AEGIS CAPITAL CORP

**Biopharmaceuticals**
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**Company Update / Estimates Change**

September 4, 2012

# Synergy Pharmaceuticals, Inc.

# Rating: Buy

## Linzess™ Approval Validates Synergy's Approach

**Key Metrics**

| | |
|---|---|
| SGYP - NASDAQ | $4.95 |
| Pricing Date | Aug 31 2012 |
| Price Target | $25.00 |
| 52-Week Range | $7.08 - $1.86 |
| Shares Outstanding (mm) | 65.8 |
| Market Capitalization ($mm) | $325.7 |
| 3-Mo Average Daily Volume | 353,871 |
| Institutional Ownership | NA |
| Debt/Total Capital | NM |
| ROE | NM |
| Book Value/Share | $0.06 |
| Price/Book | 82.5x |
| 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 | -- | (0.14)E |
| 2Q-Jun | (0.05) | (0.16)E | (0.17)A | -- | (0.14)E |
| 3Q-Sep | (0.01) | (0.18)E | (0.16)E | (0.16)E | (0.15)E |
| 4Q-Dec | (0.12) | (0.20)E | (0.18)E | (0.19)E | (0.16)E |
| FY | (0.30) | (0.67)E | (0.65)E | (0.64)E | (0.59)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 website is www.synergypharma.com.*

### Investment Highlights:

- **FDA Rubber-Stamps Linaclotide.** Last week, Ironwood Pharmaceuticals reported that the FDA had approved its lead drug candidate, linaclotide, in chronic constipation and irritable bowel syndrome of the constipation-predominant subtype (IBS-C). Linaclotide is to be marketed in the U.S. under the commercial name Linzess™. In the wake of the approval of linaclotide, which in our view validates the entire guanylyl cyclase C (GC-C) receptor sector, of which plecanatide is a part, we reiterate our Buy rating and 12-month price target of $25 per share for SGYP.
- **Phase 3 Plecanatide Data By Year-End 2012.** Synergy announced last month that it had reached the pre-specified enrollment target of 880 patients randomized in the Phase 2/3 trial of plecanatide. The study is assessing the safety and efficacy of plecanatide vs. placebo in patients with chronic idiopathic constipation (CIC). We currently expect top-line data from this trial in late 2012. Synergy could steal some of Ironwood's thunder if its Phase 3 data with plecanatide are positive, as Linzess™ is not likely to be formally launched until mid-December 2012.
- **Proof-Of-Concept Anticipated.** We would remind investors that the plecanatide study in constipation is a major component of Synergy's development strategy for the drug. This trial would qualify as one of the two pivotal studies necessary to achieve approval of plecanatide in CIC, and we further believe that if it is positive on the efficacy front without showing any evidence of stimulation of diarrhea in the wake of plecanatide therapy, this study could firmly establish plecanatide as a best-in-class gastrointestinal disorders drug. We consider the Phase 2/3 trial to be a risk-mitigated clinical program, as plecanatide was already shown to provide substantial relief to individuals with chronic constipation over a 14-day period in a previous Phase 2a trial.
- **Potential For Superior Safety Vs. Linaclotide.** Plecanatide was exceptionally well-tolerated in its original Phase 2a trial, with no incidence of diarrhea. Linaclotide caused diarrhea severe enough to prompt patient withdrawal from clinical trials in certain cases. We believe that the absence of diarrhea for plecanatide would be a significant marketing advantage.
- **In-Licensing Transaction Broadens Clinical Pipeline.** In late August, Synergy announced the in-licensing of FV-100, a novel anti-shingles drug, from Bristol-Myers Squibb for an upfront payment of only $1mm. In our view, this was a very shrewd licensing transaction that enhances Synergy's clinical-stage pipeline. FV-100 has already been tested in one Phase 2 trial, with relatively encouraging results, although optimization is needed.

The Disclosure section may be found on pages 14 - 15 of this report.

