Bi-07; and novel corticotrophin-releasing factor receptor-1 (CRF-1) antagonists, such as BMS-562086, an agent currently being developed by the established pharmaceutical firm Bristol-Myers Squibb.

Intellectual Property Risk. The company relies on patents and trade secrets to protect its products from competitors. The pharmaceutical industry is litigious, and lawsuits are considered to be a normal part of doing business. A court might not uphold Synergy's intellectual property rights, or it could find that Synergy infringed upon another party's property rights. In addition, generics firms could potentially find loopholes in Synergy's intellectual property estate, which might enable them to launch generic versions of plecanatide and/or SP-333 prior to the expiration of patent protection on the product.

Reimbursement Risk. Following the institution of broad-based healthcare reform policy, reimbursement agencies have grown more wary of systematically reimbursing for drugs that are either unnecessary or provide marginal benefit at excessive cost. If Medicare spending growth continues to outpace GDP growth, and the government's ability to fund healthcare becomes impaired, changes could be made to reimbursement policy that would negatively affect the company's business, despite what we believe to be the compelling value proposition inherent in plecanatide and SP-333.

Additional Risks. As of March 31, 2012, Synergy had $6.1 million in cash and equivalents. Subsequently, the firm raised roughly $52 million from a registered direct offering of common stock. During the next 12 months, the firm may burn around $42 million. Sources of cash could include: licensing fees from partnerships, warrant and option exercises, or issuance of more shares. Synergy may not be able to raise cash at all.

Industry Risks. Emerging biotechnology and pharmaceuticals stocks are inherently volatile and increasingly subject to development and regulatory risk. Meeting or missing commercialization milestones may result in a significant change in the perception of the company and its stock price. We do not expect volatility to subside near term. For additional risk considerations, please refer to the company's SEC filings.

Valuation

Comparables Analysis: Given that Synergy is currently unprofitable, and considering our belief that this condition is likely to persist for the foreseeable future, we use a discounted cash flow-based approach to value the shares. Based on a comparables analysis, we believe that the stock is worth $25 per share, given our estimate of a $1.75 billion risk-adjusted net present value (rNPV) for plecanatide and SP-333. This assumes that the shares trade in line with the comp group average enterprise value of roughly $1.75 billion and that the firm has roughly 80 million shares outstanding in mid-2013.

Table 1: Comparable Company Analysis

(Millions, Except Per-Share Data)

Development	Therapeutic Area	Company	Ticker	Rating	Closing price 6/11/2012	Shares (MM)	Market cap ($MM)	Cash ($MM)	Debt ($MM)	Enterprise value ($MM)
Pre-approval	Cardiovascular Diseases	Amarin Corporation	AMRN	Not Rated	$11.31	136	1543	246	124	1421
Phase 3	Inflammation	Ardea Biosciences	RDEA	Not Rated	$31.97	37	1178	213	0	966
Marketed	Infectious Diseases	Cubist Pharmaceuticals	CBST	Not Rated	$40.14	63	2542	790	462	2214
Pre-approval	GI Disorders	Ironwood Pharmaceuticals	IRWD	Not Rated	$12.41	107	1331	202	1	1129
Marketed	CNS / Orphan Diseases	Jazz Pharmaceuticals	JAZZ	Not Rated	$41.23	57	2339	244	0	2095
Pre-approval	CNS / Oncology	Medivation	MDVN	Not Rated	$84.78	36	3073	380	187	2881
Marketed	GI Disorders	Salix Pharmaceuticals	SLXP	Not Rated	$51.78	58	3006	666	851	3192
Marketed	GI Disorders	Sucampo Pharmaceuticals	SCMP	Not Rated	$7.01	42	292	75	59	277
Marketed	Infectious Diseases	ViroPharma	VPHM	Not Rated	$19.81	70	1381	473	155	1063
Pre-approval	Metabolic Disorders	VIVUS, Inc.	VVUS	Not Rated	$24.25	100	2418	333	0	2084
		Average					**1910**			**1732**
								Discrepancy		
Current valuation	**GI Disorders**	**Synergy Pharmaceuticals**	**SGYP**	**Buy**	**$4.66**	**65**	**304**	**45**	**0**	**258**
					Derived 12-month compa-month comparable value					
										Projected
Target valuation (12-month)	**GI Disorders**	**Synergy Pharmaceuticals**	**SGYP**	**Buy**	**$25.00**	**80**	**1897**	**165**	**0**	**1732**

Source: First Call and Aegis Capital Corp. estimates

Free Cash Flow: We estimate that Synergy could be free cash flow-negative for the foreseeable future. We define free cash flow as operating cash flow minus capital expenditures and dividend payments. We utilize a discounted cash flow analysis supporting a risk-adjusted Net Present Value (rNPV) framework to derive our $25 price target. This approach is described further in the next section of this report.

Our detailed analysis is split into three principal components: our discounted cash flow model, including the rNPV assessment of plecanatide (presented overleaf); our assessment of the market for plecanatide and the associated sales model for the drug; and the near-term financial outlook for the company. Our historical income statement and financial projections are presented at the back of this report.

Risk-Adjusted Net Present Value Analysis

We are projecting peak annual global sales for plecanatide (SP-304) – formerly known as guanilib – of approximately $4.1 billion in 2021, prior to projected patent expirations in the 2022 time frame. This estimate includes only sales for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome. We estimate that at a peak market share of around 24% of all patients seeking therapy, there would be approximately 3.4 million patients receiving plecanatide to treat constipation-related conditions. In valuing this drug candidate, we have assessed the probability of success at 80% – since the molecule is currently in a Phase 2/3 trial, successfully completed a Phase 2a trial, has also shown proof-of-concept efficacy in animal models, and employs a substantially validated mechanism of action – as is evidenced by the clinical success of linaclotide, a similar agent. Our risk-adjusted base case NPV calculation yields a value of around $1.5 billion, or approximately $19 per share for this drug candidate, assuming a partnership with an established pharmaceutical firm that would provide Synergy with roughly 30% royalties on net sales globally.

Currently, we are not including any potential upside that could result from combination products or the commercialization of SP-333 for ulcerative colitis. Our valuation includes a nominal amount of $250 million for SP-333 and any related peptides that might have utility for indications such as ulcerative colitis, chronic obstructive pulmonary disease (COPD, or smoker's cough), and asthma, since these are currently still in preclinical development. We assume that Synergy or a potential partner could file for approval of plecanatide by early 2015. The drug could be launched in early 2016, in our view, assuming a standard 10-month review period.

Table 2: Plecanatide (SP-304) Market Metrics

Plecanatide - Global	
Total constipation patients[1]	164MM
Patients seeking treatment[2]	14.6MM
Peak market share[3]	24%
Treatment revenue/prescription/course of therapy[4]	$1,275
Peak sales[5]	$4.1B
Launch[6]	2016
Peak sales year	2021
Protection expires[7]	2022
Discount rate	15%
Probability of success[8]	80%
Risk-adjusted NPV[9]	$1.5B
NPV per share	$19.00
Estimated Net Cash Position ($MM; end-2Q 2013)	$165MM
Additional Value Drivers (peptide pipeline, including SP-333)	$250MM
Total enterprise value	$1.9B
Shares Outstanding (MM; end-2Q 2013)	80MM
Present value-derived price target	$25.00

Notes on assumptions:

[1] Constipation patients - worldwide (only includes US and European Union) (Source: National Institute of Health, American Gastroenterological Association)

[2] Patients with moderate-to-severe chronic constipation and constipation-predominant irritable bowel syndrome (IBS-C) (Source: Aegis Capital Corp. estimates)

[3] Peak market share - blended; factoring in competition from laxatives, lubiprostone, prokinetics and linaclotide

[4] Revenue/year/prescription - estimated to be similar to linaclotide (wholesale acquisition cost)

[5] Peak sales - treatment revenue/year x treated patients x peak market share

[6] Launch in 2016 (US) / 2017 (EU)

[7] Patent expiry starting in 2022; Hatch-Waxman extensions may provide up to an additional five years of protection

[8] Probability of success - plecanatide has shown proof-of-concept, is in a Phase 2/3 trial, and is related to linaclotide, under FDA review

[9] Cash flow fully taxed at 35% following launch; upfront payments and milestones cancel out operating loss carry-forwards

Source: Company reports; Aegis Capital Corp. estimates

Linaclotide Valuation Perspectives

In this section, we provide an overview of the licensing arrangements that have thus far been consummated by Ironwood Pharmaceuticals (formerly Microbia) on linaclotide. We believe these agreements and the deal economics involved provide important perspectives on the potential value of plecanatide, given significant similarities between linaclotide and plecanatide and the fact that these agents share a mechanism of action that has now conclusively been validated in large clinical trials. Furthermore, if we assess the relative share of linaclotide presently owned by Ironwood and ascribe Ironwood's current enterprise value to this, it is possible to extrapolate to a figure corresponding to the current market value of linaclotide. We believe this number bodes well for plecanatide's prospects and, by extension, the upside potential inherent in Synergy Pharmaceuticals.

In September 2007, Ironwood entered into a partnership with Forest Laboratories to co-develop and co-market linaclotide in the U.S. Forest and Ironwood are jointly and equally funding the development and commercialization of linaclotide in the U.S., with equal share of any profits. Forest also has exclusive rights to linaclotide in Canada and Mexico, and is slated to pay Ironwood royalties in the mid-teens on any net sales in these countries. In addition to having reimbursed Ironwood for half of linaclotide's development costs since September 2007, Forest has paid Ironwood $120 million in milestone payments to date and has purchased $25 million of Ironwood's capital stock. Remaining pre-commercial milestone payments could total up to $85 million upon U.S. approval. Total payment to Ironwood under the Forest collaboration agreement could sum up to $330 million, including the $145 million that has already been paid. This included a $20 million milestone payment upon acceptance of the linaclotide NDA.

Subsequent to inking the Forest deal, Ironwood, in April 2009, entered a license agreement with Almirall S.A., a Spain-based specialty pharmaceuticals firm, over rights to linaclotide in Europe (including the Commonwealth of Independent States countries and Turkey). Almirall has paid Ironwood $57 million in license fees and milestone payments to date and has purchased $15 million of Ironwood's capital stock. Remaining pre-commercial milestone payments could total up to $20 million. Almirall is funding the development and commercialization of linaclotide. Ironwood is slated to receive gross royalties that escalate based on sales volume in the territory, beginning in the mid-twenties, minus the transfer price paid for the active pharmaceutical ingredient, or API. In November 2009, Ironwood licensed certain rights to linaclotide to Astellas Pharma, a large Japanese pharmaceutical firm, in Japan, South Korea, Taiwan, Thailand, the Philippines, and Indonesia. Astellas paid Ironwood a $30 million upfront fee. Other pre-commercial milestones could total up to $45 million. Astellas is responsible for funding all development and commercialization-related costs. If Astellas receives approval to market and sell linaclotide, Ironwood is slated to receive gross royalties that escalate based on sales volume in the territory, starting in the low-twenties, less the transfer price paid for the API. Linaclotide is covered by a U.S. composition of matter patent expiring in 2025 and European and Japanese composition of matter patents expiring in 2024.

Based on the above publicly available information, we believe Ironwood's share of linaclotide is roughly 40% of the drug's total value. Furthermore, we note that the upfront payments alone in these agreements total $140 million. Given Ironwood's market cap of $1.2 billion (~$1.5 billion fully-diluted), we believe the current market value being assigned to linaclotide is approximately $3 billion. In contrast, Synergy's 100% ownership of rights to plecanatide and related peptides is currently valued at $300 million. Despite linaclotide's substantial lead on plecanatide, the considerable discrepancy in valuation between Synergy's interest in plecanatide and the market valuation of linaclotide appears to be unwarranted, in our opinion. We would note that, if plecanatide were to be valued at a level similar to linaclotide, the implied price per share of Synergy stock would approach $40, without considering Synergy's pipeline.

Table 3: Linaclotide Licensing Agreements

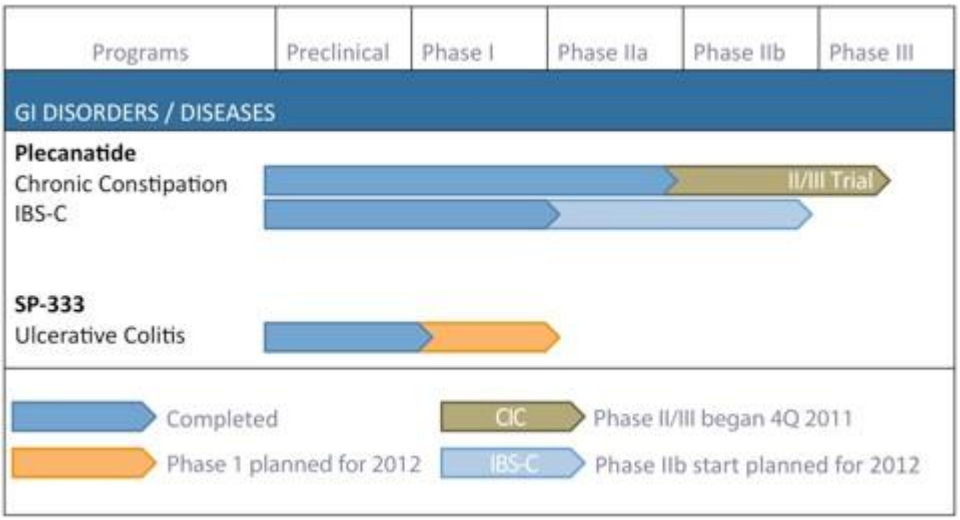
Partner	Year	Geography	Upfront Payment	Equity Stake	Pre-Commercial Milestones	Post-Commercial Milestones	Royalty Rate	Peak Sales Estimate
Forest Laboratories	2007	US	$70 million	$25 million	$155 million	$105 million	50%	$1.5 billion
Forest Laboratories	2007	Canada / Mexico	NA	NA	NA	NA	15%	$100 million
Almirall S.A.	2009	Europe (including Russia and Turkey)	$40 million	$15 million		NA	22-25%	$400 million
Astellas	2009	Japan, South Korea, Taiwan, Thailand, Philippines, Indonesia	$30 million	NA	$45 million	NA	18-20%	$250 million
		Totals	**$140 million**	**$40 million**	**$200 million**	**$105 million**	**NA**	**$2.25 billion**

Source: Company Reports

Company Overview

Synergy Pharmaceuticals was initially formed by several individuals who were originally conducting research into the function of guanylate cyclase C receptor agonists at Monsanto (MON/NYSE; Not Rated). The company's aim was to develop therapeutic agents based on this proprietary research. As a result, issued patents form the foundation of Synergy's platform technology, which is focused on addressing significant unmet medical needs in the gastrointestinal tract disorders market.

Figure 1: Synergy Pharmaceuticals Development Pipeline



Source: Company reports

Recently, Synergy's representatives attended Digestive Disease Week in San Diego, IL, which was held May 19 – 24. We would note that investors, scientists and clinicians alike remain favorably disposed towards the uroguanylin mechanism of action approach to treating chronic constipation. Furthermore, we would draw investors' attention to the fact that Mark Currie, Ironwood Pharmaceuticals' Chief Scientific Officer, formerly worked at Monsanto and shares a background with Kunwar Shailubhai, who holds the CSO position at Synergy. The patent position developed through Dr. Shailubhai's work provides Synergy with a substantial strategic advantage, in our view; this is because Synergy's patent estate covers the natural hormone sequence and related peptides. Ironwood accordingly had to resort to patenting the "ST" peptides derived from bacterial endotoxin, which have substantial homology with the uroguanylin sequence but are not identical. While we cannot confirm any speculation at this juncture, we would also draw investors' attention to the possibility that the value of linaclotide could increase near-term if any other firms aside from Ironwood's current partners attempt to acquire Ironwood. For example, AstraZeneca has had a significant interest in the gastrointestinal disorders field for some time. A substantial increase in the perceived value of linaclotide, in our view, would have a positive impact on Synergy given the potential advantages of plecanatide and the similarities in function between the two peptide products.

Firm History

Synergy Pharmaceuticals was founded by a group of ex-Monsanto employees with substantial proprietary knowledge in the field of guanylate cyclase C (GC-C) receptor agonism. These individuals are co-inventors on issued patents covering the application of GC-C receptor agonists for gastrointestinal disorders. On July 14, 2008, Pawfect Foods Inc. ("Pawfect"), a Florida company incorporated on November 15, 2005, acquired 100% of the common stock of Synergy Pharmaceuticals, Inc., and its wholly-owned

subsidiary, Synergy Advanced Pharmaceuticals, Inc. (collectively "Synergy-DE"), a Delaware corporation incorporated on September 11, 1992, under the terms of an exchange transaction among Pawfect, Callisto Pharmaceuticals, Inc. ("Callisto"), Synergy-DE, and other holders of Synergy-DE common stock ("Exchange Transaction").

On July 21, 2008, Pawfect amended its articles of incorporation to effect the actions necessary to complete the transactions contemplated by the exchange transaction. Pawfect also changed its name to Synergy Pharmaceuticals, Inc. Immediately following the exchange transaction, Synergy discontinued its pet food business and is now focused exclusively on the development of drugs to treat GI disorders and diseases. Synergy acquired the GI drugs and related technology in connection with the exchange transaction. The exchange transaction was treated as an asset acquisition by Pawfect for accounting purposes. Under this method of accounting, Pawfect is considered the acquiring entity, issuing stock for the assets and liabilities of Synergy-DE. The assets and liabilities of Synergy-DE, primarily cash and accounts payable, were stated at their fair value. Net liabilities acquired totaled $877,646. The fair value of the 45,464,760 shares issued in connection with the exchange transaction totaled $27,278,856 on July 14, 2008, based on a per-share value of $0.60, which was the per-share price the company's 5,000,000 common shares sold for in a private placement on that date. Total consideration of $28,156,502 was allocated in full to the Synergy research and development projects, which had not yet reached technological feasibility. Having no alternative use, this amount was charged to purchased in-process research and development ("IPR&D") expense as of the date of the exchange transaction. Pawfect amended its articles of incorporation in the State of Florida to effect the actions necessary to complete the transactions contemplated by the exchange transaction, including: (i) increasing the number of authorized common shares to 150,000,000, from 50,000,000; (ii) authorizing 20,000,000 shares of preferred stock; and (iii) changing the common stock par value per share from $0.001 to $0.0001.

