Zacks Small-Cap Research

January 5, 2016

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Biota Pharmact (BOTA-NASDAQ)

BOTA: Initiating Coverage

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	01/04/16
Current Price (01/05/16)	$1.98
Target Price	**$4.50**

OUTLOOK

Georgia based Biota Pharma is developing direct acting antiviral drugs for treating respiratory infections in at-risk patients with limited therapeutic options. . The company has a market cap of $76 million with a share count of 43 million (fully diluted). The company is currently in the clinical development stages of three of its products. Currently, the company's primary source of revenue is from two approved antivirals (neuraminidase inhibitors) against influenza types A & B.

We believe the cash at hand ($57.2 million in cash, cash equivalents and short term investments) is sufficient to carry them through to 2017. With a fully diluted share count of 43 million we arrive at a fair value of $4.50. We initiate coverage on Biota Pharma with a Buy rating.

SUMMARY DATA

52-Week High	**$2.85**
52-Week Low	**$1.78**
One-Year Return (%)	**-30.53**
Beta	**0.78**
Average Daily Volume (sh)	**78,913**
Shares Outstanding (mil)	**39**
Market Capitalization ($mil)	**$75**
Short Interest Ratio (days)	**1.85**
Institutional Ownership (%)	**33**
Insider Ownership (%)	**3**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**27.0**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg**
Type of Stock	**Small-Value**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(in millions of $)

	Q1 (Sep)	Q2 (Dec)	Q3 (Mar)	Q4 (Jun)	Year (Jun)
2015	$0.7A	$13.9A	$5.9A	$4.1A	$24.6A
2016	$1.7A	$7.0E	$6.2E	$2.7E	$17.6E
2017					$18.1E
2018					$18.7E

Earnings per Share

(EPS is operating earnings before non recurring items)

	Q1 (Sep)	Q2 (Dec)	Q3 (Mar)	Q4 (Jun)	Year (Jun)
2015	-0.20A	$0.19A	$0.03A	-0.57A	-0.54A
2016	-0.17A	-0.03E	-0.06E	-0.15E	-0.42E
2017					-0.46E
2018					-0.54E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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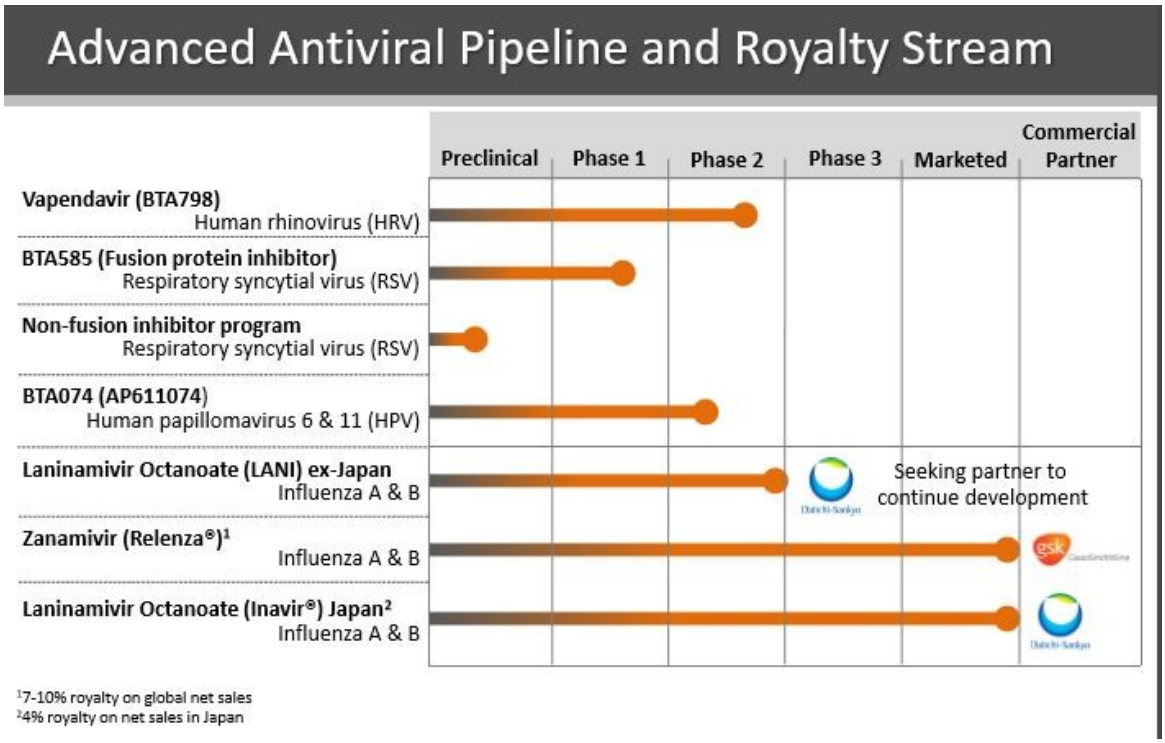
SNAPSHOT

- Biota Pharma (NASDAQ: BOTA), headquartered in Alpharetta, GA, is developing direct acting antiviral drugs for treating respiratory infections in at-risk patients with limited therapeutic options. The drugs are designed to be inhaled or taken orally.



- Currently, the company's primary source of revenue is from two approved antivirals (neuraminidase inhibitors) against influenza types A & B: 7-10% royalty on global net sales of Zanamivir, marketed worldwide as Relenza® by GlaxoSmithKline (NASDAQ: GSK) and 4% royalty on net sales of LANI, marketed in Japan as Inavir® by Daiichi-Sankyo.

- BOTA currently has three products in the clinical development stage:
  - Vapendavir, an oral treatment for human rhinovirus (HRV) infections in patients with moderate-to-severe asthma. It is currently being evaluated in the ongoing Phase 2b SPIRITUS trial
  - BTA585, an oral fusion protein inhibitor in Phase 1 development for the treatment of respiratory syncytial virus (RSV) A & B infections
  - A preclinical stage RSV non-fusion inhibitor program that complements the company's fusion-protein inhibitor BTA585
  - BTA074, a topical antiviral treatment in Phase 2 development for treating genital warts caused by human papillomavirus types 6 & 11 (HPV6 & 11)

- With $57.2 million in cash, cash equivalents and short term investments, Biota Pharma is well capitalized to run its operations which are guided by an experienced management team.