# 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 significant 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 peptide 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. Finally, Synergy recently in-licensed another drug candidate designated FV-100. This is a small molecule drug for treatment of shingles infections. In our view, this agent also has a relatively high risk profile as it previously failed to demonstrate superiority to a comparator in a Phase 2 trial.

**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, since linaclotide has already been approved while plecanatide is currently still in 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, we believe 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., as well as Forest Laboratories, Almirall, Astellas, and Ironwood Pharmaceuticals with linaclotide, which was approved by the FDA in the U.S. for both chronic constipation and constipation-predominant irritable bowel syndrome; and Shire Pharmaceuticals with Resolor, which is currently marketed only in Switzerland and the UK for the treatment of chronic constipation in women. In our view, the most significant direct competition for plecanatide is linaclotide, which is roughly 24 – 36 months ahead of plecanatide 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 the 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 as well as FV-100 prior to the expiration of patent protection on these products.

**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 potentially compelling value proposition inherent in plecanatide, SP-333 and FV-100.

**Additional Risks.** As of June 30, 2012, Synergy had approximately $43.6 million in cash and equivalents. During the next 12 months, the firm may burn around $48 million. Additional sources of cash could include: licensing fees from partnerships, warrant and option exercises, or the issuance of additional 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, it appears to us that the stock is worth approximately $25 per share, given our estimate of a $2.1 billion risk-adjusted net present value (rNPV) for plecanatide, SP-333 and FV-100. This assumes that the shares trade in line with the comp group average enterprise value of roughly $2.2 billion and that the firm has roughly 93 million shares outstanding in mid-2013.

## Table 1: Comparable Company Analysis

**(Millions, Except Per-Share Data)**

| Development | Therapeutic Area | Company | Ticker | Rating | Closing price 8/31/2012 | Shares (MM) | Market cap ($MM) | Cash ($MM) | Debt ($MM) | Enterprise value ($MM) |
|---|---|---|---|---|---|---|---|---|---|---|
| Pre-approval | Cardiovascular Diseases | Amarin Corporation | AMRN | Buy | $13.69 | 148 | 2028 | 250 | 127 | 1905 |
| Pre-approval | Oncology | Ariad Pharmaceuticals | ARIA | Not Rated | $20.56 | 166 | 3417 | 288 | 12 | 3142 |
| Marketed | Infectious Diseases | Cubist Pharmaceuticals | CBST | Not Rated | $46.20 | 64 | 2949 | 811 | 396 | 2535 |
| Pre-approval | GI Disorders | Ironwood Pharmaceuticals | IRWD | Buy | $12.53 | 107 | 1343 | 158 | 1 | 1186 |
| Marketed | CNS / Orphan Diseases | Jazz Pharmaceuticals | JAZZ | Not Rated | $45.51 | 58 | 2619 | 155 | 468 | 2932 |
| Pre-approval | CNS / Oncology | Medivation | MDVN | Buy | $104.86 | 37 | 3862 | 344 | 190 | 3708 |
| Marketed | GI Disorders | Salix Pharmaceuticals | SLXP | Not Rated | $43.96 | 59 | 2582 | 716 | 860 | 2726 |
| Marketed | GI Disorders | Sucampo Pharmaceuticals | SCMP | Not Rated | $4.77 | 42 | 199 | 75 | 59 | 183 |
| Marketed | Infectious Diseases | ViroPharma | VPHM | Not Rated | $26.60 | 69 | 1827 | 472 | 158 | 1513 |
| Pre-approval | Metabolic Disorders | VIVUS, Inc. | VVUS | Not Rated | $21.45 | 100 | 2153 | 310 | 0 | 1842 |
| | | **Average** | | | | | **2298** | | | **2167** |
| | | | | | | | | **Discrepancy** | | |
| **Current valuation** | **GI Disorders** | **Synergy Pharmaceuticals** | **SGYP** | **Buy** | **$4.95** | **66** | **326** | **44** | **0** | **282** |
| | | | | | **Derived 12-month compa-month comparable value** | | | | | |
| | | | | | | | | | | **Projected** |
| **Target valuation (12-month)** | **GI Disorders** | **Synergy Pharmaceuticals** | **SGYP** | **Buy** | **$25.00** | **93** | **2382** | **215** | **0** | **2167** |