As of March 31, 2012, Synergy's principal shareholder, Callisto, owns 41.1% of its outstanding shares. In our view, it is possible that Synergy would elect to consolidate the shareholder base by merging Callisto into Synergy and issuing new shares of Synergy to Callisto stockholders, in what would effectively constitute a "pari-passu" arrangement. We do not anticipate any substantial near-term sale of Synergy stock by Callisto, since Callisto is a virtual company and Synergy and Callisto share management team members.

On June 30, 2010, Synergy entered into securities purchase agreements to sell securities to non-U.S. investors and raised gross proceeds of approximately $2,754,000 in a registered direct offering. Synergy sold 324,000 units at $8.50 per share to investors. Each unit consists of one share of Synergy's common stock and one warrant to purchase one additional share of Synergy's common stock. The warrants expire after five years and are exercisable at $9.00 per share. In July 2010, the firm paid an aggregate $261,630 to selling agents in connection with this placement. Subsequently, on August 16, 2010, Synergy entered into a securities purchase agreement with an accredited investor to sell securities and raise gross proceeds of $400,000 in a private placement. The firm sold 49,383 units to the investor with each unit consisting of one share of Synergy common stock and one warrant to purchase one additional share of the company's common stock. The purchase price paid by the investor was $8.10 for each unit. The warrants expire after five years and are exercisable at $8.50 per share.

On July 13, 2010 and October 12, 2010 Synergy issued 670,933 shares of its common stock as consideration for an agreement by certain holders of the company's common stock to extend their lock-up of such shares from August 15, 2010 to January 15, 2011 or enter into a lock-up agreement until such date. This issuance was approved by the company's board of directors on June 22, 2010 and represents 5% of the shares of previously issued common stock currently subject to a lock-up agreement or being

requested to lock-up. The fair value of the common stock issued to accomplish this lock-up extension totaled $3,235,040, based on the estimated fair value of the shares issued in connection with the June 30, 2010 and October 6, 2010 registered direct offerings. The par value of these shares was charged to additional paid in capital as a cost of facilitating the June 30, 2010 registered direct offering.

On October 1, 2010, the company entered into a securities purchase agreement with an investor and raised gross proceeds of $2,500,000 in a registered direct offering. The company sold to the investor 500,000 shares of its common stock and warrants to purchase 200,000 shares of common stock. The common stock and warrants were sold in units consisting of one share of common stock and two-fifths of a warrant to purchase a share of common stock. The purchase price paid by the investor was $5.00 for each unit. The warrants expire after five years and each whole warrant has an exercise price of $5.50 per share. On October 18, 2010 the firm entered into a securities purchase agreement with certain investors and raised gross proceeds of $1,525,000 in a registered direct offering. Synergy sold 305,000 shares of its common stock and warrants to purchase 122,000 shares of common stock. The common stock and warrants were sold in units consisting of one share of common stock and two-fifths of a warrant to purchase a share of common stock. The purchase price paid was $5.00 for each unit. The warrants expire after five years and each whole warrant has an exercise price of $5.50 per share.

On March 4, 2011, Synergy closed a registered direct offering with a non-U.S. investor which raised gross proceeds of $1,800,000. Synergy issued to the investor 300,000 shares of its common stock and warrants to purchase 210,000 shares of common stock. The purchase price paid by the investor was $6.00 for each unit. The warrants expire after seven years and are exercisable at $6.20 per share.

As of March 31, 2011, the company had a negative working capital of $3,787,881, vs. a negative working capital position of $2,307,290 as of December 31, 2010. On February 8, 2011, Synergy entered into a loan agreement with an investor in which the investor agreed to lend an aggregate $950,000 to the firm. Concurrent with the execution and delivery of the loan agreement, Synergy issued a note to the investor in the principal amount of $500,000. The firm had the option to issue an additional note to the investor in the principal amount of $450,000 beginning February 21, 2011. The notes bore interest at 17% per annum and became payable on April 1, 2011. At that time, Synergy repaid the note in full and did not exercise the option to issue any additional notes. Currently, therefore, the firm does not have any outstanding long-term debt obligations.

On March 4, 2011, Synergy closed a financing with a non-U.S. investor, which raised gross proceeds of $1,800,000 in a registered direct offering. Synergy issued to the investor 300,000 shares of its common stock and warrants to purchase 210,000 shares of common stock. The purchase price paid by the investor was $6.00 for each unit. The warrants expire after seven years and are exercisable at $6.20 per share. From May 2 to May 23, 2011, Synergy entered into securities purchase agreements with certain investors to raise gross proceeds of $2,499,999 in a registered direct offering. The company issued to the investors 416,667 shares of its common stock and warrants to purchase 416,667 shares of common stock. The purchase price paid by the investors was $6.00 for each unit. The warrants expire after seven years, are exercisable at $4.25 per share and the exercise price is protected, in the event of subsequent equity sales at a lower price, for a period of two years from issuance.

On June 3, 2011, a Synergy warrant holder exercised his warrants and purchased a total of 80,000 shares of common stock. Synergy raised gross proceeds of $415,309 as a result of the warrant exercise. The purchase price paid by the warrant holder was $5.00 for 49,383 shares and $5.50 for 30,617 shares.

From June 3 to June 15, 2011, Synergy entered into securities purchase agreements with certain investors to raise gross proceeds of $1,161,243 in a private placement. The company issued to the investors 193,541 shares of its common stock and warrants to purchase 193,541 shares of common stock. The purchase price paid by the investors was $6.00 for each unit. The warrants expire after seven years and are exercisable at $6.50 per share. In connection with this transaction, Synergy entered into a registration rights agreement with each of the investors pursuant to which Synergy agreed to register the shares of common stock and shares of common stock underlying the warrants in a resale registration statement to be filed within 45 days after the final closing of the private placement. On December 19, 2011, Synergy filed a registration statement on Form S-3 covering the 193,541shares of common stock and the 193,541 shares of common stock issuable upon exercise of the above warrants.

On July 11, 2011, Synergy entered into a securities purchase agreement with an investor to raise gross proceeds of $242,750 in a private placement. The firm issued to the investor 40,458 shares of its common stock and warrants to purchase 40,458 shares of common stock. The purchase price paid by the investors was $6.00 for each unit. The warrants expire after seven years and are exercisable at $6.50 per share. In connection with this transaction Synergy entered into a registration rights agreement with the investor pursuant to which Synergy agreed to register the shares of common stock and shares of common stock underlying the warrants in a resale registration statement to be filed within 45 days after the final closing of the private placement.

On July 19, 2011, Synergy filed a registration statement on Form S-3 covering the 40,458 shares of common stock and the 40,458 shares of common stock issuable upon exercise of the above warrants. On July 28, 2011, Synergy entered into a securities purchase agreement with certain investors to raise gross proceeds of $2,336,472 in a registered direct offering. The company issued to the investors 333,782 shares of its common stock. The purchase price paid by the investors was $7.00 for each share of common stock and there were no warrants issued in this transaction. On December 7, 2011, Synergy issued to these investors an additional 215,981 shares of common stock which brought the purchase price per share paid by these investors to $4.25 per share.

On October 4, 2011, Synergy entered into a securities purchase agreement with certain investors for the sale of 552,647 units in a registered direct offering, with each unit consisting of one share of common stock and one warrant to purchase 0.5 shares of common stock. The firm's gross proceeds from the sale of the units were $2,348,723. The purchase price paid by the investors was $4.25 per unit. The warrants expire after five years and are exercisable at $5.50 per share. The October 4, 2011 transaction pricing resulted in the exercise price of the 416,667 warrants issued during May 2011 being reduced to $4.25 per share. The "price protection" rights attributable to the May warrants remained in effect until the firm's listing on the NASDAQ exchange, effective December 1, 2011. This exercise price reduction from $6.50 per share to $4.25 per share decreased the prospective exercise proceeds attributable to the May warrants by $937,500.

On October 19, 2011, Synergy entered into securities purchase agreements with various investors for the sale of 136,912 units in a registered direct offering, with each unit consisting of one share of common stock and one warrant to purchase 0.5 shares of common stock. The gross proceeds from the sale of the units were $581,876. The purchase price paid by the investors was $4.25 per unit. The warrants expire after five years and are exercisable at $5.50 per share. On October 28, 2011, the firm entered into securities purchase agreements with various investors for the sale of 117,647 units in a registered direct offering, with each unit consisting of one share of common stock and one warrant to purchase 0.5 shares of common stock. The gross proceeds to the firm from the unit sales were $500,000. The purchase price paid by the investors was $4.25 per unit. The warrants expire after five years and are exercisable at $5.50 per share.

On November 14, 2011, Synergy entered into a securities purchase agreement with certain accredited investors for the sale of 1,328,941 units in a private placement, with each unit consisting of one share of common stock and one warrant to purchase one share of common stock. The gross proceeds from the sale of the units were $5,648,000. The purchase price paid by the investors was $4.25 per unit. The warrants expire after five years and are exercisable at $5.50 per share.

On December 1, 2011, Synergy entered into an underwriting agreement with Aegis Capital Corp. and Early Bird Capital for the public offering and sale of 1,875,000 units, consisting of two shares of common stock and one warrant to purchase one share of common stock. On December 6, 2011 Synergy closed the offering at a price of $8.00 per unit, resulting in gross proceeds to the company of $15,000,000. Each warrant has an exercise price of $5.50 per share and will expire five years from the date of issuance. Synergy also granted the underwriters, under the terms of the underwriting agreement, an option to purchase up to an additional 281,250 units to cover over-allotments. On December 15, 2011, the over-allotment option was exercised for additional gross proceeds of $2,250,000. On December 6, 2011, in connection with this underwritten financing, Synergy issued a total of 112,500 common stock purchase options to the underwriters and several principals of the firm. The options expire three years from issuance and have an exercise price of $5.00 per share.

In 2011, Synergy paid $2,148,383 in selling agent fees and legal expenses related to the above financing transactions and issued 9,025 warrants to a selling agent which expire after seven years and are exercisable at $6.50 per share, and 77,750 units consisting of one share of common stock and one warrant to purchase one share of common stock, which expire in five years, and are exercisable at $5.50 per share. The company's up-listing from the Pink Sheets to the NASDAQ took effect on December 1, 2011.

On May 9, 2012, Synergy closed an underwritten public offering of 10 million shares of common stock at an offering price of $4.50 per share. The company received net proceeds, after deducting the underwriting discount and estimated offering expenses, of approximately $42.0 million. The firm also granted the underwriters a 45-day option to purchase up to an additional 1,500,000 shares of common stock to cover over-allotments. Subsequently, in early June 2012, the firm announced that the over-allotment option was exercised in full, in a manner analogous to that seen in the November 2011 financing. This brought the total gross proceeds from this financing round to $51.75 million. Aegis Capital Corp. acted as the sole book-running manager for the offering. Roth Capital Partners acted as lead manager, while Brean Murray, Carret & Co. and Summer Street Research Partners acted as co-managers. In our view, the proceeds from this financing are likely to be sufficient to enable the firm to complete the ongoing Phase 2/3 trial of plecanatide in chronic idiopathic constipation and facilitate completion of IND-enabling studies on SP-333, the firm's second pipeline candidate.

Synergy is slated to perform a number of critical clinical development activities during 2012. Among these are the July / August 2012 completion of enrollment in the ongoing Phase 2/3 trial of plecanatide in chronic idiopathic constipation, with the subsequent release of top-line data from that study expected in late October or early November 2012. Synergy also plans to have a pre-IND meeting with the FDA to discuss the plan to advance plecanatide into proof-of-concept clinical development in irritable bowel syndrome of the constipation-predominant subtype (IBS-C). The pre-IND meeting is scheduled to take place on June 19th, 2012, with the trial slated to start in August or September 2012. We expect SP-333 to enter a Phase 1 trial in August 2012 and potentially report initial safety data in late 2012 or early 2013. Synergy is also developing a backup to plecanatide, known as SP-373, which is purported to be more stable and less hygroscopic than plecanatide.

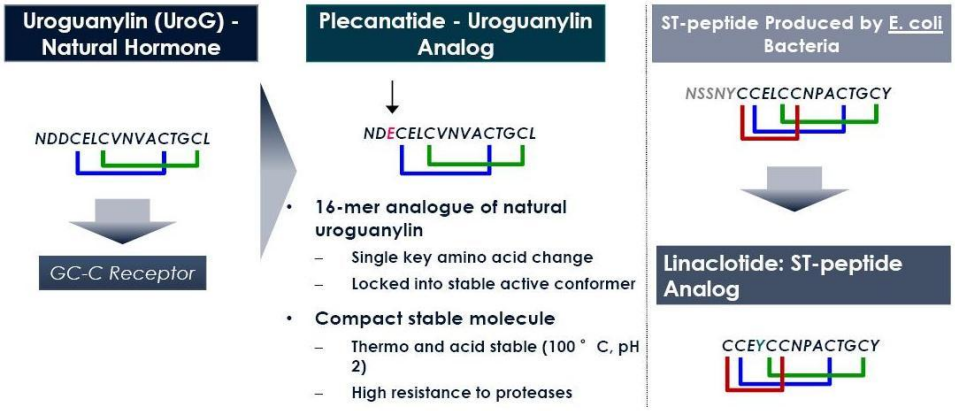
Plecanatide (SP-304) Overview

The lead Synergy candidate, plecanatide, is a 16-mer peptide analogue of the endogenous human hormone uroguanylin. Initially known as guanilib, the drug was originally developed on the basis of work done by Dr. Kunwar Shailubhai and colleagues in the laboratories of Monsanto, where the first characterization of the role of uroguanylin and its link to guanylate cyclase C receptor signaling was performed. The sequence of plecanatide is identical to that of uroguanylin, with the exception of a single change – the third amino acid in the sequence is changed from aspartic acid to glutamic acid. While both of these residues are polar and negatively charged, the change effectively provokes an alteration in the structure of the peptide, such that it is locked into a specific conformation. It is this conformation that interacts preferentially with the GC-C receptor and which exhibits substantially greater stability. The plecanatide peptide is thermostable at temperatures of 100°C and acidity levels down to pH 2. It is highly protease-resistant and behaves like a small molecule drug, with more potency at the relevant receptor level than the endogenous hormone. The binding affinity of plecanatide to the human GC-C receptor is eight-fold higher than that of uroguanylin.

Uroguanylin is a 16-amino acid peptide secreted by enterochromaffin cells in the duodenum and proximal small intestine and contains four conserved cysteine residues. It was first isolated from opossum urine due to its ability to stimulate cGMP production in T84 intestinal cells. The bioactive peptide is located at the COOH-termini of a larger precursor. The protein is structurally related to guanylin and lymphoguanylin. The gene is expressed mainly in the intestinal mucosa, but also in several different tissues, including the digestive, renal, central nervous, reproductive and lymphoid systems. As stated previously, uroguanylin acts as an agonist of the guanylyl cyclase receptor GC-C and regulates electrolyte and water transport in intestinal and renal epithelia. In humans, the uroguanylin peptide is encoded by the GUCA2B gene. The hormone functions as a natriuretic peptide – an agent that stimulates sodium excretion through urine.

Enterochromaffin cells produce about 90% of the body's store of serotonin (5-HT). In the gastrointestinal tract, 5-HT is important in response to chemical, mechanical, or pathological stimuli in the lumen. It activates both secretory and peristaltic reflexes and activates vagal afferents (via 5-HT_3 receptors) that signal to the brain (important in the generation of nausea). The primary physiological function of uroguanylin is to regulate the renal excretion of sodium, but it has also been shown that it plays a fundamental role in fluid secretion in the intestine, and therefore regulates intestinal motility.

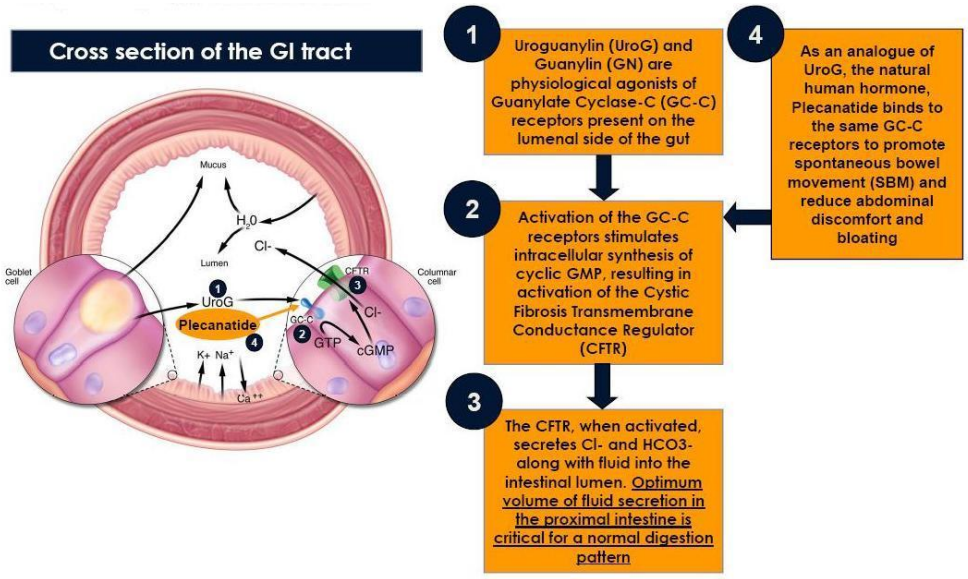
Figure 2: Plecanatide – Linaclotide – Uroguanylin Homology



Source: Synergy Pharmaceuticals

The mechanism of action for uroguanylin and related peptides involves the interaction of the GC-C receptor with the cystic fibrosis transmembrane conductance regulator (CFTR), a receptor that controls the secretion of fluid into the proximal intestine. This process is necessary for normal digestion to occur. Without adequate fluid secretion, intestinal motility is perturbed, and constipation is typically the result. Uroguanylin and its analogues stimulate intestinal fluid secretion by turning on the GC-C receptor and its downstream target, the CFTR. As shown below, this cascade primarily involves the goblet cells of the small intestine and is mediated via cyclic GMP.