- We are initiating coverage on Biota Pharma with a Buy rating and a price target of $4.50/share

INVESTMENT THESIS

Georgia based Biota Pharma is developing drugs for various infectious diseases in the direct acting antiviral therapy space. The company has a market cap of $76 million with a share count of 43 million (fully diluted). The company is currently in the clinical development stages of three of its products. Vapendavir, an oral treatment for HRV infections in patients with moderate-to-severe asthma, is currently being evaluated in the ongoing Phase 2b SPIRITUS trial. BTA585, an oral fusion protein inhibitor, is in Phase 1 development for the treatment RSV A & B infections. A preclinical stage RSV non-fusion inhibitor program that complements the company's fusion-protein inhibitor BTA585 is also in process. The molecule BTA074 is being developed as a topical antiviral treatment that is in Phase 2 development for treating genital warts caused by HPV6 & 11. Currently, the company's primary source of revenue is from two approved antivirals (neuraminidase inhibitors) against influenza types A & B: 7-10% royalties on global net sales of Zanamivir, marketed worldwide as Relenza® by GlaxoSmithKline, and 4% royalties on net sales of LANI, marketed in Japan as Inavir® by Daiichi-Sankyo.

Our research has led us to believe that asthma and COPD exacerbation is a large underserved market. Patients with asthma and COPD exacerbations experience poor quality of life with rapid decline in lung function that result in high mortality. Bronchodilators (beta2-agonists and anticholinergics) and inhaled corticosteroids are the popular therapeutic arsenal used to control symptoms and prevent disease progression. However, these treatments are inadequate as they most often offer symptomatic relief. Biota's approach to address asthma and COPD exacerbation using antiviral therapy, and in particular anti-rhinovirus therapy, is a very promising therapeutic option as its mechanism of action to control the progression of the disease is by disrupting the viral replication process.

Vapendavir has shown significant results in proof-of-concept studies. Thus far, from the Phase 1/2 studies conducted, vapendavir has demonstrated a desirable clinical pharmacology profile with high bioavailability, linear pharmacokinetic profile, remained unaffected by concomitant medications, and was not exclusively metabolized. On the basis of these findings, another Phase 2 dose-ranging study (SPIRITUS trial) is currently on-going in a selected group of HRV positive patients to demonstrate vapendavir's safety and efficacy. Vapendavir Phase 2 effectiveness study commenced in February 2015 and is expected to complete by mid-2016. If the results turn out favorable, it could lead to a Phase 3 study in 2016-2017 and potentially to a U.S. NDA filing in 2018 and launch in 2019.

The American Academy of Allergy, Asthma & Immunology (AAAAI) estimates that more than 300 million people worldwide and 26 million people in the U.S. alone are affected by asthma. A study conducted between the years 2008 and 2015 revealed 10.5 million people in the U.S. are categorized as having moderate to severe asthma. Given the large market size for asthma and COPD exacerbations and the potential for vapendavir to emerge as the preferred treatment option by physicians and patients, we forecast peak sales of $0.6 billion. Although the cost to develop is high, we believe the cash at hand ($57.2 million in cash, cash equivalents and short term investments) is sufficient to carry them through to 2017. With a fully diluted share count of 43 million we arrive at a fair value of $4.07. We initiate coverage on Biota Pharma with a Buy rating.

BACKGROUND

Viruses are known to be very adaptive and mutate at an alarming rate to produce new strains that are resistant to currently available medications. Owing to the pandemic nature of the seasonal virus and the potential for the rapid, global spread of strains with high mortality rates, along with limited suboptimal treatment options, more effective medications are necessary. The difficulty in drug development is that an effective molecule must be able to inhibit virus replication within the body without causing any harm to the host cells.

Lower respiratory tract infections are induced by various viruses. HRVs and RSVs are present in the environment throughout the year. During the beginning of fall and spring seasons, these viruses contribute significantly to the incidence of viral respiratory tract infections. Seasonal flu on the other hand, is a potentially more serious illness occurring during the winter months. Studies have shown that flu accounts for roughly 9% of total upper respiratory tract illnesses and 13% of such illnesses results in physician consultation.

CDC's National Center for Health Statistics estimates that respiratory illnesses cause roughly 20 million lost workdays in adults and 21 million lost school days in children annually. In the U.S., respiratory illness related expenditures amount to roughly $40 billion annually; with direct medical costs representing about 45% and indirect costs representing about 55% of the total expenditure[1].

A conventional strategy to fight most viruses passively is by infusing the patient with an antibody as in vaccines. However, the generation of viral mutants that are robust and less sensitive to the vaccine, make it challenging to develop drugs to treat/prevent these infectious diseases. Biota Pharma is addressing this large unmet need by developing direct acting antivirals (small molecule compounds) to treat/prevent infectious diseases. Direct acting antivirals are known to have less frequent dosing with a superior safety and tolerability profile.

Since viral replication occurs at an intracellular level utilizing host cell mechanisms, the direct acting antiviral molecules interfere with one or more specific stages of the virus replication cycle. They disrupt the

- attachment and penetration of the virus into the host cell
- uncoating of virus
- synthesis of new viral components by the host cell as directed by the virus DNA
- assembly of the components into new virus, or
- release of the virus into the body from the host cell