*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 $300 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 but are slated to enter clinical testing shortly. In addition, we are ascribing a $300 million valuation to FV-100, which has already shown clinical activity in a Phase 2 comparator-controlled trial. 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 | $16.00 |
| | |
| Estimated Net Cash Position ($MM; end-2Q 2013) | $215MM |
| Additional Value Drivers (peptide pipeline, including SP-333, and FV-100) | $600MM |
| Total enterprise value | $2.3B |
| Shares Outstanding (MM; end-2Q 2013) | 93MM |
| 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 is in a Phase 2/3 trial and is related to linaclotide, which has been approved in the U.S.

[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 related net sales. In addition to having reimbursed Ironwood for half of linaclotide's development costs since September 2007, Forest has paid Ironwood $120 million in license fees and 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 NDA approval, which we expect to be paid near-term following the recent approval of linaclotide in the U.S. Total payment to Ironwood under the Forest collaboration agreement could sum up to $330 million.

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 $1.1 billion (~$1.3 billion fully-diluted), we believe the current market value being assigned to linaclotide is approximately $2.7 billion. In contrast, Synergy's 100% ownership of rights to plecanatide and related peptides is currently valued at $325 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*

# Overview of FV-100

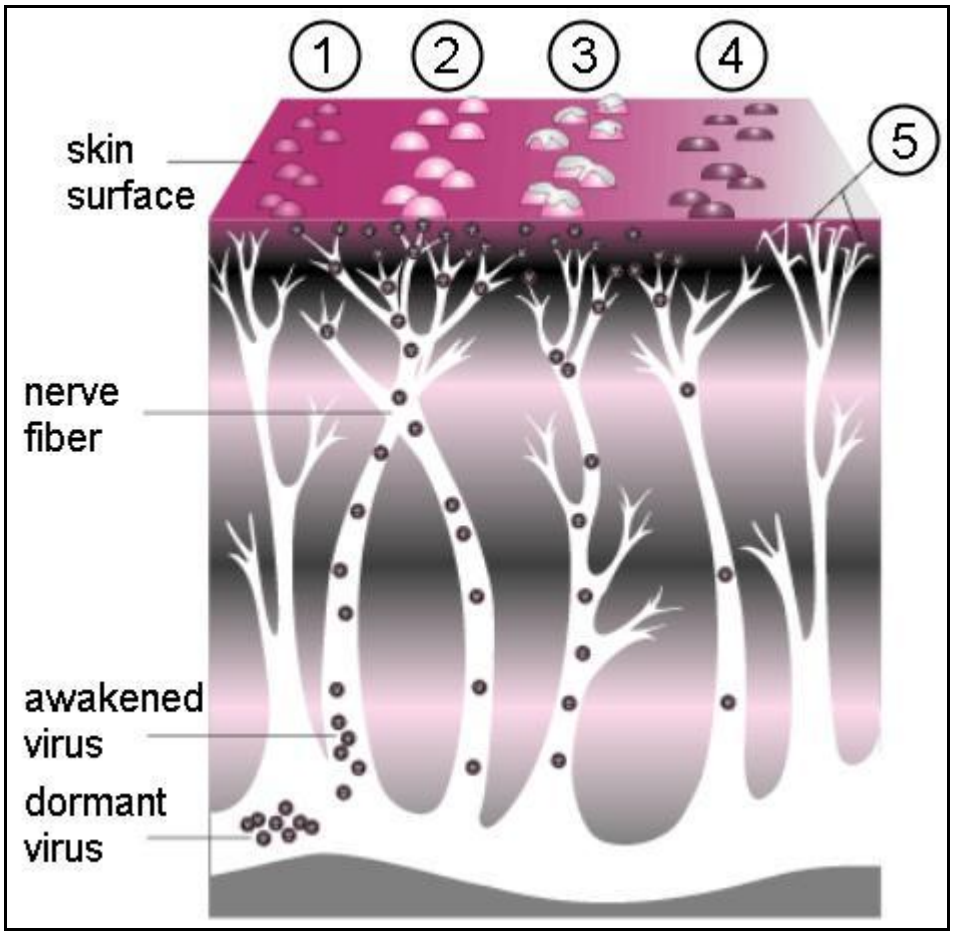
In August 2012, Synergy announced that it was in-licensing the global rights to FV-100, a drug owned by Bristol-Myers Squibb, for an upfront payment of $1 million and up to $125 million in additional contingent milestone payments dependent upon regulatory and commercial success. Synergy is also slated to pay Bristol-Myers Squibb single digit percentage royalties on net sales of FV-100 if it is ever successfully commercialized. Three components of this deal are of particular interest to Synergy investors:

- FV-100 has had a circuitous route, and in the latest transaction is actually coming back into the hands of its original developers. The drug was initially the lead candidate of a privately-held firm called FermaVir, which was acquired by Inhibitex in July 2007 for roughly $20 million. FermaVir was backed by several of the same individuals currently involved with Synergy, most notably Synergy's executive chairman Gabriele Cerrone. In a twist of fate, Inhibitex wound up being acquired by Bristol-Myers Squibb in January 2012 for $2.5 billion, in what was a record sum paid to secure the rights to a Phase 1-level compound. At the time, Inhibitex's most valuable asset was considered to be a hepatitis C-focused compound called INX-189, which was discontinued by Bristol in mid-stage testing after cardiac toxicities were discovered with the agent. Following the failure of INX-189, it appears that Bristol was all too eager to get rid of anything that even remotely reminded it of Inhibitex. Accordingly, therefore, FV-100, which was originally Inhibitex's lead drug, has now come back into the hands of a company once again backed by Gabriele Cerrone. In our view, this means the following – firstly, no one knows more about FV-100 than the current management at Synergy, since it was involved with its development initially; and secondly, Synergy was able to convince Bristol-Myers Squibb to part with FV-100 for a very small upfront consideration. In a sense, we can consider this a case of Synergy taking Bristol to the cleaners twice in the same year.
- Synergy appears to have a strategy in mind to recreate value in FV-100 by focusing on patient-reported outcomes and crafting a trial design that could potentially enable the drug to demonstrate some kind of superiority to valacyclovir in the shingles patient population, which is where the drug was originally deployed. In our view, Synergy is well-positioned to achieve this because of its in-depth knowledge of FV-100 and what the drug's main strengths are. For reasons we shall delineate later in this section, we believe that there are multiple areas in which the drug's efficacy profile could be showcased in a more optimized manner and that this could potentially permit it to be positioned as a best-in-class anti-shingles therapeutic.
- We should not discount the fact that Synergy has, with the addition of FV-100, managed to add a Phase 2 / 3 drug candidate with clear clinical efficacy demonstrated (in a comparator-controlled setting, no less) to its pipeline for an upfront outlay of only $1 million. This is a praiseworthy achievement, in our view; many pharmaceutical firms spend hundreds of millions of dollars to bring in mid- and late-stage clinical candidates. We do not believe that FV-100 is a tarnished asset; rather, it is our position that the drug was inadequately developed by Inhibitex because that firm placed substantial focus on drug development in hepatitis C, and also because Inhibitex was a small company in a capital-constrained position.

Herpes zoster (or simply zoster), commonly known as shingles and also known as zona, is a viral disease characterized by a painful skin rash with blisters. The initial infection with varicella zoster virus (VZV) causes chickenpox, which generally occurs in children and young people. Once an episode of chickenpox has resolved, the virus is not eliminated from the body but can go on to cause shingles – an illness with very different symptoms – often many years after the initial infection. Herpes zoster is not the same disease as herpes simplex, despite the name similarity (both the varicella zoster virus and herpes simplex virus belong to the same viral subfamily known as *Alphaherpesvirinae*).