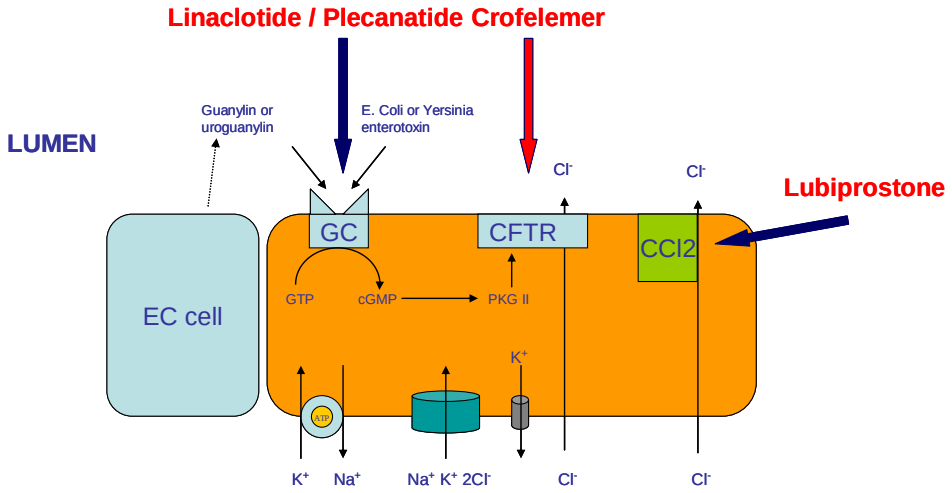
Figure 3: Mechanisms Underlying Intestinal Fluid Secretion



Source: Synergy Pharmaceuticals; Journal of Gastroenterology

The figure below shows how GC-C receptor agonists fit into the overall spectrum of therapeutic intervention for the purposes of providing relief from symptoms of constipation and other gastrointestinal disorders. The GC-C receptor plays an important role in fluid secretion, but other intervention points also exist. For example, gastrointestinal motility can be stimulated through the 5-HT_4 receptor.

Figure 4: GI Tract Receptor Targets



Source: Department of Gastroenterology, University of Leuven, Belgium

SP-333 Program Overview

An oral synthetic analog of uroguanylin, a natriuretic hormone produced in the GI tract that binds to and activates guanylate cyclase C, SP-333 is closely related to plecanatide. However, unlike plecanatide, SP-333 represents a next-generation GC-C receptor agonist with enhanced stability characteristics and more favorable pharmacokinetics. The drug is substantially more potent than plecanatide from an anti-inflammatory perspective, as *in vivo* data has demonstrated that doses of SP-333 twenty times lower than active doses of plecanatide are capable of attenuating GI tract inflammation by suppressing the production and secretion of major pro-inflammatory cytokines.

Synergy has developed SP-333 to specifically address ulcerative colitis—the hypothesis being that this agent can act as an extremely potent replacement for uroguanylin if endogenous expression of this hormone is lacking. Deficiency of this hormone is predicted to be one of the primary reasons for the formation of polyps that can lead to colon cancer, as well as debilitating and difficult-to-treat GI inflammatory disorders such as ulcerative colitis and Crohn's disease. More than 500,000 Americans are afflicted with ulcerative colitis, a type of IBD that causes chronic inflammation of the colon. Along with Crohn's disease, the other major form of IBD, ulcerative colitis is painful and debilitating, and can lead to other serious and life-threatening complications such as increased incidence of colon cancer. There is currently no medical cure for ulcerative colitis; therefore, a considerable medical need exists for its control and treatment.

Preclinical Development

Synergy Pharmaceuticals has completed the majority of non-clinical studies with SP-333 necessary to file an Investigational New Drug (IND) application. These studies include safety, toxicology, and efficacy assessments in validated animal models. Orally-administered SP-333 binds to and activates guanylate cyclase C (GC-C) expressed on epithelial cells lining the GI mucosa, resulting in activation of GC-C. In animal models, oral administration of SP-333 ameliorates GI inflammation by suppressing production of certain pro-inflammatory cytokines. Optimization of a scaled-up production process to enable cGMP commercial-scale manufacturing has been completed. The firm plans to file an IND in the late summer of 2012 and initiate a Phase 1 trial in healthy volunteers with SP-333 in the fall of 2012, with data becoming available in late 2012 or early 2013.

SP-333 could become an important value driver, given the substantial unmet need in the ulcerative colitis market. Marketed and clinical-stage drugs to treat ulcerative colitis are primarily anti-inflammatory drugs, which may have systemic side effects such as immune compromise. We believe that, in this context, SP-333 may be able to offer a compelling advantage. Synergy plans to study the drug in multiple formulations, including both orally-bioavailable immediate-release / extended-release as well as colonic formulations suitable for delivery via enema. The drug could be designed to be released preferentially in the ileum and colon using pH-sensitive coatings or linkers that are cleaved by enzymes specific to the lower GI tract, as seen with forms of mesalamine (Asacol, sulfasalazine).

Patent Protection

On February 1, 2011, the U.S. Patent and Trademark Office (USPTO) issued U.S. Patent No. 7,879,802, covering Synergy's novel drug candidate SP-333 to treat inflammatory bowel disease (IBD). The patent specifically claims the composition of matter for SP-333 and its use in the treatment of human diseases. In our view, the effective lifespan of patent protection on SP-333 could extend to 2028, not counting patent term and Hatch-Waxman extensions. Accordingly, we believe that SP-333 is an important and valuable asset to Synergy, particularly since competitors such as Ironwood cannot compete in serious inflammatory GI tract conditions such as ulcerative colitis. The competitive landscape for SP-333 in UC looks relatively favorable, with no other agents in the GC-C receptor agonist class in clinical development for this indication.

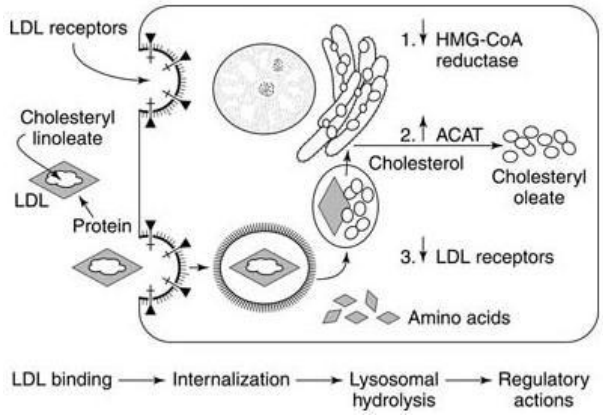
Cholesterol-Lowering Platform Potential

In addition to its work in gastrointestinal disorders, Synergy has also been engaged in characterizing the applicability of the GC-C receptor modulation approach in other areas, including cardiovascular disease. In May 2011, the company announced that it had successfully completed preclinical *in vitro* studies showing that peptides derived from its unique and proprietary platform focusing on agonism of the guanylate cyclase C (GC-C) receptor can inhibit bile acid uptake. This may indicate an important role for these peptides in managing cholesterol levels. We believe that this development showcases the breadth of Synergy's technology platform, and shows that the company's science is innovative and valuable.

While Synergy's core focus remains unquestionably on the clinical development of plecanatide for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome, we note that the discovery of cholesterol-modulating activity with related peptides clearly shows that the platform has potential beyond gastrointestinal (GI) tract disorders. The possibility of applying Synergy's GC-C receptor-modulating technology to disorders unrelated to the GI tract is not currently reflected in our valuation, and could constitute a source of upside to our projections longer-term.

The data announced in mid-2011 constituted the first time that GC-C receptor agonist activity was implicated in the inhibition of bile acid uptake. It is well documented that dietary or pharmacological manipulation of the enterohepatic circulation of either cholesterol or bile acids can potentially cause marked changes in plasma cholesterol levels. Given the massive size of the cholesterol-lowering market – Lipitor (atorvastatin) was the world's most popular drug with >$10 billion in annual sales prior to going off-patent in late 2011 – we believe that the potential for use of GC-C receptor agonists in cholesterol-lowering could be a major value driver for Synergy if the preclinical data obtained thus far can be confirmed clinically. The figure below illustrates how cholesterol is taken up and transported within cells. The detergent properties of bile acids aid in the solubilization of cholesterol and permit its cellular absorption.

Figure 5: Cholesterol Transport



Source: Cliffs Notes

Synergy has filed a patent application covering the use of proprietary GC-C agonists as drug candidates for prevention and treatment of elevated cholesterol, heart stroke, atherosclerosis, type II diabetes, coronary heart disease, gallstones, hypertension, obesity, and other cardiovascular diseases. GC-C agonists may also be used in combination with statins to produce synergistic effects to reduce the dose of statins such as Lipitor®, Zocor® and Crestor® necessary to lower low-density lipoprotein-associated cholesterol (LDL-cholesterol, also known colloquially as "bad" cholesterol).

Plecanatide Clinical Data

Phase 2/3 Clinical Trial. An ongoing clinical trial of plecanatide to treat chronic idiopathic constipation patients began in late 2011 and was designed as a Phase 2/3 trial. This 90-day repeat oral dose-ranging, randomized, double-blind, placebo-controlled study is slated to enroll approximately 880 chronic constipation patients, and has as its primary objective the measure of complete spontaneous bowel movements (CSBMs) using a responder analysis. The trial is also evaluating total spontaneous bowel movements (SBMs) and daily constipation symptoms, including straining, stool consistency, and abdominal discomfort, plus the impact of plecanatide on disease-specific quality-of-life measures. SBMs are bowel movements that occur without the use of a laxative, enema, or suppository within the preceding 24 hours; CSBMs are SBMs after which the patient reports a feeling of complete evacuation. The Phase 2/3 trial reached the halfway mark of enrollment in early 2012, with completion of enrollment projected in July 2012. Nearly 600 patients have been randomized in the trial thus far. Data could be reported in October 2012. In our view, this trial is a critical event for Synergy. If plecanatide demonstrates similar efficacy to linaclotide without substantial incidence of diarrhea, we believe that the drug could be viewed as a best-in-class agent for treatment of chronic constipation and constipation-predominant IBS.

Synergy is also preparing to initiate a Phase 2b clinical trial of plecanatide for the treatment of IBS-C in patients during 2012. This study is slated to enroll 350 patients across roughly 60 centers in the U.S. The development plan for plecanatide closely resembles the plan for linaclotide. In our view, it is likely that plecanatide would require two Phase 3 trials for chronic constipation and two more for IBS-C. We believe it is Synergy's strategic intent to fund the Phase 2/3 constipation trial and the Phase 2b IBS-C trial to completion before either inking a partnership or set of partnerships for the global commercialization of plecanatide or selling the company to an established firm.

Phase 2a Trial Design. Synergy recently completed a Phase 2a randomized, double-blind, placebo-controlled, 14-day repeat, oral, dose-ranging clinical trial of plecanatide in patients with CC. This clinical trial enrolled 78 evaluable patients at 14 U.S. sites. The primary objective of this clinical trial was to evaluate the safety of plecanatide in patients with CC. The secondary objectives of this clinical trial were to assess the pharmacokinetic profile of plecanatide and to assess bowel function, including time to first bowel movement, frequency, completeness of evacuation, stool consistency, straining, and abdominal discomfort after treatment with plecanatide. In this clinical trial, Synergy enrolled patients that met the modified Rome III criteria of CC, a standard patient assessment tool used in the diagnosis of patients with CC. Patients also had to have had a colonoscopy within five years before enrolment with no significant findings; be in good health, as determined by a physical examination and other standard assessments; and have reported less than six SBMs, and less than three CSBMs, in each week during the 14 days before treatment with plecanatide or placebo.

Figure 6: Phase 2a Trial Design

Source: Synergy Pharmaceuticals

Patients were dosed once-daily each morning for 14 consecutive days, at oral doses of 0.3 mg, 1.0 mg, 3.0 mg, or 9.0 mg, respectively. There were 20 patients per dose level, randomized on a 3:1 basis, with 15 patients in each dose level receiving plecanatide and five patients in each dose level receiving placebo. A safety review was conducted after completion of dosing for each dose cohort before initiating dosing at the next level.

Phase 2a Study Results. On October 18, 2010, Synergy presented the results of the Phase 2a plecanatide clinical trial at the American College of Gastroenterology Annual Scientific Meeting in San Antonio, Texas. Plecanatide treatment exhibited a favorable safety profile with no severe adverse events observed, and, notably, no patients receiving plecanatide reported diarrhea. In the trial, 10% (2/20) of patients receiving placebo and 17.2% (10/58) of patients receiving plecanatide, respectively, reported adverse events, or AEs, related to treatment, and 10% (2/20) of patients receiving placebo and 8.6% (5/58) of patients receiving plecanatide, respectively, reported GI-related AEs. The majority of AEs were mild to moderate and transient in nature. One patient on placebo discontinued from the clinical trial due to diarrhea. Additionally, no systemic absorption of plecanatide was detected in patients at any of the dose levels studied. The assay used had a sensitivity threshold of 10ng/ml.

Figure 7: Phase 2a Trial Adverse Event Profile

Adverse Events Related to Study Drug

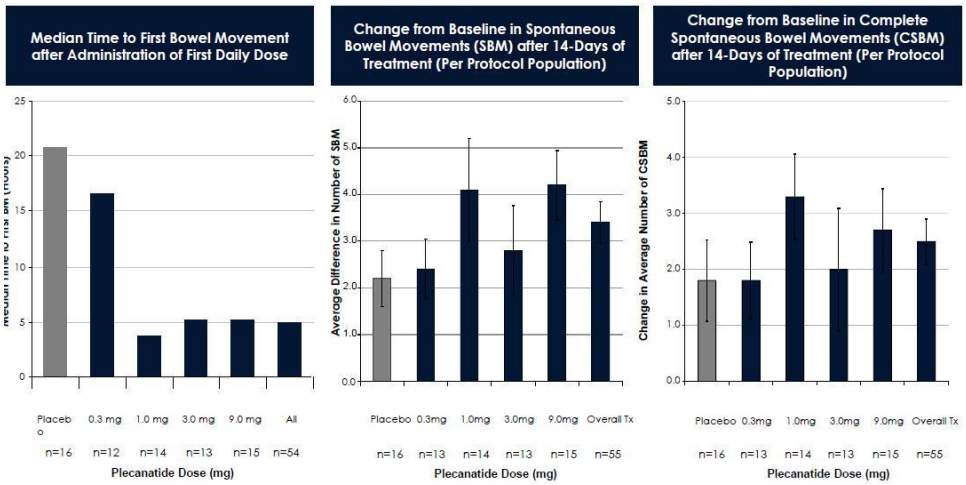
AE	Placebo n=20	0.3 mg n=14	1.0 mg n=14	3.0 mg n=15	9.0 mg n=15
Abdominal Cramping	1 (5.0%)	0	0	0	0
Abdominal Pain	1 (5.0%)	0	0	0	0
Bloating	0	0	0	0	1 (6.7%)
Diarrhea	1 (5.0%)	0	0	0	0
Flatulence	2 (10.0%)	0	0	0	0
Nausea	0	1 (7.1%)	0	0	1 (6.7%)

Source: Synergy Pharmaceuticals

In our view, the safety profile of the drug in this Phase 2a trial was extremely favorable from several vantage points. First, no subject receiving plecanatide experienced diarrhea, which contrasts with the 11.4% – 18% incidence of diarrhea seen in a late-stage trial of linaclotide. In the case of linaclotide, diarrhea was the most common adverse event and was dose-related. Second, we note that there were fewer instances of adverse events of any kind in patients taking the drug than in the placebo group. Finally, the adverse events did not appear to be dose-related, and all were mild to moderate as well as transient in nature. Accordingly, it seems that thus far plecanatide may have a safety advantage over linaclotide, although this remains to be verified in larger studies.

As shown below, patients in all plecanatide dose levels reported significant decreases in time to first bowel movement after dosing versus patients receiving placebo. Patients on plecanatide also had increases in the number of SBMs and CSBMs per week, improved stool consistency, and reduced straining during bowel movements versus pre-treatment levels for each of these measures of bowel function. In addition, a greater percentage of patients in each plecanatide dose level reported improvement in abdominal discomfort, constipation severity, and overall relief after treatment versus patients receiving placebo.

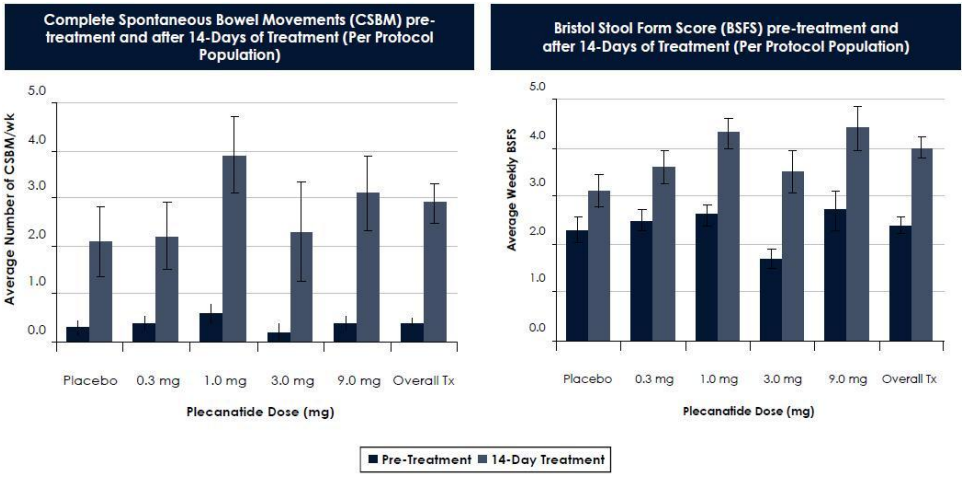
Figure 8: Phase 2a Efficacy Data



Source: Synergy Pharmaceuticals

We note the following: the efficacy data clearly showed that there was no dose-response at doses of plecanatide above 0.3 mg/day. However, the drug was clearly effective, as over 50% of the study population experienced a first bowel movement within five hours on plecanatide, versus 22 hours on placebo. Although the data on SBMs and CSBMs was not statistically significant, here plecanatide also demonstrated positive trends. The charts below show the data on CSBMs and the Bristol Stool Form Score outcome measure for the per-protocol population in this trial.