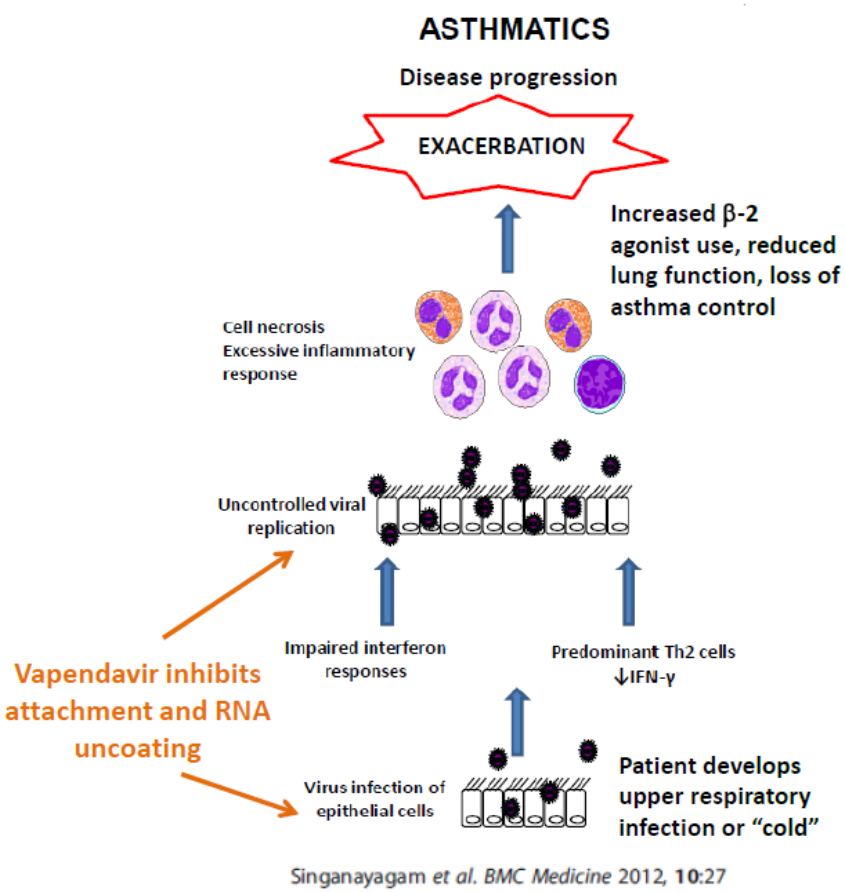
INDICATIONS

Human Rhinovirus – Trying To Control The Sneeze-to-Wheeze!

Incidence: HRV is responsible for causing upper-respiratory tract infections and cold-like symptoms. HRVs belong to a family of enteroviruses called picornaviridae. It is estimated that 30%-50% of all common cold cases are caused by HRV. Recent studies have shown that the virus is also responsible for lower respiratory tract infections, severe bronchiolitis in infants and children, and fatal pneumonia in the elderly as well as in adults whose immunity is compromised. Additionally, HRV is known to be a precursor to asthma and COPD exacerbations[2,3]. Depending on severity, between 45%-85% of exacerbations in children and between 10% and 36% of exacerbations in adults in the U.S. are due to respiratory illnesses caused by HRV[4,5] .

[1] Arch Intern Med. 2003 Feb 24;163(4):487-94.
[2] Rhinovirus-Induced Exacerbations of Asthma and COPD, Scientifica, 2013
[3] Clinical Asthma: Theory and Practice, Bernstein JA, Levy ML
[4] Arch Intern Med. 2003 Feb 24;163(4):487-94.
[5] Clin Exp Allergy. 2009 Feb; 39(2): 193–202.

Asthma and COPD are a result of interaction between the environment and a person's genetic profile that often results in irritation of the airways or causes an allergic reaction. They are both an inflammatory condition, which obstructs airflow in the lungs. Exposure to dust, smoke, noxious elements as well as bacteria are known to cause COPD (emphysema, and chronic bronchitis). COPD exacerbations are caused when the irritation of airways worsen progressively requiring treatment with antibiotics,



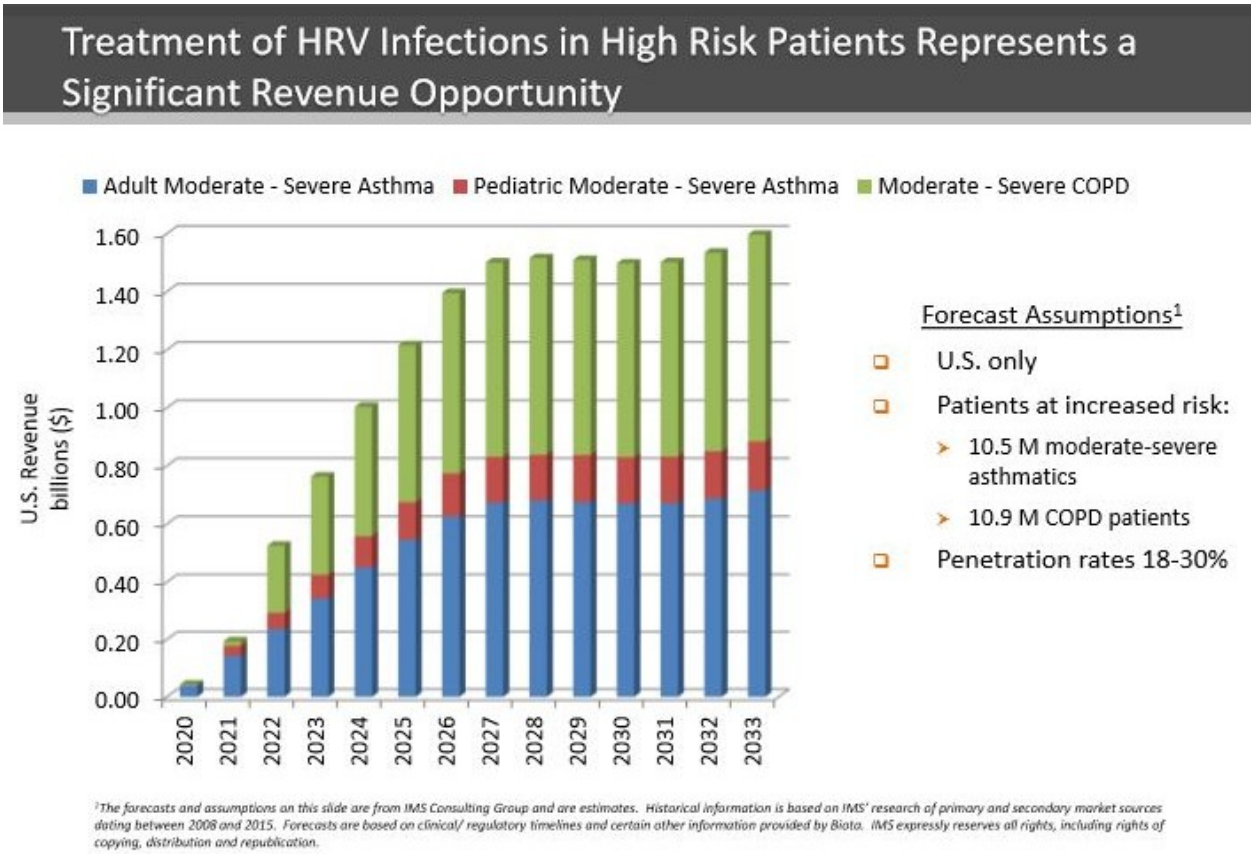
(Source: www.biotapharma.com)

systemic corticosteroids and/or hospitalization. World Health Organization (WHO) predicts that COPD will become the third leading cause of death worldwide by 2030[6].

Many studies have established plausible explanations of HRV mechanism in chronic pulmonary disease development. Although the mechanism is poorly understood, it has been deduced from studies that there are no clinical implications of HRVs in the upper respiratory tract but there is evidence of cytopathology in the lower respiratory tract.