Varicella zoster virus can become latent in the nerve cell bodies and, less frequently, in non-neuronal satellite cells of dorsal root, cranial nerve or autonomic ganglion, without causing any symptoms. Years or decades after a chickenpox infection, the virus may break out of nerve cell bodies and travel down nerve axons to cause viral infection of the skin in the region of the nerve. The virus may spread from one or more ganglia along nerves of an affected segment and infect the corresponding dermatome (an area of skin supplied by one spinal nerve) causing a painful rash. Although the rash usually heals within two to four weeks, some sufferers experience residual nerve pain for months or years, a condition called post-herpetic neuralgia (PHN). Exactly how the virus remains latent in the body, and subsequently re-activates is not understood.

**Figure 1: Herpes Virus Thymidine Kinase Enzyme Structure**



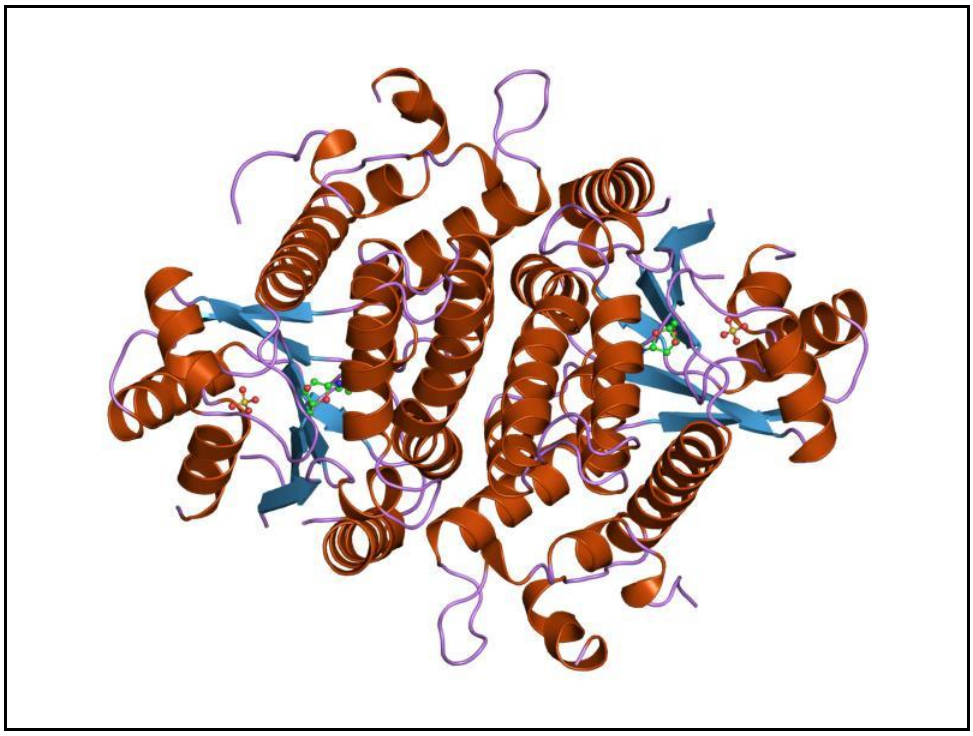

*Source: Molecular Biology of the Cell (2005)*

Throughout the world, the incidence rate of herpes zoster every year ranges from 1.2 – 3.4 cases per 1,000 healthy individuals, increasing to 3.9 – 11.8 per year per 1,000 individuals among those older than 65 years of age. While chickenpox is considered a childhood rite of passage, shingles is generally classified as a disease of older individuals.

Over a lifetime, a large fraction of people develop herpes zoster, though usually only once – in a 1960s American study, 50% of individuals living to age 85 had at least one attack, while 1% had at least two attacks. Antiviral drug treatment can reduce the severity and duration of herpes zoster if a 7 – 10-day course of these drugs is started within 72 hours of the appearance of the characteristic rash.

FV-100 is a bicyclic nucleoside analog targeting the varicella zoster virus (VZV) thymidine kinase (TK). Viral TK is a common drug target used to combat the herpes virus family. TK helps to prepare the nucleotide building blocks for the synthesis of new DNA strands by phosphorylating nucleosides (specifically, thymidine). The main feature that makes VZV TK an attractive drug target is a substantial level of differentiation from the human TK enzyme in terms of its ability to recognize other substrates.