Figure 9: Phase 2a Per-Protocol Efficacy Data

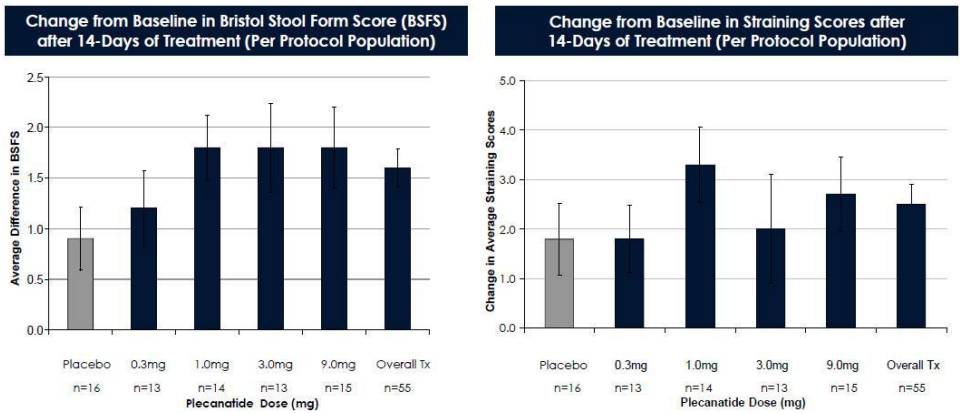


Source: Synergy Pharmaceuticals

All in all, we view the data obtained from this Phase 2a trial as encouraging. We do not consider the results to be meaningfully different on the efficacy front from those reported with linaclotide in chronic constipation after a 14-day evaluation period. We note that

linaclotide did have a statistically significant impact in a Phase 2a trial that enrolled 36 women with constipation-predominant irritable bowel syndrome (IBS-C). The drug was evaluated in a double-blind, placebo-controlled study with a five-day baseline and a five-day treatment period. While we believe these results were clearly impressive, we cannot compare linaclotide to plecanatide at this juncture, as there are currently no efficacy data for plecanatide in patients with IBS-C. We remain encouraged by the data observed with plecanatide on secondary endpoints in the Phase 2a trial evaluating patients with chronic constipation, as seen below.

Figure 10: Phase 2a Per-Protocol Secondary Endpoint Efficacy Data



Source: Synergy Pharmaceuticals

Phase 1 Plecanatide Data. A Phase 1 trial with plecanatide was initiated in June 2008, with data released in December of that year. The data set was presented for the first time at the Digestive Disease Week (DDW) annual meeting in Chicago in mid-2009. This first study was a double-blind, placebo-controlled, randomized single, oral, ascending dose trial performed in 71 healthy male and female volunteers.

The primary objective of the Phase 1 clinical trial with SP-304 was to characterize the safety, tolerability, pharmacokinetic, and pharmacodynamic effects of the drug in healthy volunteers. The doses tested were 0.1, 0.3, 0.9, 2.7, 5.4, 8.1, 16.2, 24.3, and 48.6 mg/day. The trial was set up to enroll eight patients per cohort, of whom six were given active drug and two were administered placebo.

Data from this study showed that the drug was safe and well-tolerated, with no serious adverse events occurring and no incidence of diarrhea in subjects exposed to the agent. Importantly, no systemic absorption of the drug was observed, confirming the hypothesis that—despite oral administration—this is a localized and not a systemic therapy. Pharmacokinetic data were collected through 48 hours post-dosing. Plecanatide did not reach a maximum tolerated dose (MTD). Based on this data set, Synergy embarked upon an initiative to test the drug in patients with constipation, as described previously.

Key Takeaways. Our overall conclusions are that plecanatide has thus far demonstrated what may be an important safety advantage over linaclotide—the absence of diarrhea in patients exposed to the drug. However, thus far we cannot draw firm conclusions regarding the relative efficacy of plecanatide versus linaclotide. Nevertheless, we can observe that plecanatide is undoubtedly an active drug. Therefore, we are optimistic regarding the potential for this agent to demonstrate statistically significant efficacy in the proposed Phase 2/3 programs in both chronic constipation and IBS-C. Considering the affinity of plecanatide for the GC-C receptor and the drug's highly stable conformation, we would expect that the efficacy of plecanatide should be comparable to that seen with linaclotide when evaluated over a lengthier time frame in late-stage trials.

Gastrointestinal Disorders Overview

The market opportunity being targeted by Synergy's drug candidates is significant, exhibiting both high prevalence and incidence. Herein, we discuss chronic constipation, constipation-predominant irritable bowel syndrome (IBS-C), and ulcerative colitis, which we consider to be the main target indications for Synergy's pipeline.

Chronic Constipation

Constipation (also known as costiveness, dyschezia, and dyssynergic defaecation) refers to bowel movements that are infrequent and/or hard to pass[1]. Constipation is a common cause of painful defecation. Severe constipation includes obstipation (failure to pass stools or gas) and fecal impaction, which can lead to bowel obstruction and tissue necrosis. Constipation is extremely common; in the general population, incidence of constipation varies from 2 to 30%. Causes of constipation typically fall into two main categories: obstructed defecation and colonic slow transit (or hypomobility). Roughly 50% of patients evaluated for constipation at tertiary referral hospitals have obstructed defecation. This type has mechanical and functional causes. Causes of colonic slow transit constipation include diet, hormones, side effects of medications, and heavy metal toxicity. Treatments include changes in dietary habits, laxatives, enemas, biofeedback, and surgery. Since constipation is a symptom, not a disease, effective treatment of constipation may require first determining the cause. Constipation is defined as follows:

- infrequent bowel movements (typically three times or fewer per week)
- difficulty during defecation (straining during more than 25% of bowel movements or a subjective sensation of hard stools), or
- the sensation of incomplete bowel evacuation.

Diagnosis. The Rome III criteria are widely used to diagnose chronic constipation and can separate cases of chronic functional constipation from less-serious instances[2]. The causes of constipation can be divided into congenital, primary, and secondary. The most common cause is primary and not life-threatening. In the elderly, causes include: insufficient dietary fiber intake, inadequate fluid intake, decreased physical activity, side effects of medications, hypothyroidism, and obstruction by colorectal cancer.

Primary or functional constipation is defined as ongoing symptoms for more than six months not due to any underlying cause such as medication side effects or an underlying medical condition. It is not associated with abdominal pain, thus distinguishing it from irritable bowel syndrome, which we shall discuss in a later section. It is the most common cause of constipation. In addition, the condition can be caused or exacerbated by a low fiber diet, low liquid intake, or dieting. Many medications have constipation as a side effect. Some include (but are not limited to) opioids (e.g., common pain killers), diuretics, antidepressants, antihistamines, antispasmodics, anticonvulsants, and aluminum antacids. Metabolic and endocrine problems that may lead to constipation include: hypercalcemia, hypothyroidism, diabetes mellitus, cystic fibrosis, and celiac disease. Constipation is also common in individuals with muscular and myotonic dystrophy.

Etiology. There are a number of structural (mechanical, morphological, anatomical) contributors to constipation, including spinal cord lesions, Parkinson's, colon cancer, anal fissures, proctitis, and pelvic floor dysfunction. Constipation also has functional (neurological) causes, including anismus, descending perineum syndrome, and Hirschsprung's disease. In infants, Hirschsprung's disease is the most common medical disorder associated with constipation. The diagnosis is essentially made from the

[1] Chatoor and Emmanuel, Best Practices in Gastroenterology 23: 517–530 (2009)
[2] Selby and Corte, Australian Prescriber 33 (4): 116–119 (2010)

patient's description of the symptoms. Bowel movements that are difficult to pass, very firm, or made up of small hard pellets (like those excreted by rabbits) qualify as constipation, even if they occur every day. Other symptoms related to constipation can include bloating, distension, abdominal pain, headaches, a feeling of fatigue and nervous exhaustion, or a sense of incomplete emptying. Scybala (manually palpable lumps of stool) may be detected on palpation of the abdomen. Physical examination may be done manually by the physician or by using a colonoscope. X-rays of the abdomen, generally only performed if bowel obstruction is suspected, may reveal extensive impacted fecal matter in the colon, and confirm or rule out other causes of similar symptoms. Rectal examination is typically performed to identify the presence or absence of hemorrhoids, polyps, or tumorigenic tissue. Chronic constipation (symptoms present at least three days per month for more than three months) with abdominal discomfort is often diagnosed as irritable bowel syndrome (IBS) when no obvious cause is found[3].

Colonic propagating pressure wave sequences (PSs) are responsible for discrete movements of the bowel contents and are vital for normal defecation. Deficiencies in PS frequency, amplitude, and the extent of propagation are all implicated in severe defecatory dysfunction (SDD). Mechanisms that can normalize these aberrant motor patterns may help rectify the problem. Recently the novel therapy of sacral nerve stimulation (SNS) has been utilized for the treatment of severe constipation.

The main treatment of constipation involves the increased intake of water and fiber (either dietary or as supplements). Routine use of laxatives is problematic, as having bowel movements may come to be dependent upon their use. Enemas can be used to provide a form of mechanical stimulation. However, enemas are generally useful only for stool in the rectum, not in the intestinal tract. Complications that can arise from constipation include hemorrhoids, anal fissures, rectal prolapse, and fecal impaction. Straining to pass stool may lead to hemorrhoids. In later stages of constipation, the abdomen may become distended, hard, and diffusely tender. Severe cases ("fecal impaction," or malignant constipation) may exhibit symptoms of bowel obstruction (vomiting, very tender abdomen) and encopresis, where soft stool from the small intestine bypasses the mass of impacted fecal matter in the colon.

Epidemiology. Constipation is the most common digestive complaint in the U.S. as per survey data. Depending on the definition employed, it occurs in 1.9% to 27.2% of the population[4]. It is more common in women, the elderly, and children. The reason it occurs more frequently in the elderly is thought to be due to an increasing number of health problems as individuals experience aging and decreased physical activity.

- 12% of the population worldwide reports having constipation[5]
- Chronic constipation accounts for 3% of all pediatric outpatient clinic visits annually
- Constipation-related healthcare costs total $6.9 billion in the US annually[6]
- More than four million Americans have frequent constipation, accounting for 2.5 million physician visits a year[7]
- In the U.S., roughly $725 million is spent on laxative products annually
- It is believed that poor dietary habits, particularly over-consumption of processed foods with high starch and sugar content, along with insufficient fiber intake, may be the main contributors to the high incidence of constipation in the U.S.

[3] Longstreth *et al.*, Gastroenterology 130: 1480–1491 (2006)
[4] Higgins and Johanson, American Journal of Gastroenterology 99: 750-759 (2004)
[5] Wald *et al.*, Digestive Disorders Week Abstract T1255 (2006)
[6] Locke *et al.*, Gastroenterology 119: 1761–1766 (2000)
[7] http://digestive.niddk.nih.gov/ddiseases/pubs/constipation/#treatment

Irritable Bowel Syndrome

Also sometimes known as spastic colon, irritable bowel syndrome (IBS) is a functional bowel disorder characterized by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits in the absence of any detectable organic cause. In some cases, the symptoms are relieved by bowel movements. Diarrhea or constipation may predominate, or they may alternate (classified as IBS-D, IBS-C, or IBS-A, respectively). IBS may begin after an infection (post-infectious, IBS-PI), a stressful life event, or onset of maturity without any other medical indicators. Although there is no cure for IBS, there are treatments that attempt to relieve symptoms, including dietary adjustments, medication, and psychological interventions. Several conditions may present as IBS, including celiac disease, fructose mal-absorption, mild infections, parasitic infections like giardiasis, several inflammatory bowel diseases, bile acid mal-absorption, functional chronic constipation, and chronic functional abdominal pain. In IBS, routine clinical tests yield no abnormalities, although the bowels may be more sensitive to certain stimuli such as balloon insufflation testing. The exact cause of IBS is unknown. The most common theory is that IBS is a disorder of the interaction between the brain and the gastrointestinal tract, although there may also be abnormalities in the gut flora or the immune system. Although IBS is not typically associated with the emergence of serious complications in the majority of patients, it is a source of chronic pain, fatigue, and other symptoms and contributes to work absenteeism. Researchers have reported that the high prevalence of IBS, in conjunction with increased costs, produces a disease with a high social cost. It is also regarded as a chronic illness and can dramatically affect the quality of a sufferer's life.

Classification. IBS can be classified as either diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), or IBS with alternating stool pattern (IBS-A, or pain-predominant). In some individuals, IBS may have an acute onset and develop after an infectious illness characterized by two or more of the following: fever, vomiting, diarrhea, or positive stool culture. This post-infective syndrome has consequently been termed “post-infectious IBS” (IBS-PI).

Symptomatology. The primary symptoms of IBS are abdominal pain or discomfort in association with frequent diarrhea or constipation, representing a significant change in bowel habits. There may also be urgency for bowel movements, a feeling of incomplete evacuation (tenesmus), bloating, or abdominal distention. People with IBS are more likely to have gastroesophageal reflux, symptoms relating to the genitourinary system, chronic fatigue syndrome, fibromyalgia, headache, backache, and psychiatric symptoms such as depression and anxiety. Some studies indicate that up to 60% of IBS sufferers also have a psychological disorder, typically anxiety or depression.

Etiology. The cause of IBS is unknown, but many theories abound. The risk of developing IBS increases six-fold after acute gastrointestinal infection. Post-infection, further risk factors are young age, prolonged fever, anxiety, and depression. Publications suggesting the role of the brain-gut “axis” appeared in the 1990s, such as a study entitled “Brain-Gut Response to Stress and Cholinergic Stimulation in IBS,” published in the *Journal of Clinical Gastroenterology* in 1993. A 1997 study published in *Gut* magazine suggested that IBS was associated with a “derailing of the brain-gut axis.” Given these hypotheses, it has been suggested that psychological factors may be important in the etiology of IBS.

There is research to support IBS being caused by an as-yet undiscovered active infection. Some investigators have focused on an unrecognized protozoal infection as a cause of IBS, since certain protozoal infections occur more frequently in IBS patients. Two of the protozoa investigated have a high prevalence in industrialized countries and infect the bowel, but little is known about them, as they are recently emerged pathogens. *Blastocystis* is a single-cell organism that has been reported to produce symptoms of

abdominal pain, constipation, and diarrhea in patients, though these reports are contested by some physicians. Studies from research hospitals in various countries have identified high *Blastocystis* infection rates in IBS patients, with 38% being reported from the London School of Hygiene & Tropical Medicine, 47% reported from the Department of Gastroenterology at Aga Khan University in Pakistan, and 18.1% reported from the Institute of Diseases and Public Health at the University of Ancona in Italy. Reports from all three groups indicate a Blastocystis prevalence of roughly 7% in non-IBS patients. *Dientamoeba fragilis* is a single-cell organism that produces abdominal pain and diarrhea. Studies have reported a high incidence of infection in developed countries, and symptoms of patients resolve following antibiotic treatment. One study reported that a large group of patients with IBS-like symptoms was found to be infected with *Dientamoeba fragilis* and experienced resolution of symptoms following treatment. Researchers have noted that methods used clinically may fail to detect some *Dientamoeba fragilis* infections. It is also found in people without IBS.

Diagnosis. There is no specific laboratory or imaging test that can be performed to diagnose irritable bowel syndrome. Diagnosis of IBS involves excluding conditions that produce IBS-like symptoms and then following a procedure to categorize the patient's symptoms. Ruling out parasitic infections, lactose intolerance, small intestinal bacterial overgrowth, and celiac disease is recommended for all patients before a diagnosis of irritable bowel syndrome is made. In patients over 50 years old, it is recommended that they undergo a screening colonoscopy.

Since there are many causes of diarrhea that give IBS-like symptoms, the American Gastroenterological Association published a set of guidelines for tests to be performed to rule out other causes of these symptoms. These include gastrointestinal infections, lactose intolerance, and celiac disease. Once other causes have been excluded, the diagnosis of IBS is performed using a diagnostic algorithm. Well-known algorithms include the Manning Criteria, the obsolete Rome I and II criteria, and the Kruis Criteria, and studies have compared their reliability. The more recent Rome III Process was published in 2006. The algorithm identifies a name to be applied to the patient's condition based on the combination of the patient's symptoms of diarrhea, abdominal pain, and constipation. For example, the statement "50% of returning travelers had developed functional diarrhea while 25% had developed IBS" would mean that half the travelers had diarrhea while a quarter had diarrhea with abdominal pain. Various treatable causes of diarrhea are often misdiagnosed as IBS. Common examples include infectious diseases, celiac disease, *Helicobacter pylori*, and intestinal parasites. Celiac disease, in particular, is often misdiagnosed as IBS. The American College of Gastroenterology recommends that all patients with symptoms of IBS be tested for celiac disease. Bile acid mal-absorption is also often missed in patients with diarrhea-predominant IBS. Chronic use of certain sedative-hypnotic drugs—especially the benzodiazepines—may cause irritable bowel-like symptoms that can lead to a misdiagnosis of irritable bowel syndrome.

Some researchers have suggested that IBS is a type of low-grade inflammatory bowel disease (IBD). Others have suggested that IBS and IBD are interrelated diseases, noting that patients with IBD experience IBS-like symptoms when their IBD is in remission. A three-year study found that patients diagnosed with IBS were 16.3 times more likely to be diagnosed with IBD during the study period. Serum markers associated with inflammation have also been found in patients with IBS.

Therapy. Various therapeutic approaches have been developed to address IBS. Many of the most widely used involve some form of dietary management strategy. Many different dietary modifications have been attempted to improve the symptoms of IBS. Some are effective in certain sub-populations. As lactose intolerance and IBS have such similar symptoms, a trial of a lactose-free diet is often recommended. A diet restricting fructose

and fructan intake has been shown to successfully treat the symptoms in a dose-dependant manner in patients with fructose mal-absorption and IBS. While many IBS patients believe they have some form of dietary intolerance, tests attempting to predict food sensitivity in IBS have been disappointing. One study reported that an IgG antibody test was effective in determining food sensitivity in IBS patients, with patients on the elimination diet experiencing 10% greater symptom reduction than those on a sham diet. More data is necessary before IgG testing can be recommended. There is no evidence that digestion of food or absorption of nutrients is problematic for those with IBS at rates different from those without IBS. However, the very act of eating or drinking can provoke an overreaction of the gastrocolic response in some patients with IBS due to their heightened visceral sensitivity, and this may lead to abdominal pain, diarrhea, and/or constipation.