Immunocompromised adults and a person's genetic makeup play a role in predisposing some of the patients to HRV. On behalf of Biota Pharma, IMS Consulting Group conducted market research on adult asthma and COPD patients with pulmonologists, internists, and general practitioners. As compared to healthy individuals, asthma patients seemed to be more susceptible to colds and are affected four to six times in a year. As per the report, asthma affects an estimated 300 million people worldwide and 26 million people in the U.S. alone. A study conducted between the years 2008 and 2015 revealed 10.5 million people in the U.S. are categorized as having moderate to severe asthma. Currently, HRV is considered the primary cause for asthma exacerbations and there are no known effective treatment options for HRV infection[7].

[6] H.J. Thibaut et al. / Biochemical Pharmacology 83 (2012) 185–192
[7] Clin. Microbiol. Rev. 2013, 26(1):135



(Source: www.biotapharma.com)

Preventive Care: Strategies to prevent and reduce respiratory viral transmission include distancing from affected individuals, use of respiratory masks, washing hands frequently, as well as taking Echinacea and Vitamin C on a regular basis[8].

FDA approved treatment on market: Early intervention is the most effective strategy for managing asthma exacerbations. Pharmacologic treatments using bronchodilators, inhaled corticosteroids, long-acting beta-agonists, leukotriene modifiers, and anti-immunoglobulin therapy yields symptomatic relief. Daily inhaled glucocorticoids and short-acting beta2 agonist are the first-line of treatment for moderate to severe asthma management. These are known to be the most effective medications to reduce airway inflammation, mucus production, cause fewer symptoms and flare-ups and decreases the need for hospitalization. Studies have shown that multiple doses of inhaled anticholinergic medication combined with beta2 agonists or a dose of intravenous magnesium sulfate improve lung function and decrease hospitalization in kids with severe asthma exacerbations. Adults experiencing severe exacerbations are administered with corticosteroids within one hour of seeking help in the ER, which results in a pronounced improvement in breathing capacity and therefore decreases the need for hospitalization[9]. In the event of hospitalization, physicians resort to oxygen therapy as the line of treatment for COPD exacerbations. Thus far, no antiviral therapy currently exists on the market to treat asthma exacerbations[7] although many are under clinical evaluations.

The compounds currently under clinical evaluation are pleconaril (Viropharma, Exton, USA, licensed to Schering-Plough in 2003), and pocapavir (V-073, ViroDefense Inc., Rockville, USA). The mechanism of action for both these compounds is by binding the capsid in the canyon. Although Pleconaril displayed broad-spectrum activity against most, but not all EVs, the treatment did not show significant improvement in patients. Pocapavir demonstrated tolerability in trials but failed to demonstrate an antiviral effect**Error! Bookmark not defined.**.

Advair ®, a combination of bronchodialator and steroid that prevents the release of substances that cause airway inflammation, has been the superstar drug from Glaxo-SmithKline (GSK) for the past ten years until its patent expired a few years ago (2010) making it vulnerable to generic competition. GSK is currently coming out with a portfolio of inhalable drugs, Breo Ellipta and Anoro Ellipta, (fluticasone furoate and umeclidinium bromide) for addressing asthma

[8] Jornal de Pediatria, 2014, 90(6):542-555
[9] Am Fam Physician. 2011 Jul 1;84(1):40-47.

and COPD. Thus far, Advair is facing generic competition, and Breo and Anoro Ellipta, have underperformed analyst expectations since their FDA approvals in 2013.

Asthma in adults causes chronic airway changes, and few adult asthmatics have comorbidities associated with age. The existing therapies are used to treat the symptoms rather than addressing the underlying condition. Although it has been proven that inhaled corticosteroids and bronchodilators improve lung function and reduce disease exacerbations and are endorsed in international treatment guidelines, concerns have emerged regarding the use of inhaled steroids in patients with co-morbidities. Therefore, this set of population which responds poorly to corticosteroids requires a more effective and safe treatment option that could be provided by antivirals.

Biota's Molecule: HRV is mainly made of four proteins that make up the viral capsid encasing the RNA genome. Three proteins are responsible for the virus' antigenic activity and one protein secures the RNA in the capsid. The canyon in one of the proteins (VP1) serves as the site of attachment to cell surface receptors[7]. Proteins on the surface of the virus interact with target cell's surface receptors. The virus uses its envelope (lipid bilayer) to penetrate the host cell membrane and uses the host's cellular mechanics to replicate. HRV viruses are single stranded RNA viruses.

With substantial insight on the structural and molecular make-up of HRV, Biota has developed a molecule that targets the viral capsid with vapendavir (BTA798), a potent, orally bioavailable, broad spectrum inhibitor of the large group of HRVs. Vapendavir binds tightly to VP1's canyon and disrupts the ability of the capsid to bind to a specific cell surface receptor. This further inhibits the release of the viral RNA into the cell cytoplasm during the viral uncoating process (removing the lipid bilayer), thereby disrupting viral replication. Vapendavir is designed to be dosed orally.

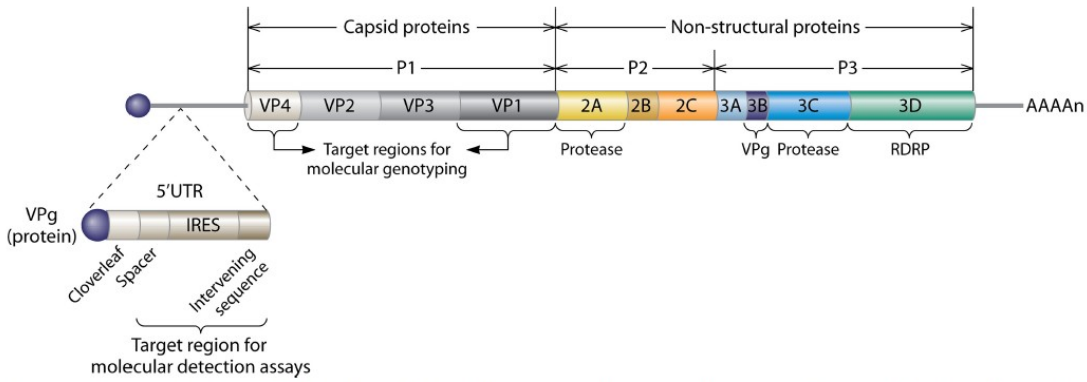


FIG 1 HRV genomic structure. HRV is a 7.2-kb single-stranded, positive-sense RNA virus with a single open reading frame joined to a 5′ untranslated region and a short viral priming protein (VPg). The P1 protein is processed to form the HRV capsid, and P2 and P3 are processed to produce VPg, protease, and RNA-dependent RNA polymerase (RDRP) (6). IRES, internal ribosomal entry subunit.