**Figure 2: Herpes Virus Thymidine Kinase Enzyme Structure**



*Source: Brookhaven Protein Data Bank*

One issue with drugs in the bicyclic nucleoside analog class is poor aqueous solubility, which can impact their utility as orally-bioavailable therapeutics. FV-100 is a 5'-valyl ester pro-drug of Cf1743, possessing improved aqueous solubility and bioavailability. Various *in vitro* activity assays have demonstrated that FV-100 possesses picomolar activity against VZV and has nearly 1,000x greater activity against VZV than valacyclovir or acyclovir. No apparent cytotoxicity problems have been observed.

In February 2009, the original sponsor of FV-100, Inhibitex, completed Phase 1 trials of the compound in healthy volunteers to assess its safety and pharmacokinetics. An additional Phase 1 study was performed in a separate healthy, elderly cohort (over 65 years of age) in order to determine potential differences in drug disposition compared to younger patients. Overall, the drug was well tolerated in healthy volunteers.

In the first trial, FV-100-treated patients had similar adverse event (AE) rates as placebo-administered patients. In the second trial, there appeared to be a slightly higher AE incidence versus placebo treated patients. The younger FV-100 group had an increased incidence of Grade 1 AEs compared to placebo, but was still similar to the elderly FV-100 cohort in terms of AE incidence. No Grade 2 or higher AEs were reported in the young cohort. One potential explanation for the higher AE incidence in elderly patients in the multiple dose cohort was likely variability in FV-100 pharmacokinetics.

It appeared that elderly patients had lower drug exposures than younger patients in the single dose cohort, while in the multiple dose cohort, the situation was reversed. Elderly patients exhibited higher area under the curve (AUC) values than younger patients. Results from the Phase 1 single and multiple dose cohort studies are depicted below:

**Table 4: FV-100 Phase 1 Design and Safety Data in Healthy Subjects**

| | Placebo | 100mg FV-100 | 200mg FV-100 | 400mg FV-100 | 800mg FV-100 | 400mg FV-100 |
|---|---|---|---|---|---|---|
| N = | 12 | 6 | 6 | 6 | 6 | 6 |
| Active agent/placebo dosing | QD/BID 7d | QD 7d | QD 7d | QD 7d | QD 7d | BID 7d |
| ***AE's by severity*** | | | | | | |
| Grade 1 | 4 (33.3%) | 3 (50.0%) | 3 (50.0%) | 5 (83.3%) | 3 (50.0%) | 4 (66.7%) |
| Grade 2 | 1 (8.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| ***AE's by type*** | | | | | | |
| Headache | 3 (25.0%) | 3 (50.0%) | 0 (0.0%) | 2 (33.3%) | 0 (0.0%) | 1 (16.7%) |
| Nausea | 0 (0.0%) | 0 (0.0%) | 1 (16.7%) | 1 (16.7%) | 1 (16.7%) | 1 (16.7%) |
| Abdominal pain | 2 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Back pain | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (16.7%) | 0 (0.0%) | 1 (16.7%) |
| Dizziness | 0 (0.0%) | 1 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (16.7%) |

*Source: Company reports*

**Table 5: FV-100 Phase 1 Design and Safety Data in Healthy Subjects**

| | Single dose cohort | | | Multiple dose cohort | | |
|---|---|---|---|---|---|---|
| | Elderly | | Young | Elderly | | Young |
| | Placebo | 400mg FV-100 | 400mg FV-100 | Placebo | 400mg FV-100 | 400mg FV-100 |
| N = | 2 | 13 | 6 | 6 | 10 | 6 |
| ***AE's by severity*** | | | | | | |
| Grade 1 | 1 (50.0%) | 6 (46.2%) | 4 (66.7%) | 1 (50.0%) | 7 (70.0%) | 5 (83.3%) |
| Grade 2 | 1 (50.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (20.0%) | 0 (0.0%) |
| Grade 3 | 1 (50.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