There is convincing evidence that soluble fiber supplementation (e.g., psyllium) is effective in the general IBS population. It acts as a bulking agent, and for many IBS-D patients, it allows for a more consistent stool. For IBS-C patients, it seems to allow for a softer, moister, more easily passable stool. However, insoluble fiber (e.g., bran) has not been found to be effective for IBS. In some people, insoluble fiber supplementation may aggravate symptoms. Fiber might be beneficial to those who have a predominance of constipation. In patients who have constipation-predominant irritable bowel syndrome (IBS-C), soluble fiber at doses of 20 g/day can reduce overall symptoms but will not reduce pain. The research supporting dietary fiber contains conflicting, small studies that are complicated by the heterogeneity of types of fiber and doses used.

Medications used to treat IBS may routinely consist of stool softeners and laxatives in constipation-predominant IBS, and anti-diarrheal drugs (e.g., opiate, opioid, or opioid analogs such as loperamide, codeine, diphenoxylate) in diarrhea-predominant IBS for mild symptoms. For patients who do not adequately respond to dietary fiber, osmotic laxatives such as polyethylene glycol, sorbitol, and lactulose can help avoid "cathartic colon," which has been associated with stimulant laxatives. Among the osmotic laxatives, 17–26 grams/day of polyethylene glycol (PEG) has been well studied.

Lubiprostone (Amitiza) is a gastrointestinal agent used for the treatment of idiopathic chronic constipation and constipation-predominant IBS. It is well-tolerated in adults, including elderly patients. Amitiza is a bicyclic fatty acid (prostaglandin E1 derivative) that acts by specifically activating ClC-2 chloride channels on the apical aspect of gastrointestinal epithelial cells, producing a chloride-rich fluid secretion. These secretions soften the stool, increase motility, and promote spontaneous bowel movements (SBM). Unlike many laxative products, Lubiprostone does not show signs of tolerance, dependency, or altered serum electrolyte concentration.

Tegaserod (Zelnorm), a selective 5-HT_4 agonist for IBS-C, is available for relieving IBS constipation in women and chronic idiopathic constipation in men and women. It was the only agent approved to treat the multiple symptoms of IBS (in women only), including constipation, abdominal pain, and bloating. On March 30, 2007, the Food and Drug Administration (FDA) requested that Novartis Pharmaceuticals (NVS/NYSE; Not Rated) voluntarily discontinue the marketing of tegaserod based on the recently identified finding of an increased risk of serious cardiovascular adverse events (heart problems) associated with use of the drug. Novartis agreed to voluntarily suspend marketing of the drug in the U.S. and in many other countries. On July 27, 2007, the FDA approved a limited treatment IND program for tegaserod in the U.S. to allow restricted access to the medication for patients in need if no comparable alternative drug or therapy is available to treat the disease. The FDA had issued two previous warnings regarding tegaserod safety risks. In 2005, tegaserod was rejected by the European Medicines Agency (EMA).

Selective serotonin reuptake inhibitor anti-depressants (SSRIs), because of their serotonergic effect, would seem to help IBS, especially patients who are constipation-predominant. Initial crossover studies and randomized controlled trials support this role. In addition, alosetron, a selective 5-HT_3 antagonist for IBS-D, and cilansetron (also a selective 5-HT_3 antagonist) were tested in IBS patients. Due to severe adverse effects, namely ischemic colitis and severe constipation, they are not available or recommended for treatment of IBS. Nevertheless, a blockade of specific serotonin receptors may have therapeutic benefits in the future for sufferers of the condition. Magnesium aluminum silicates and alverine citrate drugs may also be effective at treating IBS.

The 5-HT_4 agonist drugs prucalopride and cisapride have also been tested in patients with chronic constipation and IBS-C. Both of these agents demonstrated positive activity, but cisapride was pulled off the market in the U.S. after it was discovered that the drug had substantial Q_T prolongation issues that placed patients at heightened risk of cardiac side-effects. Prucalopride, a first-in-class dihydrobenzofurancarboxamide, is a selective, high affinity serotonin (5-HT_4) receptor agonist with enterokinetic activities. Prucalopride alters colonic motility patterns via serotonin 5-HT_4 receptor stimulation; it stimulates colonic mass movements, which provide the main propulsive force for defecation. The observed effects are exerted via highly selective action on 5-HT_4 receptors: prucalopride has >150-fold higher affinity for 5-HT_4 receptors than for other receptors. Prucalopride differs from other 5-HT_4 agonists such as tegaserod (Zelnorm, discussed above) and cisapride, which at therapeutic concentrations also interact with other receptors (5-HT1B/D and the cardiac human ether-a-go-go K^+ channel, respectively), and this may account for the adverse cardiovascular events that have resulted in the restricted availability of these drugs. Clinical trials evaluating the effect of prucalopride on Q_T interval and related adverse events have not demonstrated significant differences compared with placebo. Prucalopride has been approved in Europe since October 2009 under the name Resolor. It was developed by the European firm Movetis, which was acquired for €428 million by Shire Pharmaceuticals in August 2010. Peak Resolor sales are estimated at roughly €300 million. ARYx Therapeutics (ARYX.PK/Other OTC; Not Rated) was developing an agent designated ATI-7505, which was originally partnered with the pharmaceuticals unit of Procter & Gamble (PG/NYSE; Not Rated); however, P&G elected to give back the rights to the compound, known colloquially as the "son of cisapride," and ARYx has subsequently not developed it further. The concept was for ATI-7505 to retain the efficacy of cisapride without the Q_T prolongation susceptibility. ARYx has run into financial difficulties and the future of this compound seems in doubt.

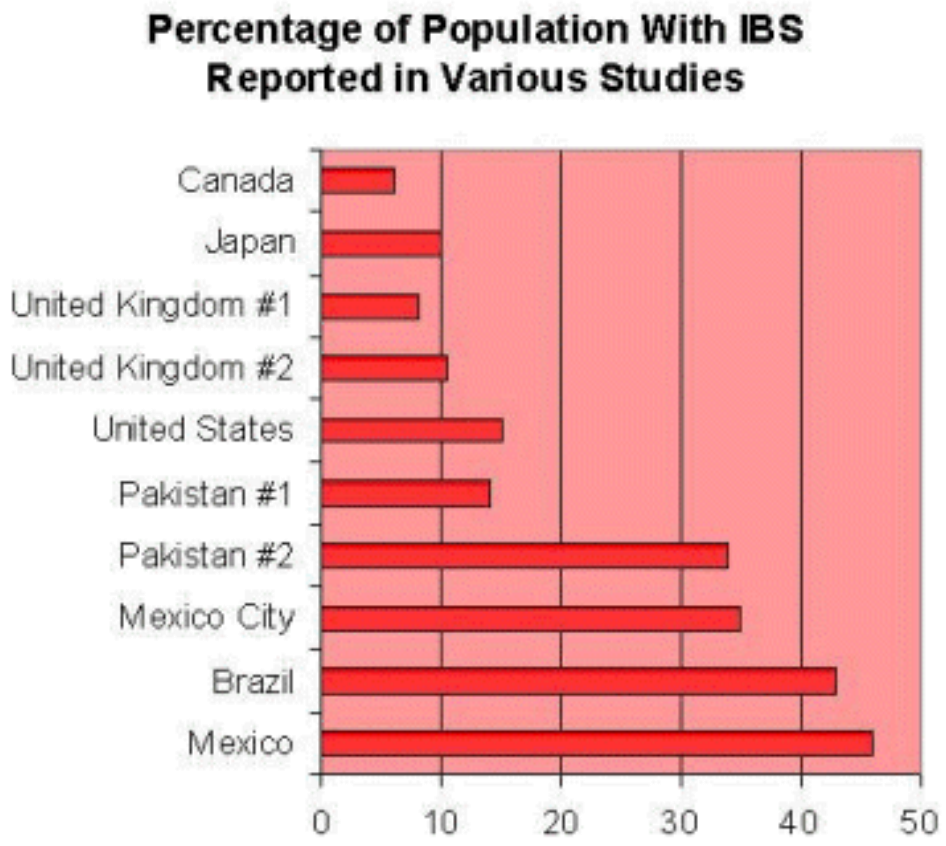
The use of antispasmodic drugs (e.g., anticholinergics such as hyoscyamine or dicyclomine) may help patients, especially those with cramps or diarrhea. A meta-analysis by the Cochrane Collaboration concludes that if six patients are treated with antispasmodics, one patient will benefit. Antispasmodics can be divided into two groups: neurotropics and musculotropics. Neurotropics, such as atropine, act at the nerve fiber of the parasympathicus but also affect other nerves and have side effects. Musculotropics such as mebeverine act directly on the smooth muscle of the gastrointestinal tract, relieving spasms without affecting normal gut motility. Since this action is not mediated by the autonomic nervous system, the usual anticholinergic side effects are absent. There is strong evidence that low doses of tricyclic antidepressants can be effective for IBS. This data thus far appears stronger than that supporting the effectiveness of other antidepressant classes, such as SSRIs.

Domperidone, a dopamine receptor blocker and a parasympathomimetic, has been shown to reduce bloating and abdominal pain as a result of an accelerated colon transit time and reduced fecal load, which is a relief from hidden constipation; defecation was similarly improved. The use of opioids in IBS therapy is controversial due to the lack of evidence supporting their benefit and the risks of tolerance, physical dependence, and addiction.

Probiotics can be helpful in the treatment of IBS—taking 10 billion to 100 billion active beneficial bacteria per day is recommended for therapeutic results[8]. However, further research is likely needed on individual strains of beneficial bacteria for more refined recommendations. A number of probiotics have been found to be effective, including: *Lactobacillus plantarum* and *Bifidobacteria infantis*; however, one review found that only *Bifidobacteria infantis* showed efficacy[9]. Some yogurt is made using probiotics that may help ease symptoms of irritable bowel syndrome. In addition to probiotics, herbal remedies such as iberogast, peppermint oil, and kiwi fruit-based preparations have been employed, with some success reported.

Epidemiological Data. Studies have noted that the prevalence of IBS varies by country and by age range examined. The bar graph below shows the percentage of the population reporting symptoms of IBS in studies from various geographic regions.

Figure 11. Irritable Bowel Syndrome Prevalence



Source: World Health Organization

Economic Impact. The aggregate cost of irritable bowel syndrome in the U.S. is estimated to be considerable. This reflects the disease's nature as a chronic affliction with the ability to substantially impact quality-of-life measures. The management of the condition is complicated by the fact that the etiology remains unclear, and by the various co-morbidities that typically afflict long-term sufferers. Such co-morbidities include often-debilitating neuropsychiatric symptoms such as depression and anxiety. In many cases, the use of laxatives may induce temporary constipation relief, but has no impact on neuropsychiatric co-morbidities, thus restricting therapeutic effect.

[8] Nikfar *et al.,* Dis. Colon Rectum 51: 1775–1780 (2008)
[9] Brenner *et al.,* American Journal of Gastroenterology 104: 1033–1049 (2009)

The main economic impact of IBS is in reduction of worker productivity and time spent in hospitals or clinics, often without significant resolution of symptoms. This is reflected in the statistics below:

- The aggregate cost of IBS in the U.S. has been estimated at $1.7 billion – $10 billion in direct medical costs, with a further $20 billion in indirect costs, for a total of $21.7 billion – $30 billion.[10]
- A study by a managed care company comparing medical costs of IBS patients to non-IBS controls identified a 49% annual increase in medical costs due to a diagnosis of IBS.[11]
- A 2007 study from a managed care organization found that IBS patients incurred average annual direct costs of $5,049 and $406 in out-of-pocket expenses.
- A study of workers with IBS found that they reported a 34.6% loss in productivity, corresponding to 13.8 hours lost per 40-hour week.
- Employer-related health costs from a Fortune 100 company, based on 1990s data, found that IBS sufferers incurred $4,527 in claims costs on average, versus $3,276 for controls.
- A study on Medicaid costs conducted in 2003 by the University of Georgia's College of Pharmacy and Novartis found that IBS was associated with an increase of $962 in Medicaid costs in California, and $2,191 in North Carolina—IBS patients had higher costs for physician visits, outpatients visits, and prescription drugs.
- The Medicaid study suggested that the additional costs for patients diagnosed with IBS, versus non-IBS sufferers, were comparable to those found in asthma patients.

Ulcerative Colitis

An extreme and severe form of inflammatory bowel disease (IBD), ulcerative colitis is a form of colitis—a disease of the intestine, specifically the large intestine or colon, which includes characteristic ulcers, or open sores, in the colon. The main symptom of active disease is usually constant diarrhea mixed with blood, of gradual onset. IBD is often confused with irritable bowel syndrome (IBS), a troublesome, but much less serious, condition. Ulcerative colitis has similarities to Crohn's disease, another form of IBD. Ulcerative colitis is an intermittent disease, with periods of exacerbated symptoms and periods that are relatively symptom-free.

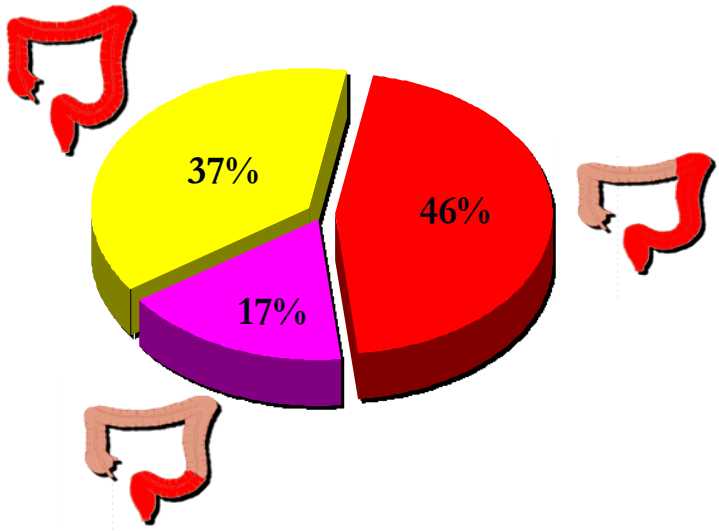
Etiology. The symptoms of ulcerative colitis can sometimes diminish spontaneously; however, the disease usually requires treatment to go into remission. Ulcerative colitis has no known cause, although there is a presumed genetic component to susceptibility. The disease may be triggered in a susceptible person by environmental factors. Dietary modification may reduce the discomfort of a person with the disease, but ulcerative colitis is not thought to be caused by dietary factors. Although ulcerative colitis is treated as though it were an autoimmune disease, there is no consensus on this issue.

Patients with ulcerative colitis usually have an intermittent course, with periods of disease inactivity alternating with "flares" of disease, in a manner similar to what is seen in other autoimmune disorders such as multiple sclerosis. There is a significantly increased risk of colorectal cancer in patients with ulcerative colitis after ten years if involvement is beyond the splenic flexure. It is recommended that patients have screening colonoscopies with random biopsies to look for dysplasia after eight years of disease activity. Ulcerative colitis has a significant association with primary sclerosing cholangitis (PSC), a progressive inflammatory disorder of small and large bile ducts. It is estimated that up to 5% of all patients diagnosed with ulcerative colitis may progress to develop primary sclerosing cholangitis.

[10] Hulisz. Journal of Managed Care Pharmacy 10: 299–309 (2004)
[11] Levy *et al.,* American Journal of Gastroenterology 96: 3122–3129 (2001)

Epidemiology. Ulcerative colitis occurs in 35–100 people for every 100,000 in the U.S., or less than 0.1% of the population, and is more prevalent in northern countries of the world, as well as in northern areas of individual countries or other regions. As such, ulcerative colitis is much more of a niche indication than either chronic constipation or irritable bowel syndrome. However, it constitutes a substantially greater unmet medical need in light of the lack of effective therapies and the severity of the symptoms. The pie chart below shows the ulcerative colitis patient population segmentation in terms of the area of the GI tract that is afflicted. As seen below, over a third of afflicted patients present with symptoms along the entire length of the large intestine, while nearly half are afflicted with symptoms spanning the length of the sigmoid colon, rectum and anus.

Figure 12: Ulcerative Colitis Patient Population Breakdown



Source: Khaled Jadallah, King Abdullah University Hospital, Saudi Arabia

Symptomatology: The symptoms of ulcerative colitis are typical of an autoimmune disorder, and are generally abdominal and gastrointestinal in nature. The disease is primarily distinguishable from other GI tract disorders by its severity, which can be extreme. Multiple categories of ulcerative colitis exist, as described below.

- Mild disease correlates with fewer than four stools daily, with or without blood, no systemic signs of toxicity, and a normal erythrocyte sedimentation rate (ESR). There may be mild abdominal pain or cramping. Patients may believe they are constipated when in fact they are experiencing tenesmus, which is a constant feeling of the need to empty the bowel accompanied by involuntary straining efforts, pain, and cramping with little or no fecal output. Rectal pain is uncommon.
- Moderate disease correlates with more than four stools daily, but with minimal signs of toxicity. Patients may display anemia (not requiring transfusions), moderate abdominal pain, and low grade fever, corresponding to a body temperature range of 38°C to 39°C (100°F to 102°F).
- Severe disease, correlates with more than six bloody stools a day or observable massive and significant bloody bowel movement, and evidence of toxicity as demonstrated by fever, tachycardia, anemia or an elevated ESR.
- Fulminant disease correlates with more than ten bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement and colonic dilation (expansion). Patients in this category may have inflammation extending beyond just the mucosal layer, causing impaired colonic motility and leading to toxic megacolon. If the serous membrane is involved, colonic perforation may ensue. Untreated fulminant disease soon leads to death.

Therapy. Anti-inflammatory drugs are often the first step in the treatment of inflammatory bowel disease. They include:

- Sulfasalazine (azulfidine) can be effective in reducing the symptoms of ulcerative colitis, but it has a number of side effects, including nausea, vomiting, diarrhea, heartburn, and headache. Patients allergic to sulfa drugs cannot take this medication.
- Mesalamine (Asacol, Rowasa, others), balsalazide (Colazal) and olsalazine (Dipentum), may have milder side effects than sulfasalazine and can be taken in tablet form or rectally in the form of enemas or suppositories, depending on the area of the colon affected by ulcerative colitis. Mesalamine can relieve signs and symptoms in >90% of people with mild ulcerative colitis.
- Corticosteroids work on specific steroid receptors. These drugs can help reduce inflammation, but they have numerous side effects, including weight gain, excessive facial hair, high blood pressure, type 2 diabetes, osteoporosis, and an increased susceptibility to infections. Doctors generally use corticosteroids only in cases of highly refractory disease, as these drugs cannot be used long term and are generally prescribed for periods of only three to four months.