(Source: Clin. Microbiol. Rev. 2013, 26(1):135.)

Clinical Efficacy Using vapendavir: Vapendavir has been evaluated in a number of clinical trials. In the following paragraphs, the results of these studies are discussed.

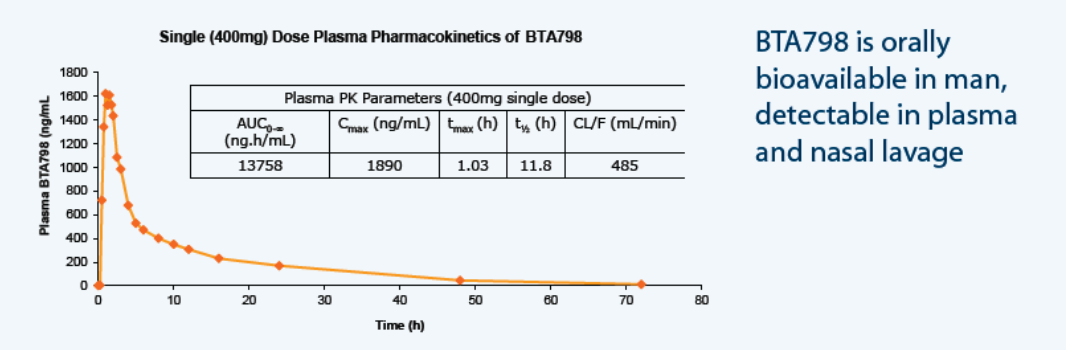
- ***Phase 1 Dosing study:*** Biota completed a placebo-controlled, single and multiple ascending oral dose of vapendavir, safety, tolerability and pharmacokinetic studies in 56 healthy volunteers in 2006. Single oral doses of 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg or 1600 mg of vapendavir were assessed. The study revealed that vapendavir was generally well tolerated and there were no dose limiting toxicities, trends in adverse events, or laboratory parameters observed. Subsequently, the company conducted a multiple ascending dose trial to evaluate 200 and 400 mg of vapendavir. It was administered either once or twice daily for seven consecutive days. Vapendavir was well tolerated with no adverse events, dose limiting toxicities or clinically relevant changes in vital signs, ECG or laboratory parameters observed.

- ***Phase 1 Drug interaction study:*** Drug interaction studies are conducted with metabolizing enzymes to better understand the investigational drug's pharmacokinetic profile. The interaction of two drugs taken concomitantly depends on the relative affinity of each drug for the binding site on the metabolizing enzyme and the free drug available for binding. The suitability of midazolam has caused it to be the widely used in drug interaction studies[10].

[10] http://www.fda.gov/OHRMS/DOCKETS/98fr/06d-0344-gdl0001.pdf

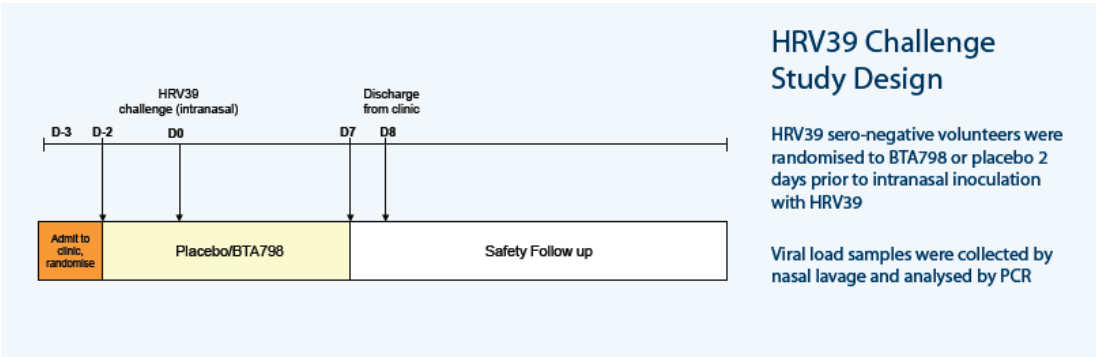
Additionally, the company conducted a study in 2014 to assess the interaction between vapendavir daily doses of 528 mg daily and 264 mg twice daily on the pharmacokinetic profile of midazolam (the clinical standard), a CYP3A4 substrate, in 24 healthy volunteers. Increased activity of this enzyme CYP3A4 would imply an increase in metabolism and therefore decreased efficacy of vapendavir. Vapendavir's pharmacokinetic profile was found to be similar to those from prior clinical trials. The results demonstrated that vapendavir was found to be a weak-to-moderate inducer of CYP3A4 and is not likely to markedly affect the pharmacokinetics of CYP3A4 metabolized drugs. Vapendavir was also well tolerated.

- ***Phase 1 Bioavailability study:*** This randomized, single-center, open-label, two-period, two-sequence, crossover, comparative study was done to compare the oral bioavailability of single doses of two vapendavir drug formulations in 36 healthy volunteers. The subjects received a single dose of the capsule formulation (two 132mg) or the tablet formulation (one 300mg) in period 1 and, after a washout, crossed over to receive a single dose of the other formulation in period 2 of the study. The pharmacokinetic results demonstrated that vapendavir's formulations are equivalent. The free-base tablet formulation achieved approximately 60% of the mean bioavailability as the phosphate salt capsule formulation.



(Source: www.biotapharma.com)

- ***Phase 2a Challenge Study:*** A Phase 2a placebo-controlled, double-blind, randomized, parallel group dose-defining study was conducted in 2009 to determine the potential of 25 mg, 100 mg and 400 mg of vapendavir in 41 healthy volunteers. Subjects were inoculated with a challenge strain HRV39 and after the incubation period were dosed twice daily for 10 days to prevent infection. Subjects who received 400 mg of vapendavir achieved a statistically significant reduction in mean viral load compared to the placebo group on days two to five inclusive. In the treatment group, the overall incidence of adverse events was low. There was one adverse event of neutropenic sepsis in a subject in the 100 mg arm of the trial. This study helped in achieving clinical proof-of-concept, as well as demonstrating that oral vapendavir significantly reduced the incidence of infection and viral shedding.