*Source: Company reports*

The current shingles market is dominated by generic drugs with the standard of care being valacyclovir (originally marketed by GlaxoSmithKline under the commercial name Valtrex), which is currently dosed three times per day. Valtrex went generic in November 2009. In 2008, Valtrex had sales in excess of $1.2 billion. Valacyclovir is a prodrug, an esterified version of acyclovir (an earlier-generation drug originally marketed under the names Acivir and Zovirax) that has greater oral bioavailability (about 55%) than acyclovir (10–20%). It is converted by esterases to the active drug acyclovir, as well as the amino acid valine, via hepatic first-pass metabolism. FV-100 has a differentiating pharmacokinetic profile, which allows it to be dosed at a once-daily schedule vs. valacyclovir's thrice-daily dosing schedule.

Phase 2 data for FV-100 were released by Inhibitex in December 2010, comparing FV-100 to valacyclovir for the treatment of shingles. The primary endpoint for FV-100 had been set at a 25% reduction in shingles-related pain compared to valacyclovir control arms after 30 days treatment. The trial enrolled 350 patients, randomized into three arms (200mg FV-100 once-daily; 400mg FV-100 once-daily; 1000mg valacyclovir thrice-daily). The results did not meet the primary endpoint of a 25% reduction in shingles-related pain reduction after 30 days of treatment. The 200mg dose showed a 3% reduction and the 400mg showed a 7% reduction at 30 days. The side effect profile of FV-100 was equivalent to valacyclovir in both arms. Though the high bar of 25% was not reached, we would point investors to a number of positive aspects in the data set:

- First, a dose escalation effect was clearly observed with FV-100. Given the obviously greater potency of the drug vs. valacyclovir, it seems reasonable to assume that above 400mg once/day, there is still plenty of room to increase the dose while remaining substantially lower than the 3000mg/day valacyclovir dosage.
- The safety profile of FV-100 was encouraging. Given roughly equivalent safety vs. valacyclovir, we believe that there is still a reasonable possibility of FV-100 achieving superiority to valacyclovir while maintaining once-daily dosing.
- Additionally, a number of secondary endpoints also showed encouraging efficacy data. After 90 days of treatment, patients randomized to the 200mg arm experienced a 4% reduction in pain vs. valacyclovir, while the 400mg arm experienced a 14% reduction in pain vs. valacyclovir. In our view, this appears to be relatively strong evidence that FV-100 works better than valacyclovir over time. The dose escalation hypothesis also appears to hold true over longer treatment times.

Perhaps the most significant secondary endpoint was the dose-escalating effect observed at reducing the incidence of post-herpetic neuralgia (PHN) compared to valacyclovir. The 400mg patients saw a 39% reduction in PHN incidence rate compared to valacyclovir (12.4% vs. 20.2%). At 200mg, there was a slight reduction in the PHN incidence rate compared to valacyclovir (17.8% compared to 20.2%). These results were further validated by the observation that only 42% of patients on the 400mg dose of FV-100 used opioid painkillers, compared to 52% of valacyclovir patients. Opioids are often prescribed to shingles patients due to the intense pain associated with shingles, particularly those who develop PHN. The pain associated with shingles – particularly in the form of PHN – is a major unmet medical need in the shingles-infected patient population and has proven recalcitrant to therapy with standard painkillers. Therefore, we believe the potential for FV-100 to achieve statistically significant reductions in PHN incidence rates that are superior to those achievable with valacyclovir could represent a major differentiating factor for this agent. We would, therefore, predict that PHN incidence reduction could be used as a primary or co-primary endpoint in future studies with FV-100. The pain associated with PHN is perhaps the most clinically significant concern to physicians attempting to treat shingles.