In situations where anti-inflammatory drugs do not produce symptom relief, doctors can prescribe immunosuppressants. However, these drugs are often extremely toxic and can only be taken for short periods of time, essentially to control severe episodes in patients with ulcerative colitis.

- Because azathioprine (Azasan, Imuran) and mercaptopurine (Purinethol) act slowly—taking three months or longer to start working—they are sometimes initially combined with a corticosteroid, but in time, they seem to produce benefits on their own. Side effects can include allergic reactions, bone marrow suppression, infections, and inflammation of the liver and pancreas. There also is a small risk of development of cancer with these medications.
- Cyclosporine (Gengraf, Neoral, Sandimmune) is normally reserved for people who do not respond well to other medications or who face surgery because of severe ulcerative colitis.
- Infliximab (Remicade) is specifically for those with moderate to severe ulcerative colitis who are refractory to other treatments. It works by neutralizing a pro-inflammatory cytokine produced by the immune system, known as tumor necrosis factor (TNF). People with heart failure, multiple sclerosis, cancer, or a history of cancer cannot take infliximab. The drug has been linked to an increased risk of infection, especially tuberculosis and reactivation of viral hepatitis, and may increase the risk of blood problems and cancer. A skin test for tuberculosis must be performed before taking infliximab. Also, because infliximab contains mouse protein sequences, it can cause serious allergic reactions in some people. Once started, infliximab is often continued as long-term therapy, although its effectiveness may wear off over time.

We note that recently, two anti-TNF inhibitors – Remicade and Humira (adalimumab) – have reported positive clinical data in ulcerative colitis patients. Data from a Phase 3 randomized, multicenter, open-label study reported in May 2011 demonstrated clinical response with Remicade in the treatment of pediatric patients with moderately to severely active ulcerative colitis, and showed a safety profile consistent with previous clinical trials conducted in an adult population. The pediatric ulcerative colitis findings, presented at Digestive Disease Week in Chicago, showed that Remicade induced clinical responses in 73% of patients aged 6-17 years at week 8, the primary endpoint of the trial. Remicade has been approved for treatment of ulcerative colitis in adults since 2005.

In the case of Humira, the drug was assessed in 494 adult patients with ulcerative colitis who had not responded well to conventional therapy. Co-primary endpoints were the proportion of patients with clinical remission at week 8 and clinical remission at week 52. Clinical remission was defined as a Mayo Score of 2 or less with no individual sub-score >1. The Mayo Score uses a 12-point scoring system using the following parameters: stool frequency, rectal bleeding, endoscopy findings and physicians global assessment. A higher Mayo Score indicates greater severity. Among the 248 patients treated with Humira, 16.5% achieved clinical remission vs. 9.3% on placebo at week 8 p=0.019). At week 52, 17.3% achieved remission vs. 8.5% on placebo (p=0.004). The safety results were consistent with the known safety profile of Humira, with the incidence of injection site reaction-related adverse events and hematologic adverse events being greater in treated patients compared to placebo. We believe that plecanatide and linaclotide could both be used alongside anti-TNF inhibitors – potentially in both adults and children.

Nicotine skin patches—the same kind used to quit smoking—seem to provide short-term relief from flare-ups of mild ulcerative colitis for some people. However, the mechanism via which this occurs remains unclear. Some medications may control symptoms:

- Antibiotics. People with ulcerative colitis who run fevers will likely be given antibiotics to help prevent or control infection.
- Anti-diarrheal agents—a fiber supplement such as psyllium powder (Metamucil) or methylcellulose (Citrucel) can help relieve signs and symptoms of mild to moderate diarrhea by adding bulk to stool. For more severe diarrhea, loperamide (Imodium) may be effective. However, these agents may increase the risk of toxic megacolon.
- Pain relievers. For mild pain, acetaminophen (Tylenol, others) may be employed. Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen (Advil, Motrin, others), or naproxen (Aleve) are not used, as they have gastrointestinal side-effects and may exacerbate symptoms in patients with ulcerative colitis.
- Iron supplements. Chronic intestinal bleeding may cause iron-deficiency anemia. Taking iron supplements may help restore iron levels to normal and reduce this type of anemia once the bleeding has stopped or diminished.

Surgery can often eliminate ulcerative colitis, but, as mentioned previously, this usually means removing the entire colon and rectum (proctocolectomy). After undergoing this procedure, patients were typically required to wear a small bag over an opening in the abdomen (ileostomy) to collect stool. Currently, however, a procedure called ileoanal anastomosis eliminates the need to wear a bag. Instead, a pouch is constructed from the end of the small intestine. The pouch is then attached directly to the anus, allowing the patient to expel waste more normally, although individuals who have had this procedure may have more-frequent bowel movements that are soft or watery, because they no longer have a colon to absorb water. Generally, 25%-40% of people with ulcerative colitis eventually need surgery.

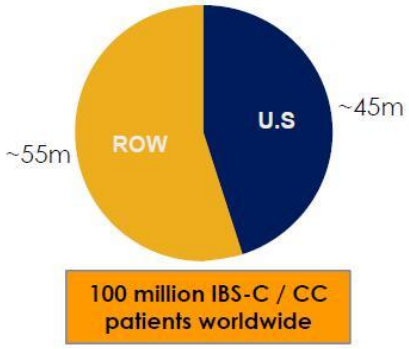
We do not expect an agent like SP-333 to necessarily be dramatically effective in treating severe or fulminant ulcerative colitis, which are conditions that often necessitate acute immunosuppressive therapy. However, SP-333's potential utility could be primarily in mild-to-moderate forms of the disease, in which the drug could provide significant pharmacoeconomic and clinical benefits by delaying disease progression and preventing the transition of ulcerative colitis into colorectal cancer, which is a well-known consequence of the condition in chronic sufferers.

Furthermore, the fact that existing therapies for ulcerative colitis are systemic, non-specific and immunosuppressive in nature means that a locally-acting agent like SP-333 could have significant safety advantages as well. Finally, we note that drug pricing flexibility for a peptide-based agent in a chronic autoimmune disease setting is likely to be much greater than what is expected for plecanatide in IBS-C and chronic constipation.

Market Opportunity

In this section, we provide some perspectives on the market potential for a drug aimed at treating constipation-related disorders, particularly chronic constipation (CC) and constipation-predominant irritable bowel syndrome (IBS-C). As shown in the figure below, over 100 million people worldwide are estimated to suffer from these disorders, with a high incidence of the severe form occurring in the U.S., Europe, and Japan. It is believed that up to 20 million individuals in just these three geographies suffer from a severe form of these disorders.

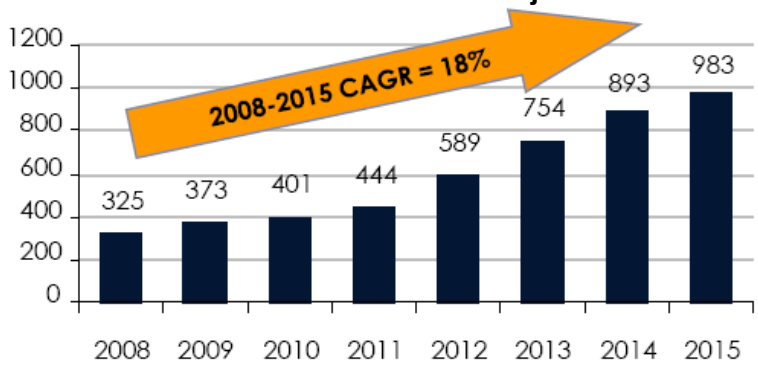
Figure 13: Global Constipation Disorders Patient Population



Source: Market research

The figure below shows the growth projections for only the laxatives segment of the IBS therapeutics market in the U.S. This segment is projected to have an average compound annual growth rate of roughly 18% out to 2015. In our view, given the fact that laxatives are viewed primarily as a palliative form of therapy for IBS, the growth rate is encouraging and clearly indicative of the substantial demand in this indication. Since there is really only marginal effectiveness for laxatives in the treatment of both IBS and chronic constipation, we believe the projected growth rate for this market segment is a positive indication for the potential demand that could exist for agents like linaclotide and plecanatide. We also note that laxatives are not recommended for chronic use because of the risk of long-term side effects.

Figure 14: U.S. Laxatives Market Growth Projections



Source: Market research; IMS Health

Since market estimates typically ascribe the bulk of the global constipation market to the US, we have made assumptions accordingly. However, we note that in our current modeling framework we have not included any contribution to plecanatide future cash flows from sales of the product in Asia. Clearly, this could provide additional upside to our current estimates. We also surmise that Ironwood's partner in Asia, Astellas, believes that there is substantial potential for a drug like linaclotide in the Asian market.

Competitive Landscape

On the following page, we provide a table assessing the current competitive landscape in the CC and IBS-C markets. Although there are many minor products—laxatives, probiotic agents, antibiotics, etc.—being employed in this market, we believe the fundamental competitive landscape relevant to plecanatide's prospects consists primarily of the 5-HT_4 receptor agonist and chloride C-2 channel activator drug classes, along with linaclotide. As shown in the table, the main representatives of these drug classes are Amitiza (lubiprostone), which is marketed by Takeda and Sucampo Pharmaceuticals (SCMP/NASDAQ; Not Rated), and Resolor (prucalopride), which is marketed by Shire Pharmaceuticals in Europe only. Amitiza provides several encouraging frames of reference. It has relatively modest efficacy and causes sometimes-severe nausea in roughly 30% of patients, yet it has been priced at roughly $3.80 per day in the U.S. Currently, it is the only drug indicated in the U.S. market for treatment of IBS-C.

Prokinetic agents like Resolor, Zelnorm, cisapride, and others constitute a relatively effective group of drugs. However, all of these agents—with the exception of Resolor—have issues because of poor receptor specificity. Zelnorm was pulled from the U.S. market in 2007 after data emerged demonstrating that the drug carried substantial cardiovascular risk, particularly an elevated risk of stroke. Resolor, which was approved in late 2009, is a highly specific agonist of the 5-HT_4 receptor and does not appear to carry the same side effects as Zelnorm. However, for the moment, this drug is not available in the U.S., and is only marketed in Switzerland and the UK. Nevertheless, we believe that it is largely perceived favorably by physicians and patients, and it was considered an attractive enough product that Shire Pharmaceuticals acquired Movetis, the developer of the drug, for €428 million in 2010, only several months after the drug was launched. Resolor has achieved impressive traction in European markets to date.

The clinical benefits and the favorable safety profile of Resolor have been demonstrated in a substantial clinical program conducted in chronic constipation, which enrolled adults, including the elderly, who were predominantly female. This program comprised three large and identically designed pivotal Phase 3 studies evaluating Resolor in the treatment of chronic constipation in adults not adequately relieved by laxatives. The overall prucalopride clinical development program contained over 3,000 patients who received about 2,600 combined years of therapy. In the three pivotal double-blind placebo-controlled Phase 3 trials, Resolor consistently demonstrated sustained clinically meaningful effects throughout the twelve-week treatment period and was effective in normalizing impaired bowel habits (increase to at least three spontaneous complete bowel movements per week) of chronically constipated patients in 25%-30% of patients. The most frequently reported side effects with prucalopride included headache, diarrhea, and nausea. These effects were transient and occurred predominantly during the first days of treatment. In-depth analysis of the safety database of all double-blind trials, a series of specific safety trials, and long-term follow up trials with duration of up to 2.6 years showed no significant difference in adverse events between Resolor and placebo.

Despite the presence of entrenched competitors, we believe that plecanatide could be successful in the IBS-C and chronic constipation markets because of its positive safety profile and encouraging efficacy shown thus far. We also believe that the "fast follower" approach is likely to prove beneficial for plecanatide, since linaclotide—a very similar agent that works in the same manner as plecanatide—has already demonstrated Phase 3 efficacy results that are extremely positive. If plecanatide shows efficacy similar to linaclotide in pivotal trials, we believe that it could be a "best in class" agent, given the lack of diarrhea as a side effect and the fact that the existing competitors do not offer substantial efficacy. We believe that the GC-C agonist class is likely to offer greater benefits for patients with significantly fewer side effects. In particular, we would point out that these drugs are not systemically absorbed.

Table 4: Competitive Landscape in the CC and IBS-C Markets

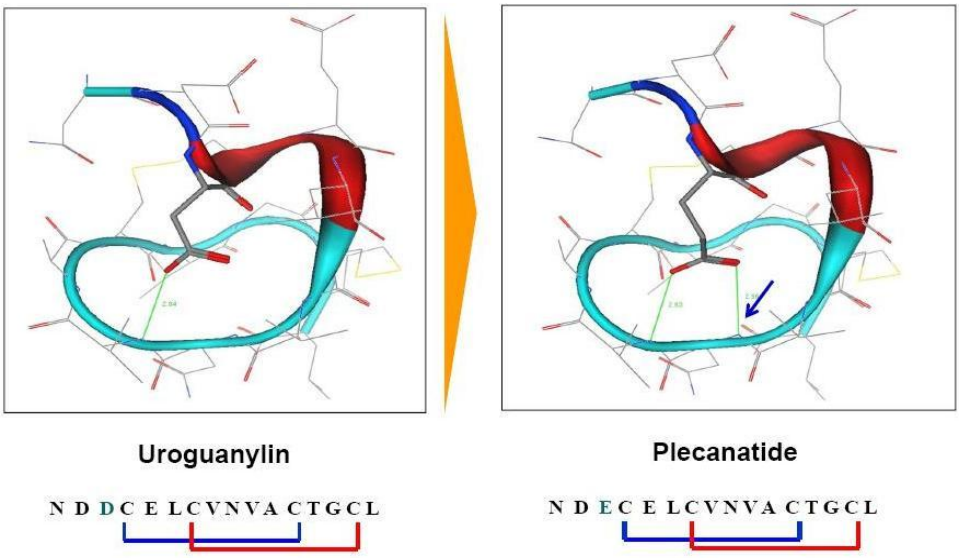
Drug Name	Generic Name	Sponsor	Mechanism of Action	Status	Dosing	Pricing	Safety Profile	Efficacy Data
Amitiza	lubiprostone	Takeda Pharmaceuticals Sucampo Pharmaceuticals	Chloride C-2 channel activator	Marketed in US	8 µg, twice-daily, oral	$3.80 / day	Nausea (30% of patients)	Overall symptom improvement of 12% - 13% vs. 6% - 7% on placebo
Zelnorm	tegaserod	Novartis	Serotonin (5-HT_4) receptor agonist	Withdrawn from US market	6 mg, twice-daily, oral	roughly $1 / pill	Dizziness, nausea, diarrhea, risk of stroke	12 - 15% gain in subject global assessment of relief
Resolor	prucalopride	Shire Pharmaceuticals (formerly Movetis)	Serotonin (5-HT_4) receptor agonist	Marketed in Switzerland and UK	1 - 2 mg, once-daily, oral	€2.20 - €2.70 per day	Diarrhea, headache, nausea	Normalized bowel function in 25-30% of patients
ASP0456	linaclotide	Ironwood Pharmaceuticals Forest Laboratories Almirall S.A. Astellas	GC-C receptor agonist	Pre-approval in US	133 - 266 µg, once-daily, oral	NA	Diarrhea	19.5% improvement in bowel function vs. 6.3% on placebo in IBS-C trial
SP-304	plecanatide	Synergy Pharmaceuticals	GC-C receptor agonist	Phase 2 / 3	1 - 9 mg, once-daily, oral	NA	Bloating, nausea (1 patient in Phase 2a trial)	Over 50% of patients in Phase 2a trial had first bowel movement within 5 hrs vs. 22 hrs on placebo

Source: Company Reports, EvaluatePharma, ADIS R&D Insight

Plecanatide vs. Linaclotide

In our opinion, one of the most important advantages Synergy holds is the fact that its primary asset, plecanatide, is based on an endogenous hormone with a well-established mechanism of action. As shown in the figure below, plecanatide is identical to the sequence of uroguanylin, which is produced endogenously except for a single crucial amino acid change. At the third position, an aspartic acid residue (D) is changed to glutamic acid (E). This makes the overall conformation of the plecanatide peptide substantially more stable. The formation of inter-converting isomers is also attenuated.

Figure 15: Plecanatide Conformation



Source : Synergy Pharmaceuticals

We believe the safety profile of plecanatide has a significant likelihood of being more favorable long term than that of linaclotide, since plecanatide is virtually identical to the native uroguanylin sequence, with the exception of a single amino acid residue. Linaclotide, by contrast, is homologous with uroguanylin but is actually derived from a bacterial enterotoxin (derived from *E. coli*). We must note here that we are not disputing the efficacy of linaclotide. In our view, it is clearly a highly potent and effective agent. Nevertheless, we believe that the mechanism of action shared by linaclotide and plecanatide permits plecanatide to have the advantage of being a "fast follower," with the an improved side-effect profile: unlike linaclotide, plecanatide is based on the native uroguanylin sequence. However, only further large-scale studies assessing the long-term impact of plecanatide therapy are likely to provide conclusive evidence of plecanatide's relative efficacy. We note that the possible approval of linaclotide in September 2012 could boost prospects for Synergy by reducing perceived regulatory risk for plecanatide.

While we do not currently believe that the FDA would require head-to-head trials versus linaclotide, this may not be the case once plecanatide has completed initial pivotal trials. If linaclotide were approved and considered the standard of care in CC or IBS-C, it is conceivable that head-to-head trials might be necessary. However, we think there is probably room for both agents in the GI disorders market—although, all other attributes being equal, we believe that, over time, plecanatide might begin to take the upper hand because of its safety advantages. The strategic advantage that Synergy might hold over Ironwood may only become apparent in the case of SP-333, which is designed to target ulcerative colitis—an area Ironwood and its partners do not intend to pursue with linaclotide. However, the UC market may prove more competitive given the presence of other potently anti-inflammatory agents both on the market and in development.

Plecanatide Market Model

We have modeled sales of plecanatide in select indications within the gastrointestinal (GI) disorders market. These are as follows:

- Chronic constipation, wherein the drug has already shown positive and statistically significant therapeutic impact, and which represents a logical choice for deploying plecanatide given the mechanism that it shares with linaclotide and uroguanylin.
- Constipation-predominant irritable bowel syndrome (IBS-C), wherein the drug has not yet been tested but where we believe it would – in keeping with its activity profile in chronic constipation – show statistically significant activity in patients suffering from this condition. Again, our expectations are driven by the efficacy data that has already been demonstrated with linaclotide in this indication.