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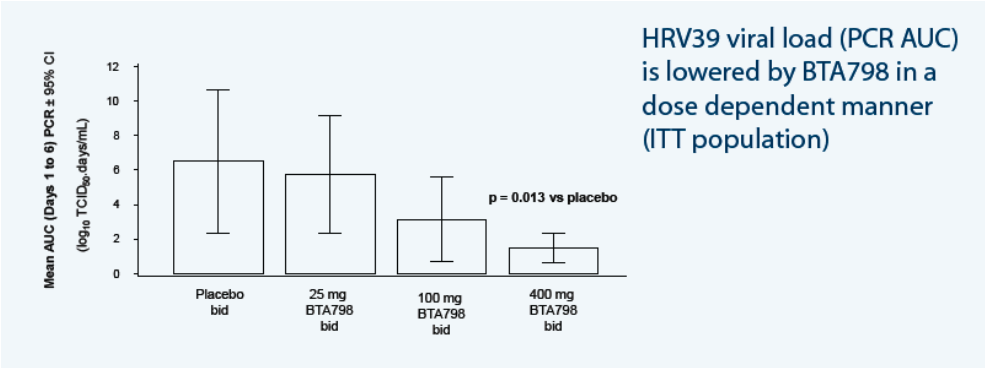
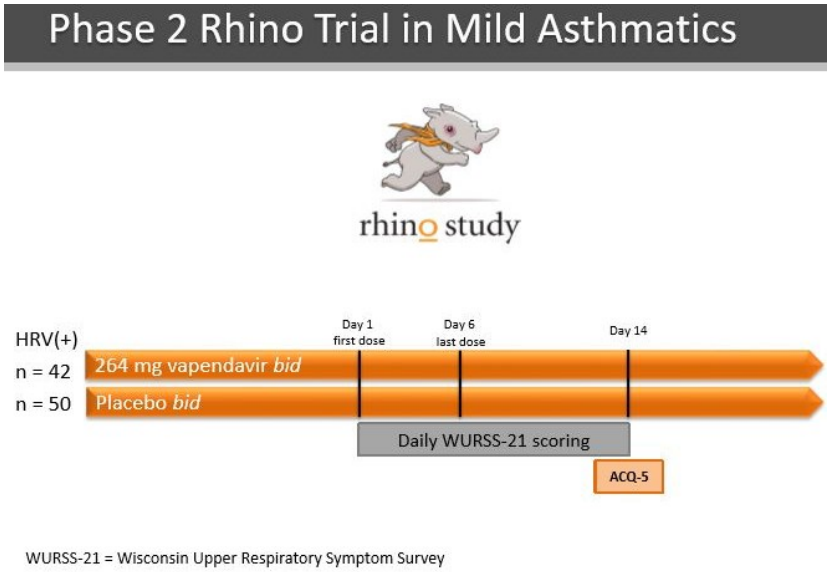


(Source: www.biotapharma.com)

- ***Phase 2b Asthma control study:*** In 2012, the company conducted a 300-patient, multicenter, randomized, double-blind, placebo-controlled study of vapendavir in adults with mild to moderate asthma who also had symptoms of HRV infection. The purpose of the study was to evaluate the safety, tolerability and effectiveness of vapendavir in reducing the duration and symptoms of common cold, asthma, and lowering the risk of asthma exacerbation. The study was conducted over two HRV seasons (18 months). Roughly 1200 individuals were screened in order to randomize 300 subjects, 155 in the vapendavir arm and 145 in the placebo group. Vapendavir was given two times daily for six consecutive days. Subjects who received 264 mg of vapendavir showed significant reduction in mean viral load.



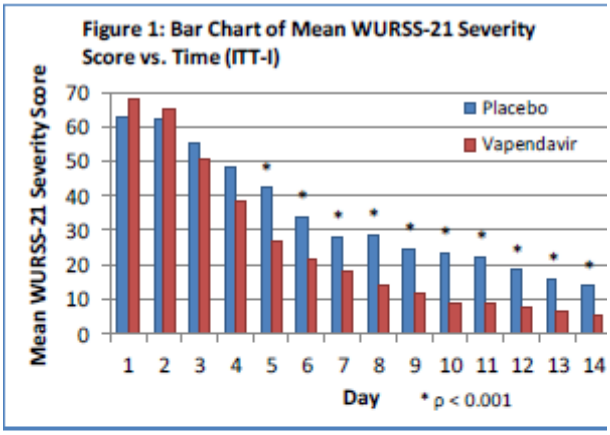
(Source: www.biotapharma.com)

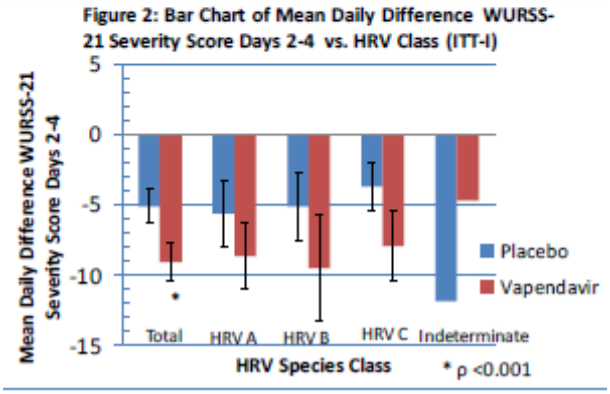
Table 1: Mean ACQ-5 Score Change from Day 1 (Intent-to-Treat Infected [ITT-I])

Least Square Mean (95% CI)	PLACEBO	VAPENDAVIR	p-value
Day 14	-0.20 (-0.42,0.01)	-0.47 (-0.72,-0.21)	0.107
Day 28	-0.53 (-0.75,-0.32)	-0.63 (-0.88,-0.38)	0.545
Overall	-0.17 (-0.33,-0.01)	-0.30 (-0.49,-0.11)	0.266

Table 2: Ave Daily ß-2 Agonist Use Over Days 1 to 14 (ITT-I)