Nevertheless, we would caution investors that with the shingles market currently dominated by cheap generics, it will be likely that robust clinical superiority to valacyclovir would need to be demonstrated on validated clinical endpoints in order to enable Synergy to generate substantial revenue from FV-100. We certainly are not assuming that FV-100 could recapitulate the blockbuster product levels attained with Valtrex. However, despite the fact that the primary endpoint was not met in the initial Phase 2 proof-of-concept trial with FV-100, we believe that there is still significant room for optimizing the future clinical development of this drug and consider the transaction with Bristol-Myers Squibb to have been a shrewd piece of business development on the part of Synergy's management team, which has a proven track record in this regard. Investors should be encouraged by the fact that Synergy has managed to add an arguably Phase 2 / 3 ready asset to its pipeline for the modest upfront sum of only $1 million.

## Table 6: 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 | 2QA | 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 | 7,626 | 8,000 | 10,000 | 30,964 | 8,000 | 9,000 | 10,000 | 11,000 | 38,000 |
| Selling and marketing | - | - | - | - | - | - | - | - | - | - | - | - | - |
| General and administrative | 3,943 | 6,563 | 6,746 | 1,731 | 1,918 | 3,000 | 4,000 | 10,650 | 4,000 | 4,000 | 4,000 | 4,000 | 16,000 |
| **Total expenses** | 8,200 | 16,121 | 20,164 | 7,069 | 9,545 | 11,000 | 14,000 | 41,614 | 12,000 | 13,000 | 14,000 | 15,000 | 54,000 |
| **Gain (loss) from operations** | (8,200) | (16,121) | (20,164) | (7,069) | (9,545) | (11,000) | (14,000) | (41,614) | (12,000) | (13,000) | (14,000) | (15,000) | (54,000) |
| Other income/expense | | | | | | | | | | | | | |
| Interest and investment income | - | - | 90 | 39 | 48 | 55 | 45 | 187 | 75 | 60 | 50 | 45 | 230 |
| Interest income/expense | 75 | 109 | (12) | - | - | - | - | - | - | - | - | - | - |
| Change in fair value of derivative instruments-warrants | - | 297 | 5,257 | 8 | (1,317) | - | - | (1,309) | - | - | - | - | - |
| Other income/expense | - | 494 | 362 | - | 256 | 256 | 256 | 767 | - | - | - | - | - |
| **Total investment income and other** | 75 | 900 | 5,697 | 47 | (1,014) | 311 | 301 | (356) | 75 | 60 | 50 | 45 | 230 |
| **Loss before provision for income taxes** | (8,125) | (15,221) | (14,467) | (7,023) | (10,558) | (10,689) | (13,699) | (41,970) | (11,925) | (12,940) | (13,950) | (14,955) | (53,770) |
| Deferred income tax benefit | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Net loss/income** | (8,125) | (15,221) | (14,467) | (7,023) | (10,558) | (10,689) | (13,699) | (41,970) | (11,925) | (12,940) | (13,950) | (14,955) | (53,770) |
| **Net loss per share (basic)** | (0.11) | (0.17) | (0.30) | (0.13) | (0.17) | (0.16) | (0.18) | (0.65) | (0.14) | (0.14) | (0.15) | (0.16) | (0.59) |
| Net loss per share (diluted) | (0.11) | (0.17) | (0.30) | (0.13) | (0.17) | (0.16) | (0.18) | (0.65) | (0.14) | (0.14) | (0.15) | (0.16) | (0.59) |
| Weighted average number of shares outstanding (basic) | 73,281 | 89,751 | 47,598 | 54,298 | 60,416 | 68,446 | 75,460 | 64,655 | 86,560 | 93,310 | 93,360 | 93,385 | 91,654 |
| Weighted average number of shares outstanding (diluted) | 73,281 | 89,751 | 47,598 | 54,298 | 60,416 | 68,446 | 75,460 | 64,655 | 86,560 | 93,310 | 93,360 | 93,385 | 91,654 |

*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 $2 billion risk-adjusted net present value (rNPV) for the firm's pipeline. This assumes that the shares trade in line with the comp group average enterprise value of roughly $2 billion and that the firm has roughly 85 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.

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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] | 93.75 | 20.00 |
| HOLD [HOLD] | 6.25 | 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

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