Both of the above are extremely large commercial opportunities within the healthcare space. Chronic constipation results from a lack of an adequate number of bowel movements (typically less than three per week) over an extended period of time (usually defined as greater than six months). When suffering from chronic constipation, patients often try laxatives and fiber supplements prior to physician prescribed therapy. Due to limitations in existing treatments, a significant need exists for a safe and effective chronic constipation therapy. Based on a 2004 epidemiology review, it is estimated that between 36 and 57 million people in the US have chronic constipation and that approximately 33% of them see a physician for this condition. Other estimates have placed the number of chronic constipation sufferers in the US as high as 80 million.

IBS is a set of chronic symptoms associated with the lower GI tract, particularly the colon, and is usually experienced as abdominal pain, bloating and discomfort. This can include constipation with difficult or painful bowel movements or diarrhea due to excess fluid in the colon. While the etiology of IBS remains unclear, lack of colonic motility may be a significant contributory factor. As with chronic constipation, patients need an effective motility agent when other remedies, such as change in diet, reduction of stress or consumption of laxatives or fibers, do not relieve the IBS symptoms. Plecanatide is targeted for use among IBS patients who have constipation-predominant disease. According to a 2005 article in the *Alimentary Pharmacology and Therapeutics* journal, an estimated 5.5 million adults in the US suffer from IBS with constipation and a further 28 million adults suffer from IBS with intermittent constipation.

We have modeled sales of plecanatide in the treatment of IBS-C and chronic constipation as shown overleaf (see Table 5, overleaf). According to our assumptions, we believe that plecanatide could reach peak worldwide annual sales of ~$4 billion in 2021. This peak sales figure represents ~2.2 million patients on therapy. We assume penetration would be highest among those ~10 million patients in the US who currently are classified with severe constipation and who actively seek treatment for the condition. Furthermore, we also expect substantial use of the drug in severe IBS-C. We do not assume substantial penetration of the patient population segment suffering from IBS with intermittent constipation. In addition, we do not currently model sales of SP-333 in any indication at this juncture, since this agent has yet to begin human clinical testing.

Although we fully expect linaclotide to reach the market prior to plecanatide, with a lead time of approximately 24 months or more, we believe that the market presence of linaclotide would likely have a positive impact on receptivity for plecanatide among patients and physicians, since linaclotide would serve as a trailblazer for a completely new class of anti-constipation therapies and thus could facilitate understanding of plecanatide and its attributes.

Table 5: Plecanatide Sales Estimates – GI Tract Disorders Market Size Model

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
US Population	311,000,000	314,887,500	318,823,594	322,808,889	326,844,000	330,929,550	335,066,169	339,254,496	343,495,177	347,788,867	352,136,228	356,537,931	360,994,655	365,507,088	370,075,927	374,701,876	379,385,649	384,127,970	388,929,570
Patients with chronic constipation	62,200,000	62,977,500	63,764,719	64,561,778	65,368,800	66,185,910	67,013,234	67,850,899	68,699,035	69,557,773	70,427,246	71,307,586	72,198,931	73,101,418	74,015,185	74,940,375	75,877,130	76,825,594	77,785,914
Patients seeking treatment for constipation	6,220,000	6,297,750	6,376,472	6,456,178	6,536,880	6,618,591	6,701,323	6,785,090	6,869,904	6,955,777	7,042,725	7,130,759	7,219,893	7,310,142	7,401,519	7,494,038	7,587,713	7,682,559	7,778,591
Patients with constipation-predominant irritable bowel syndrome (IBS-C)	15,550,000	15,744,375	15,941,180	16,140,444	16,342,200	16,546,477	16,753,308	16,962,725	17,174,759	17,389,443	17,606,811	17,826,897	18,049,733	18,275,354	18,503,796	18,735,094	18,969,282	19,206,398	19,446,478
Patients seeking treatment for IBS-C	2,332,500	2,361,656	2,391,177	2,421,067	2,451,330	2,481,972	2,512,996	2,544,409	2,576,214	2,608,417	2,641,022	2,674,034	2,707,460	2,741,303	2,775,569	2,810,264	2,845,392	2,880,960	2,916,972
Plecanatide Penetration Rates																			
Chronic constipation					2.5%	7%	11%	15%	21%	25%	21%	17%	11%	9%	7%	6%	4.5%	3.5%	1%
Constipation-predominant irritable bowel syndrome (IBS-C)					6%	11%	18%	25%	29%	33%	30%	24%	18%	11%	9%	7%	6%	4%	2%
Patients on plecanatide (SP-304)					310,502	736,318	1,189,485	1,653,866	2,189,782	2,599,722	2,271,279	1,853,997	1,281,531	959,456	767,908	646,361	512,171	384,128	136,125
Average cost per chronic constipation patient ($)					180	495	916	1,145	1,259	1,322	1,362	1,403	1,445	1,488	1,533	1,579	1,626	1,675	1,725
Average cost per IBS-C patient ($)					350	788	1,378	1,516	1,592	1,639	1,689	1,739	1,792	1,845	1,901	1,958	2,016	2,077	2,139
US plecanatide (SP-304) sales ($ MM)					**81**	**444**	**1,298**	**2,129**	**3,006**	**3,710**	**3,352**	**2,817**	**2,020**	**1,535**	**1,269**	**1,095**	**899**	**690**	**259**
European Population	395,000,000	399,937,500	404,936,719	409,998,428	415,123,408	420,312,451	425,566,356	430,885,936	436,272,010	441,725,410	447,246,978	452,837,565	458,498,035	464,229,260	470,032,126	475,907,527	481,856,371	487,879,576	493,978,071
Patients with chronic constipation	47,400,000	47,992,500	48,592,406	49,199,811	49,814,809	50,437,494	51,067,963	51,706,312	52,352,641	53,007,049	53,669,637	54,340,508	55,019,764	55,707,511	56,403,855	57,108,903	57,822,765	58,545,549	59,277,368
Patients seeking treatment for constipation	2,370,000	2,399,625	2,429,620	2,459,991	2,490,740	2,521,875	2,553,398	2,585,316	2,617,632	2,650,352	2,683,482	2,717,025	2,750,988	2,785,376	2,820,193	2,855,445	2,891,138	2,927,277	2,963,868
Patients with constipation-predominant irritable bowel syndrome (IBS-C)	19,750,000	19,996,875	20,246,836	20,499,921	20,756,170	21,015,623	21,278,318	21,544,297	21,813,600	22,086,271	22,362,349	22,641,878	22,924,902	23,211,463	23,501,606	23,795,376	24,092,819	24,393,979	24,698,904
Patients seeking treatment for IBS-C	1,975,000	1,999,688	2,024,684	2,049,992	2,075,617	2,101,562	2,127,832	2,154,430	2,181,360	2,208,627	2,236,235	2,264,188	2,292,490	2,321,146	2,350,161	2,379,538	2,409,282	2,439,398	2,469,890
Plecanatide Penetration Rates																			
Chronic constipation						0.5%	2%	6%	9%	11%	13%	14%	15%	16%	14%	12%	6%	4.5%	2%
Constipation-predominant irritable bowel syndrome (IBS-C)						2%	5%	8%	12%	15%	18%	21%	23%	25%	22%	14%	10%	7%	3%
Patients on plecanatide (SP-304)						54,641	157,460	327,473	497,350	622,833	751,375	855,863	939,921	1,025,947	911,862	675,789	414,396	302,485	133,374
Average cost per chronic constipation patient ($)						120	288	432	475	499	514	529	545	562	578	596	614	632	651
Average cost per IBS-C patient ($)						230	403	543	571	588	605	623	642	661	681	702	723	744	767
European plecanatide (SP-304) sales ($ MM)						**11**	**58**	**161**	**261**	**340**	**423**	**498**	**564**	**634**	**581**	**438**	**281**	**210**	**95**
Total plecanatide (SP-304) sales ($ MM)					**81**	**456**	**1,356**	**2,290**	**3,267**	**4,050**	**3,775**	**3,314**	**2,584**	**2,170**	**1,849**	**1,533**	**1,180**	**900**	**354**

Source: Company Reports and Aegis Capital Corp. estimates

Intellectual Property Portfolio

As of March 14, 2012, Synergy holds rights to six issued U.S. patents. Two of these patents cover the composition-of-matter of plecanatide and were issued on May 9, 2006 and September 21, 2010; they will expire in 2023 and 2022, respectively. A third patent covers the composition-of-matter of SP-333 issued on February 1, 2011 and expires in 2028. A fourth patent granted October 11, 2011 covers composition-of-matter of analogs related to plecanatide and SP-333 and will expire in 2028. A fifth patent granted February 14, 2012 covers a method of treating inflammatory bowel disease using plecanatide. In addition, Synergy has three granted foreign patents which cover composition-of-matter of plecanatide and expire in 2022. These foreign patents cover Austria, Belgium, Switzerland, Cyprus, Germany, Denmark, Spain, Finland, France, United Kingdom, Greece, Ireland, Italy, Liechtenstein, Luxembourg, Monaco, Netherlands, Portugal, Sweden, Turkey, Hong Kong, Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyz Republic, Moldova, Russian Federation, Tajikistan, Turkmenistan, and Japan. Additionally, Synergy is pursuing seven pending U.S. patent applications and 39 pending foreign patent applications covering plecanatide and SP-333 and various derivatives and analogs, including a more stable plecanatide analog designated SP-373.

Plecanatide for treating chronic constipation and constipation-predominant IBS

- new chemical entities receive five years of market exclusivity post-launch in the US and up to 10 years of market exclusivity in Europe
- composition-of-matter protection on plecanatide lasting until at least 2022
- potential for additional patent protection via allowed term extensions and Hatch-Waxman term extensions

SP-333 for treatment of ulcerative colitis

- new chemical entities receive five years of market exclusivity post-launch in the US and up to 10 years of market exclusivity in Europe (see above)
- US Patent No. 7,879,802, providing composition-of-matter protection to SP-333 until 2028 without factoring in contributions from allowed patent term extensions and / or Hatch-Waxman patent term extensions

In our view, the patent estate protecting plecanatide and SP-333 creates two fundamental barriers to generic entry: composition-of-matter protection, provided both by the patent application covering the specific composition of guanylate cyclase C receptor agonists; and method-of-use protection, which covers the idea of selective application of GC-C receptor agonists to the treatment of gastrointestinal disorders, including those of inflammatory or autoimmune etiology.

In April 2010, two parties filed an opposition to Synergy's granted patent with the European Patent Office. An opposition hearing was held December 14, 2011, which resulted in the European Patent Office issuing the following statement: "Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the European Patent Convention (Art.101(3)(a)EPC)." In particular, the composition-of-matter claim covering plecanatide was upheld. While we are aware that Ironwood Pharmaceuticals has been issued a patent for the use of plecanatide for treatment of constipation or constipation predominant irritable bowel syndrome, we believe that Synergy's composition-of-matter protection of plecanatide will supersede Ironwood's patent claims and that Synergy retains freedom to operate. Furthermore, we would note that one of the parties that attempted to oppose the Synergy composition-of-matter patent estate in Europe was Ironwood Pharmaceuticals; in our view, the resolution of the patent issuance opposition case was a victory for Synergy and prevented Ironwood from pursuing a strategy of first attempting to overturn the Synergy IP in Europe, which, if successful, would have paved the way for Ironwood to attempt to overturn Synergy's

issued U.S. patents covering plecanatide as well. We believe that Ironwood's attempts to invalidate Synergy's IP estate on plecanatide and related compounds are clear evidence that Ironwood views Synergy as a strategic and commercial threat. In addition, Ironwood has a clear reason for wanting to keep Synergy's drug off the market; since Synergy's IP expires before Ironwood's, plecanatide would go generic before linaclotide's patent protection expires, thus reducing the overall NPV of the linaclotide revenue stream.

Table 6: Synergy IP Estate – Issued & Allowed Patents

Country	Patent Number	Application Number	Expiration Date	Title
United States	7,041,786	10/107814	3/28/2022	Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis (composition-of-matter on plecanatide)
United States	7,799,897	11/347115	2/2/2026	Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis
United States	8,114,831	12/763707	4/20/2030	Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis
United States	7,879,802	12/133344	6/4/2028	Agonists of Guanylate Cyclase Useful for the Treatment of Gastrointestinal Disorders, Inflammation, Cancer and Other Disorders (covers SP-333)
United States	Allowed	12/478505	NA	Agonists of Guanylate Cyclase Useful for the Treatment of Gastrointestinal Disorders, Inflammation, Cancer and Other Disorders (covers SP-373)
United States	8,034,782	12/504288	7/16/2029	Agonists of Guanylate Cyclase Useful for the Treatment of Gastrointestinal Disorders, Inflammation, Cancer and Other Disorders
European Union	1,379,224	02721604.3	3/28/2022	Guanylate Cyclase Receptor Agonists for Treatment of Tissue Inflammation and Carcinogenesis (composition-of-matter on plecanatide)
European Union	Allowed	08770135.5	NA	Guanylate Cyclase Receptor Agonists for Treatment of Tissue Inflammation and Carcinogenesis (composition-of-matter on plecanatide)
Canada	Allowed	2441970	NA	Guanylate Cyclase Receptor Agonists for Treatment of Tissue Inflammation and Carcinogenesis (composition-of-matter on plecanatide)
Japan	4206272	2002-576949	NA	Guanylate Cyclase Receptor Agonists for Treatment of Tissue Inflammation and Carcinogenesis (composition-of-matter on plecanatide)
Eurasia	06651	200301070	NA	Guanylate Cyclase Receptor Agonists for Treatment of Tissue Inflammation and Carcinogenesis (composition-of-matter on plecanatide)

Source: Synergy Pharmaceuticals, U.S. Patent & Trademark Office

The above table lists Synergy's granted and allowed patents in the U.S., European Union, Canada, Japan and Asia. The firm has composition-of-matter protection on plecanatide in all of these geographies. Synergy has also received notices of allowance for composition-of-matter protection on the follow-on molecules SP-333 and SP-373. In addition, Synergy has issued method-of-use patents covering its proprietary GC-C receptor agonists in GI tract disorders, cancer, inflammation and cardiovascular diseases.

Financial Review and Outlook

Revenue: We do not forecast any revenue in 2012 and 2013, respectively. Management does not provide guidance.

- **Plecanatide Phase 2/3 Study Initiation:** We forecast completion of a Phase 2/3 trial with plecanatide in chronic constipation in 2012. This study may cost $50 – $60 million to run, given the proposed design.

- **Synergy Acquisition or Worldwide Licensing Agreement:** We believe Synergy could be the subject of an acquisition transaction, with the price point possibly significantly above our 12-month price target given the current valuation of a similar molecule to plecanatide, the GC-C receptor agonist linaclotide.

- **Plecanatide Launch in Early 2016:** We estimate that the drug could secure regulatory approval in 2H 2015. Revenue generation is possible starting in early- to mid-2016, when we estimate sales could exceed $80 million.

Gross Margins: As a development-stage company, there are historically no costs of goods sold. We project that the gross margins on plecanatide could exceed 85%, in line with similar peptide-based products currently sold by other biotech companies.

Operating Expenses: For 2012 and 2013, we estimate operating expense levels that are $43.6 million and $54 million respectively. We estimate R&D of $30.3 million in 2012, as the firm completes Phase 2/3 development with plecanatide in chronic constipation and potentially starts Phase 2 development in IBS and initial clinical testing with SP-333.

Taxes: At December 31, 2011, Synergy-DE has net operating loss carryforwards ("NOLs") aggregating approximately $60 million, which, if not used, expire beginning in 2012 through 2030. The utilization of these NOLs is subject to limitations pursuant to Internal Revenue Code Section 382. Ownership changes have occurred for Internal Revenue Code Section 382 purposes and therefore, the firm's ability to utilize its NOLs is limited. Synergy has no other material deferred tax items. The firm records a valuation allowance against deferred tax assets to the extent that it is more likely than not that some portion, or all of, the deferred tax assets will not be realized. Due to the substantial doubt related to Synergy's ability to continue as a going concern and utilize its deferred tax assets, a valuation allowance for the full amount of the deferred tax assets has been established. As a result, there are no income tax benefits reflected in the accompanying consolidated statements of operations to offset pre-tax losses.

Share Count: The outstanding share count stands at approximately 65.8 million shares, including 6.7 million vested stock options and 5.6 million warrants.

EPS: We forecast EPS of ($0.69) and ($0.68) for 2012 and 2013, respectively. We do not currently have an estimate as to when Synergy might achieve profitability.

Balance Sheet: The firm held $6.1 million in cash at end-1Q 2012. Synergy Pharmaceuticals recently completed a financing transaction that yielded net proceeds to the company of $42 million, not counting proceeds from over-allotment exercises.

Cash Flow: Further funding will need to be secured if Synergy is to successfully complete pivotal clinical development for plecanatide and formally initiate proof-of-concept mid-stage clinical trials with SP-333 in various inflammatory bowel conditions.

Guidance: The firm does not provide financial guidance.

Management Team

The company seeks to align the management team's interests with those of shareholders by using equity-based long-term incentive awards, which generally consist of either stock options or shares of restricted stock that vest over time or upon achievement of a milestone, such as product approval. In addition, management is motivated to achieve product development and operating objectives via a compensation program that rewards the achievement of predetermined performance objectives in areas that the Board of Directors believes are critical to the company's success.

Gary S. Jacob, Ph.D.
Chief Executive Officer
Gary Jacob has served as President, Chief Executive Officer and a Director since July 2008 and as Chairman of Synergy from October 2003 until July 2008. Dr. Jacob currently also serves as Chief Executive Officer and a Director of Callisto Pharmaceuticals, Inc. Prior to his involvement with Callisto and Synergy, Dr. Jacob was at Monsanto/G.D. Searle, where he served as Director of Glycobiology and Monsanto Science Fellow, specializing in the field of glycobiology and drug discovery. From 1986 to 1990, Dr. Jacob managed the G.D. Searle Glycobiology Group located at Oxford University, England. 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. (formerly known as Xenomics, Inc.)