Puffs	PLACEBO	VAPENDAVIR
Mean (SD)	1.33 (1.256)	0.99 (1.309)
p-value		0.094



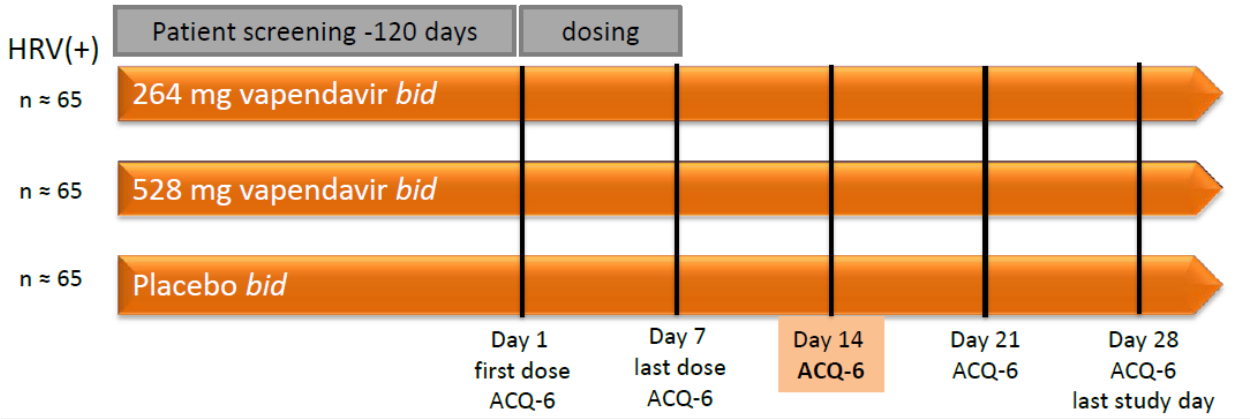


(Source: www.biotapharma.com)

The trial successfully met its primary endpoint. The Wisconsin Upper Respiratory Symptom Survey (WURSS) is an instrument for measuring the severity and functional impact of a specific illness. It provides a comprehensive set of questions covering the symptoms and related quality-of-life outcomes experienced by patients having the illness. The mean daily reduction in Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21: short version) severity score averaged over days two to four was significantly greater in the vapendavir treated group compared to the placebo group (p = 0.020). The mean WURSS-21 severity scores were lower in the vapendavir group than in the placebo group from day 3 onwards, with statistically significant differences observed each day from days 5 through day 14 (Figure 1). Vapendavir reduced cold symptoms across all HRV species A, B and C (Figure 2). The mean reduction in Asthma ACQ-5 score (ACQ-5 is a validated tool designed to assess asthma control and utilizes both patient reported outcomes) from baseline was greater in the vapendavir group than in the placebo group following day 7, approaching statistical significance on day 14 (Table 1). In lung function tests, evening peak expiratory flow (PEF) was higher in the vapendavir group than in the placebo group on day 5, and the difference between the groups was statistically significant (p = 0.038). Reduced daily use of asthma reliever medication showed a positive trend towards improvement in the vapendavir group as early as day 3 of treatment, approached statistical significance averaged over days 1 to 14, and reached significance on day 13 (p = 0.045, Table 2).

Vapendavir was generally tolerated and most treatment-related adverse events were of mild intensity, with moderate treatment-related events reported in 2.3% of subjects. No severe adverse events occurred during the study.

- ***Phase 2 Dose Ranging Trial (SPIRITUS) - Ongoing:*** In February 2015, the company initiated a third Phase 2 randomized, double-blind, placebo-controlled dose-ranging trial (SPIRITUS). The trial is being conducted at 60 sites across six to eight countries in North America and Central Europe. The goal is to enroll approximately 190 laboratory-confirmed HRV-infected patients for the ITT-i population. Patients aged 18-70 years of age who have a history of moderate-to-severe asthma and a history of having asthma exacerbation in the last 14 months due to presumed viral respiratory infections that required asthma rescue medication treatment will be eligible to be enrolled in the trial.



(Source: www.biotapharma.com)

About 480 asthma subjects will be screened in order to randomize 190 into the trial so the study is powered well. Screening period is 120 days, drug treatment period has a duration of 7 days and follow-up study visits to the clinic occur on study days 1, 3, 5, 7, 14, 21, and 28 with a telephonic final safety follow-up visit conducted on study day 35. Thus, depending on the duration of the screening period, a subject's duration of participation can be estimated to last from approximately 37 days up to 155 days.

The screening commenced in February 2015, which is atleast a couple of months before the allergy season begins. Patients with an established clinical history of moderate-severe asthma for at least 1 year, and a history within the last 14 months of asthma exacerbation due to presumed viral respiratory infections that required asthma rescue medication treatment will be included in the study. Only patients who are HRV positive will be randomized into the trial. Anyone who tests positive for flu will be eliminated from the study.

The study is planned for two different doses (264mg and 528mg) of vapendavir to determine the lower and upper limits of the dose range, optimal dose and the dose-effect relationship. The phosphate salt form of vapendavir was selected for use in this trial. This study also helps dose selection for Phase 3 clinical trials.

The primary endpoint is the Least Square (LS) mean change from baseline to study day 14 in asthma control questionnaire (ACQ)-6 total score. Secondary endpoints are focused on safety and tolerability, lung function assessments such as forced expiratory volume in one second (FEV1), incidence of asthma exacerbations, assessments of the severity and duration of cold symptoms measured by the WURSS-21, and virology assessments such as changes in viral load and viral shedding.

The outcome of the SPIRITUS trial is keenly awaited. The study is estimated to complete by Q2 2016 and the results with the primary endpoint are expected in 2H 2016. Phase 2a human rhinovirus (HRV) challenge study successfully demonstrated proof-of-concept. Two Phase 2 studies conducted during the 2009-2012 flu season, using 264mg dose of vapendavir demonstrated significant reduction in cold symptoms. A favorable safety profile was seen among 263 unique subjects from Phase 2 studies using vapendavir. If Biota can replicate these results, it would stand a good chance of having a pre-NDA meeting with the FDA to conduct Phase 3 trials.

Market Opportunity: Adults experience an average of 2-4 and children, 6-8 common colds per year. Studies have shown that HRV is the etiology of one-half to two-thirds of common colds[7]. Recent research studies in molecular viral

diagnostics have shed light on the role of viruses in bronchiolitis in infancy, childhood pneumonia, and acute exacerbations of chronic respiratory diseases such as asthma, chronic obstructive lung disease, and cystic fibrosis. Most drugs currently on the market are able to control mild-to-severe cases of asthma. However, there is a large unmet medical need in patients with severe asthma and chronic respiratory diseases who constitute a small but high-risk group. Biota intends marketing vapendavir to patients with moderate-severe asthma, COPD and those undergoing chemotherapy or have transplants that compromise their immune system.

In 2013 CDC estimated that 22.2 million people suffer from asthma in the U.S.[11] The statistics showed that asthma exacerbations resulted in 14.7 million outpatient visits, 1.8 million emergency room visits, 497,000 hospitalizations and about 4000 deaths in the U.S. alone in 2004. Even though only 20% of asthmatics have had exacerbations that required them to seek treatment in the ER, these patients account for more than 80% of total direct costs associated with asthma care. Asthma treatments requiring hospitalizations cost roughly $9000[5]. GBI Research says that the treatment for asthma in the U.S. is estimated to be $14 billion by 2020.