Kunwar Shailubhai, Ph.D. MBA
Chief Scientific Officer
Kunwar Shailubhai, Ph.D., M.B.A has served as Synergy's Chief Scientific Officer since July 2008. From 2003 until July 2008, Dr. Shailubhai served as Senior Vice President, Drug Discovery, of Synergy Pharmaceuticals Inc. From 2001 to 2003, Dr. Shailubhai held the position of Vice President, Drug Discovery at Synergy Pharmaceuticals Inc., where 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. Between 1993 and 2000, he worked for Monsanto, serving as Group Leader of the cancer chemoprevention group. Dr. Shailubhai previously served as a Senior Staff Fellow at the National Institutes of Health, and as an Assistant Professor at the University of Maryland. He received his Ph.D. in microbiology from the University of Baroda, India, and his MBA from the University of Missouri, St. Louis.

Bernard F. Denoyer, CPA MBA
Senior Vice President, Finance
Bernard Denoyer has been in the role of Senior Vice President, Finance and Secretary at Synergy Pharmaceuticals since July 2008. Since January 2004, Mr. Denoyer has also served as the Senior Financial Officer and Secretary of Callisto Pharmaceuticals, Inc. From 2001 through 2003, Mr. Denoyer was an independent consultant providing interim CFO services to emerging firms, including Callisto. From 1994 through 2000, Mr. Denoyer served as Chief Financial Officer and Senior Vice President at META Group, Inc., where he was instrumental in their 1995 IPO. From 1990 to 1993 he served as Vice President Finance of Environetics, Inc., a pharmaceutical water diagnostic business. Mr. Denoyer received a BA in Economics from Fairfield University, earned his MBA in Finance from the Columbia Business School, and his CPA while at Ernst and Young.

Craig Talluto, Ph.D.
Executive Director, Clinical Operations
Craig Talluto has served as Executive Director and formerly the firm's Senior Director, Clinical Operations since July 2008. Dr. Talluto has also served as Senior Director, Clinical Operations at Callisto Pharmaceuticals since August 2006. Prior to joining

Synergy and Callisto Dr. Talluto had over 10 years of broad pharmaceutical industry experience as an independent contractor working with clients in all phases of clinical trial development for both therapeutic and diagnostic product candidates. These clients included Amgen, Hoffman-La Roche and Kos Pharmaceuticals (subsequently acquired by Abbott Laboratories.) Dr. Talluto completed his residency and earned his Ph.D. in Physiology, with a supporting field in Clinical Immunology, from the University of Miami. He earned his MS in Physiology and his BS in Marketing and Business Administration from the University of New Orleans.

Stephen Comiskey, Ph.D.
Senior Director, Product Development
Stephen Comiskey has served as Senior Director and formerly Director, Product Development since July 2008. Dr. Comiskey previously served as Director of Product Development at Nucleonics, Inc. and at Orapharma, Inc. and Group Leader at Aventis and American Home Products (Wyeth), now part of Pfizer, Inc. Dr. Comiskey is a pharmaceutical scientist with considerable experience in the development of biologics and drugs including formulation development, clinical supply manufacture and distribution. Dr. Comiskey received his BS in Biochemistry, MS in Food Chemistry, and Ph.D. in Pharmaceutics from the University of Wisconsin-Madison.

Laura Barrow, Pharm.D.
Vice President, Clinical Operations
Dr. Barrow joined the Synergy management team in March 2011. She is responsible for developing and guiding the Phase 2/3 clinical development program for plecanatide, Synergy's lead drug candidate for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome. Dr. Barrow has more than 25 years of experience in the pharmaceutical industry, having spent seven years in clinical research at Hoffmann–La Roche; 17 years in project management and organizational effectiveness at Bristol-Myers Squibb; and, most recently, time as Worldwide Head of Clinical and Regulatory Standard Operating Procedures at Pfizer. She has managed and led project teams that launched successful products in infectious disease and was executive director and coordinator for the exploratory development operating committee at Bristol-Myers for more than 10 years.

Gail M. Comer, M.D.
Chief Medical Officer
Dr. Barrow joined the Synergy management team in May 2012 as Chief Medical Officer, reporting to CEO Gary Jacob. A board-certified gastroenterologist and hepatologist, Dr. Comer has more than 14 years of experience in the pharmaceutical industry, having spent seven years at Abbott Laboratories as a Medical Director, six years in clinical development at Wyeth Research as Senior Medical Director, and most recently time as Senior Director of the BioTherapeutics Research Unit at Pfizer. While at Wyeth, Dr. Comer was Medical Research Leader in Gastroenterology, and more recently, at Pfizer, she was the clinical lead for multiple biologic compounds in inflammatory bowel disease. Prior to entering the pharmaceutical industry, Dr. Comer was an Associate Professor of Clinical Medicine at The State University of New York at Stony Brook. She is to play a lead role in the clinical development of plecanatide and the design of clinical studies to establish proof-of-concept for Synergy's follow-on agents, including SP-333 and SP-373.

Board of Directors

The firm's Board of Directors includes several senior-level individuals with substantial expertise in the biopharmaceutical industry, along with individuals with significant track records in the venture capital and private equity domains. In our view, Synergy's board possesses the necessary knowledge base and experience to provide appropriate guidance to the company's senior executives as the firm seeks to build shareholder value.

Gabriele M. Cerrone, MBA
Chairman of the Board, Non-independent Director
Gabriele M. Cerrone has served as Chairman of the Synergy Pharmaceuticals Board of Directors since July 2008. From March 1999 to January 2005 Mr. Cerrone served as a Senior Vice President of Investments of Oppenheimer & Co. Inc., a financial services firm. Prior to such affiliation, Mr. Cerrone held the position of Managing Director of Investments at Barrington Capital, L.P., a merchant bank, between March 1998 and March 1999. Mr. Cerrone was also a founder of FermaVir Pharmaceuticals, Inc., a biotech firm, and served as Chairman from 2005 to 2007, when FermaVir was acquired by Inhibitex, Inc., another biotech firm. Mr. Cerrone was also a founder of Xenomics, Inc. (currently known as TrovaGene, Inc.), a diagnostic company, and served as Chairman from 2004 until 2006. Mr. Cerrone currently serves as a director of Inhibitex, Inc. and as Chairman of Callisto Pharmaceuticals, Inc. From 2001 to 2003, Mr. Cerrone also served on the board of directors of SIGA Technologies, Inc., and led the successful restructuring of that firm. Mr. Cerrone is the managing partner of Panetta Partners Ltd., a Colorado limited partnership investing in both public and private companies in the life sciences and technology arena as well as real estate. Mr. Cerrone graduated from New York University's Stern School of Business with a Masters degree in Finance.

Gary S. Jacob, Ph.D.
Director, President and Chief Executive Officer
See bio above.

Thomas H. Adams, Ph.D.
Non-Executive Director
Dr. Adams has served as a Director of Synergy since July 2008. Since June 2005, Dr. Adams has served as a director of IRIS International, Inc., a diagnostics company, and as Chief Technology Officer of IRIS since April 2006. Dr. Adams served as Chairman and Chief Executive Officer of Leucadia Technologies, a privately held medical-device company, from 1998 to April 2006, when Leucadia was acquired by IRIS. In 1989, Dr. Adams founded Genta, Inc., a publicly held biotechnology company in the field of antisense technology, and served as its Chief Executive Officer until 1997. Dr. Adams founded Gen-Probe, Inc. in 1984 and served as its Chief Executive Officer and Chairman until its acquisition by Chugai Biopharmaceuticals, Inc. in 1989. Before founding Gen-Probe, Dr. Adams held management positions at Technicon Instruments and the Hyland Division of Baxter Travenol. He has significant public-company experience serving as a director of Biosite Diagnostics, Inc., a publicly held medical research firm, from 1989 to 1998 and as a director of Invitrogen, a publicly held company that develops, manufactures and markets research tools and products, from 2000 to 2002. Dr. Adams currently serves as a director of La Jolla Pharmaceutical Co. (NASDAQ: LJPC), a publicly held company that develops and markets novel therapeutics for antibody-mediated autoimmune diseases. He holds a Ph.D. in Biochemistry from the University of California, at Riverside.

John P. Brancaccio, CPA
Non-Executive Director
John P. Brancaccio, a retired CPA, has served on the Synergy Board of Directors since July 2008. Since April 2004, Mr. Brancaccio has been the Chief Financial Officer of Accelerated Technologies, Inc., an incubator for medical device companies. From May 2002 until March 2004, Mr. Brancaccio was the Chief Financial Officer of Memory Pharmaceuticals Corp., a biotechnology company, which was recently acquired by Hoffmann-La Roche. From 2000 to 2002, Mr. Brancaccio was the Chief Financial Officer/Chief Operating Officer of Eline Group, an entertainment and media company. Mr. Brancaccio is currently a director of Alfacell Corporation as well as a director of Xenomics, Inc. (now known as TrovaGene, Inc.) and Callisto Pharmaceuticals, Inc.

Chris McGuigan, Ph.D.
Non-Executive Director
Dr. McGuigan has served as a Director since July 2008. Since 1995, Dr. McGuigan has been Professor at the Welsh School of Pharmacy, Chairman of Departmental Research Committee and Director of Research, Head of Medicinal Chemistry. He is the Chemistry Editor for Antiviral Chemistry and Chemotherapy. Prof. McGuigan is an Editorial Board Member for the *Journal of Medicinal Chemistry*, a highly respected peer-reviewed journal. He is a board member and former President of the International Society for Antiviral Research. Dr. McGuigan received a B.S. and Ph.D. in Anticancer Drug Design from the University of Birmingham. He also served as a director of Inhibitex, Inc., until that firm's acquisition by Bristol-Myers Squibb in January 2012.

Melvin K. Spigelman, M.D.
Non-Executive Director
Dr. Spigelman has served as a Director on the Synergy Board since August 2008. He is currently Chief Executive Officer of the Global Alliance for TB Drug Development, a non-profit organization which seeks to accelerate the discovery and development of faster-acting and affordable drugs to fight tuberculosis. Before joining the Global Alliance for TB Drug Development, Dr. Spigelman was President of Hudson-Douglas Ltd, a consulting company, from June 2001 to June 2003. From 1992 to 2001, Dr. Spigelman served as a Vice President and head of R&D at Knoll Pharmaceuticals, a pharmaceutical unit of BASF Pharma. Dr. Spigelman has been a director of The Medicines Company since 2005. Dr. Spigelman received a B.A. in engineering from Brown University and an M.D. from The Mount Sinai School of Medicine; and is board certified in internal medicine, medical oncology and preventive medicine.

Alan F. Joslyn, Ph.D.
Non-Executive Director
Dr. Joslyn has served as a Director since October 2009. He is currently the Chief Executive Officer of Edusa Pharmaceuticals, a privately held biotechnology company. Prior to his association with Edusa, he served as the President and Chief Executive Officer of Mt. Cook Pharma from 2007 to 2009, and as Senior Vice President of Research & Development at Penwest Pharmaceuticals from 2004 to 2007. From 1995 to 2004, Dr Joslyn held a number of leadership positions within Johnson & Johnson, focusing on development of gastroenterology products including Propulsid®, Motilium®, Aciphex® and prucalopride. Prior to joining Johnson & Johnson, Dr. Joslyn was engaged in clinical research at Glaxo from 1988 to 1995. Dr. Joslyn received his B.S. in Medicinal Chemistry, B.A. in Biology and Ph.D. in Biochemical Pharmacology from the State University of New York at Buffalo.

Public Companies Mentioned in this Report:

Laboratorios Almirall S.A. (ALM.MC/MCE – €5.66)

Amarin Corporation (AMRN/NASDAQ – $11.31)

Ardea Biosciences (RDEA/NASDAQ – $31.97)

ARYx Therapeutics (ARYX.PK/PNK – $0.01)

Astellas Pharma (ALPMF/OTC – $39.00)

Bristol-Myers Squibb (BMY/NYSE – $34.18)

Cubist Pharmaceuticals (CBST/NASDAQ – $40.14)

Forest Laboratories (FRX/NYSE – $34.43)

Ironwood Pharmaceuticals (IRWD/NASDAQ – $12.41)

Jazz Pharmaceuticals (JAZZ/NASDAQ – $41.23)

Johnson & Johnson (JNJ/NYSE – $62.12)

Medivation (MDVN/NASDAQ – $84.78)

Novartis Pharmaceuticals (NVS/NYSE – $52.02)

Procter & Gamble (PG/NYSE – $62.54)

Salix Pharmaceuticals (SLXP/NASDAQ – $51.78)

Sucampo Pharmaceuticals (SCMP/NASDAQ – $7.01)

Takeda Pharmaceuticals (TKPHF.PK/PNK – $41.99)

TrovaGene (TROV/NASDAQ – $3.76)

ViroPharma (VPHM/NASDAQ – $19.81)

VIVUS (VVUS/NASDAQ – $24.25)

Table 7: Synergy Pharmaceuticals, Inc. (SGYP) – Historical Income Statements, Financial Projections

FY end December 31

$ in thousands, except per share data

				2012E					2013E				
	2009A	2010A	2011A	1QA	2QE	3QE	4QE	2012E	1QE	2QE	3QE	4QE	2013E
Revenue													
Total revenue	-	-	-	-	-	-	-	-	-	-	-	-	-
Expenses													
Cost of product and service revenue	-	-	-	-	-	-	-	-	-	-	-	-	-
Research & development	4,257	9,559	13,419	5,338	7,000	8,000	10,000	30,338	7,000	7,000	9,000	11,000	34,000
Selling and marketing	-	-	-	-	-	-	-	-	-	-	-	-	-
General and administrative	3,943	6,563	6,746	1,731	2,500	4,000	5,000	13,231	5,000	5,000	5,000	5,000	20,000
Total expenses	8,200	16,121	20,164	7,069	9,500	12,000	15,000	43,569	12,000	12,000	14,000	16,000	54,000
Gain (loss) from operations	(8,200)	(16,121)	(20,164)	(7,069)	(9,500)	(12,000)	(15,000)	(43,569)	(12,000)	(12,000)	(14,000)	(16,000)	(54,000)
Other income/expense													
Interest and investment income	-	-	90	39	65	55	45	204	75	60	50	45	230
Interest income/expense	75	109	(12)	-	-	-	-	-	-	-	-	-	-
Change in fair value of derivative instruments-warrants	-	297	5,257	8	-	-	-	8	-	-	-	-	-
Other income/expense	-	494	362	-	-	-	-	-	-	-	-	-	-
Total investment income and other	75	900	5,697	47	65	55	45	212	75	60	50	45	230
Loss before provision for income taxes	(8,125)	(15,221)	(14,467)	(7,023)	(9,435)	(11,945)	(14,955)	(43,358)	(11,925)	(11,940)	(13,950)	(15,955)	(53,770)
Deferred income tax benefit	-	-	-	-	-	-	-	-	-	-	-	-	-
Net loss/income	(8,125)	(15,221)	(14,467)	(7,023)	(9,435)	(11,945)	(14,955)	(43,358)	(11,925)	(11,940)	(13,950)	(15,955)	(53,770)
Net loss per share (basic)	(0.11)	(0.17)	(0.30)	(0.13)	(0.16)	(0.18)	(0.21)	(0.69)	(0.15)	(0.15)	(0.17)	(0.20)	(0.68)
Net loss per share (diluted)	(0.11)	(0.17)	(0.30)	(0.13)	(0.16)	(0.18)	(0.21)	(0.69)	(0.15)	(0.15)	(0.17)	(0.20)	(0.68)
Weighted average number of shares outstanding (basic)	73,281	89,751	47,598	54,298	59,730	65,405	71,055	62,622	78,155	79,905	79,955	79,980	79,499
Weighted average number of shares outstanding (diluted)	73,281	89,751	47,598	54,298	59,730	65,405	71,055	62,622	78,155	79,905	79,955	79,980	79,499

Source: Company Reports and Aegis Capital Corp. estimates

Required Disclosures

Price Target

Our 12-month price target for SGYP is $25 per share.

Valuation Methodology

Given that Synergy is currently unprofitable, and considering our belief that this condition is likely to persist for the foreseeable future, we use a discounted cash flow-based approach to value the shares. Based on a comparables analysis, we believe that the stock is worth $25 per share, given our estimate of a $1.75 billion risk-adjusted net present value (rNPV) for plecanatide and SP-333. This assumes that the shares trade in line with the comp group average enterprise value of roughly $1.75 billion and that the firm has roughly 80 million shares outstanding in mid-2013.

Risk Factors

Issues that could prevent the achievement of our price objective include, but are not limited to, clinical, regulatory, competitive, reimbursement and financial risks. Drugs in clinical development may not advance due to inadequate safety, efficacy, or tolerability. Regulatory agencies may decline to approve regulatory submissions in a timely manner, or may not approve a drug candidate at all. The firm may require substantial funding to advance the clinical progress of its candidates, which could be dilutive to current shareholders. We expect competition for the company's drugs from several public and private companies developing pharmaceuticals. Sales of the firm's drugs could depend upon reimbursement from private, as well as public, reimbursement agencies.

For important disclosures go to www.aegiscap.com.

We, Raghuram Selvaraju and Yi Chen, the authors of this research report, certify that the views expressed in this report accurately reflect our personal views about the subject securities and issuers, and no part of our compensation was, is, or will be directly or indirectly tied to the specific recommendations or views contained in this research report.

Research analyst compensation is dependent, in part, upon investment banking revenues received by Aegis Capital Corp.

Aegis Capital Corp. intends to seek or expects to receive compensation for investment banking services from the subject company within the next three months.

Aegis Capital Corp. has performed investment banking services for Synergy Pharmaceuticals, Inc. within the past 12 months.

Aegis Capital Corp. makes a market in Synergy Pharmaceuticals, Inc..

Rating	Percent	Investment Banking Services/Past 12 Mos. Percent
BUY [BUY]	80.00	25.00
HOLD [HOLD]	20.00	0.00
SELL [SELL]	0.00	0.00

Meaning of Ratings

A) A Buy rating is assigned when we do not believe the stock price adequately reflects a company's prospects over 12-18 months.
B) A Hold rating is assigned when we believe the stock price adequately reflects a company's prospects over 12-18 months.
C) A Sell rating is assigned when we believe the stock price more than adequately reflects a company's prospects over 12-18 months.

Other Disclosures

The information contained herein is based upon sources believed to be reliable but is not guaranteed by us and is not considered to be all inclusive. It is not to be construed as an offer or the solicitation of an offer to sell or buy the securities mentioned herein. Aegis Capital Corp., its affiliates, shareholders, officers, staff, and/or members of their families, may have a position in the securities mentioned herein,

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Aegis Capital Corp.
(212) 813-1010
810 Seventh Avenue, 18th Floor
New York, New York 10019