Advair, introduced in 2000 by GSK, the respiratory blockbuster drug for asthma and COPD, represented 70% of GSK's respiratory portfolio sales and generated roughly $8 billion in sales in 2013. Advair accounted for more than 20% of total revenues for GSK owing its success to increase in asthma prevalence, compelling trial studies, and competitive pricing and marketing strategies. Advair enjoyed a market share of roughly 30% in the U.S.

Since an effective and easy-to-use delivery device is crucial for asthma and COPD patients as it ensures the appropriate dose of medicine delivered to the lungs, most manufacturers patent the unique molecule and the associated delivery device for asthma medications. Although, the U.S. patent for Advair (the medication) expired in 2010, the patent for the Diskus (inhaler) lasts until 2016. The complexity of the inhaler has kept generic manufacturers at bay thus far. Despite this fact, Advair sales are on a downward swing and may drop more when faced with competition from generics once the patent on the inhaler expires.

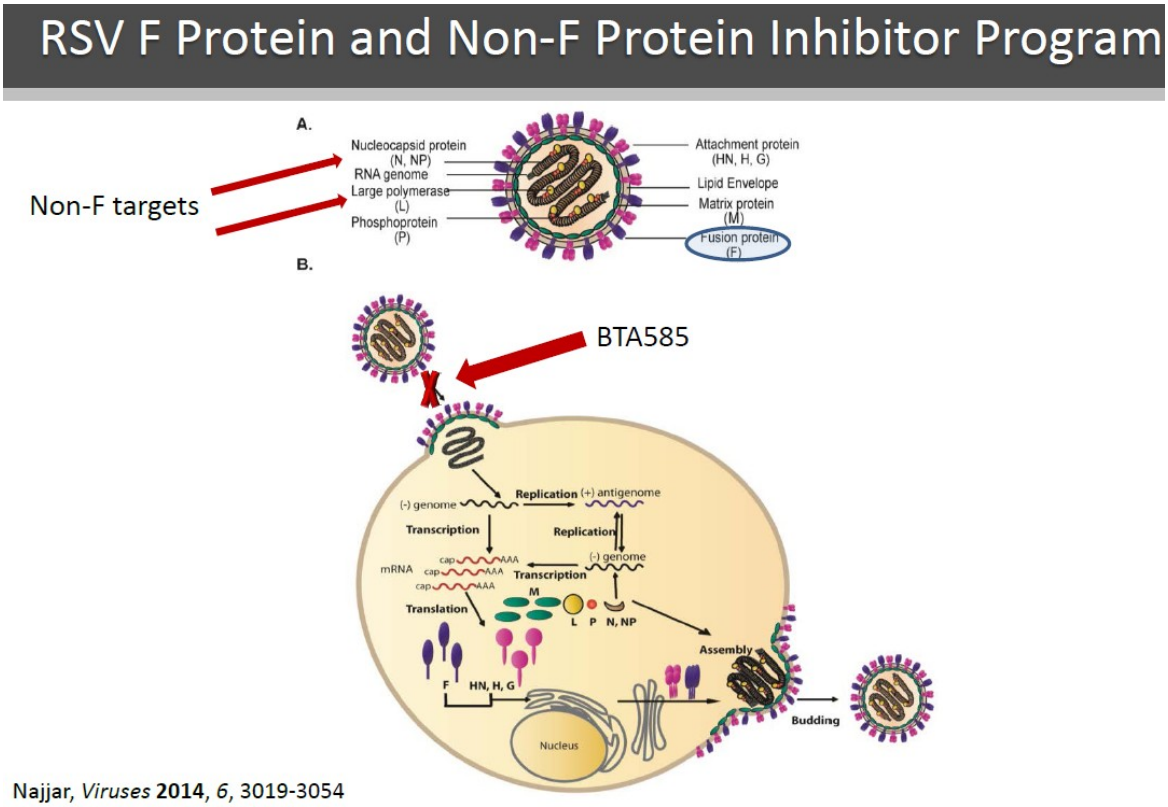
GSK's new product, Breo Ellipta got FDA approval in May 2013. Breo Ellipta's label reads "Long-term, once-daily, maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease. Once-daily treatment of asthma in patients aged 18 years and older". Revenues amounted to $13 million in the first year of launch. Breo has been estimated to bring in $0.8 billion in sales revenues in the next two decades. Combination drug therapy using cortecosteroids/long acting beta agonists (ICS/LABA) are currently available and have been demonstrated to be effective and well tolerated[12]. AstraZeneca's Symbicort (ICS/LABA) with adjustable dosing capabilities and Merck's Dulera have steadily trimmed Advair's U.S. market share.

Big pharmas are diversifying their own portfolio of respiratory drugs to retain their market share and keep their revenues intact. Breo and Symbicort are filling up the hole created by Advair's patent loss. If Biota's vapendavir yields favorable results from clinical trials, gets FDA approval and is marketed as a drug to reduce asthma and COPD exacerbations in adults, and if the momentum continues in slumping Advair sales, we expect vapendavir to gain competitive market share in this space.

[11] http://www.cdc.gov/asthma/most_recent_data.htm
[12] J Asthma Allergy. 2009; 2: 63–72.

Respiratory Syncitial Virus - Common But Contagious!

Incidence: RSV is an enveloped, single-stranded, RNA virus belonging to the Paramyxoviridae family. RSV causes acute upper and lower respiratory tract infections in infants, young children, and adults. High-risk populations who are affected by RSV are people with COPD. Airway inflammation causes bronchitis, pneumonia and respiratory failure. The virus is very contagious and spreads by coughing, sneezing or coming into close contact[13]. The peak incidence of infections occurs in the winter months, usually coinciding with the influenza epidemic. RSV symptoms begin near the time of initial viral detection, about 2 days before peak viral load. The viral load appears to drive the symptoms of RSV infection. Symptoms peak in severity and subside corresponding to the viral load.



(Source: www.biotapharma.com)

CDC estimates 2.3 million children are infected by RSV in the U.S. annually, of which approximately 150,000 are hospitalized. RSV infections are responsible for approximately 40-50% of hospitalizations for pediatric bronchiolitis and 25% of hospitalizations for pediatric pneumonia. RSV is also known to be a major cause of morbidity in immunocompromised adults and in the elderly.

Preventive Care: Preventive measures against infection include avoiding close contact, not sharing common items, and frequent washing of hands.

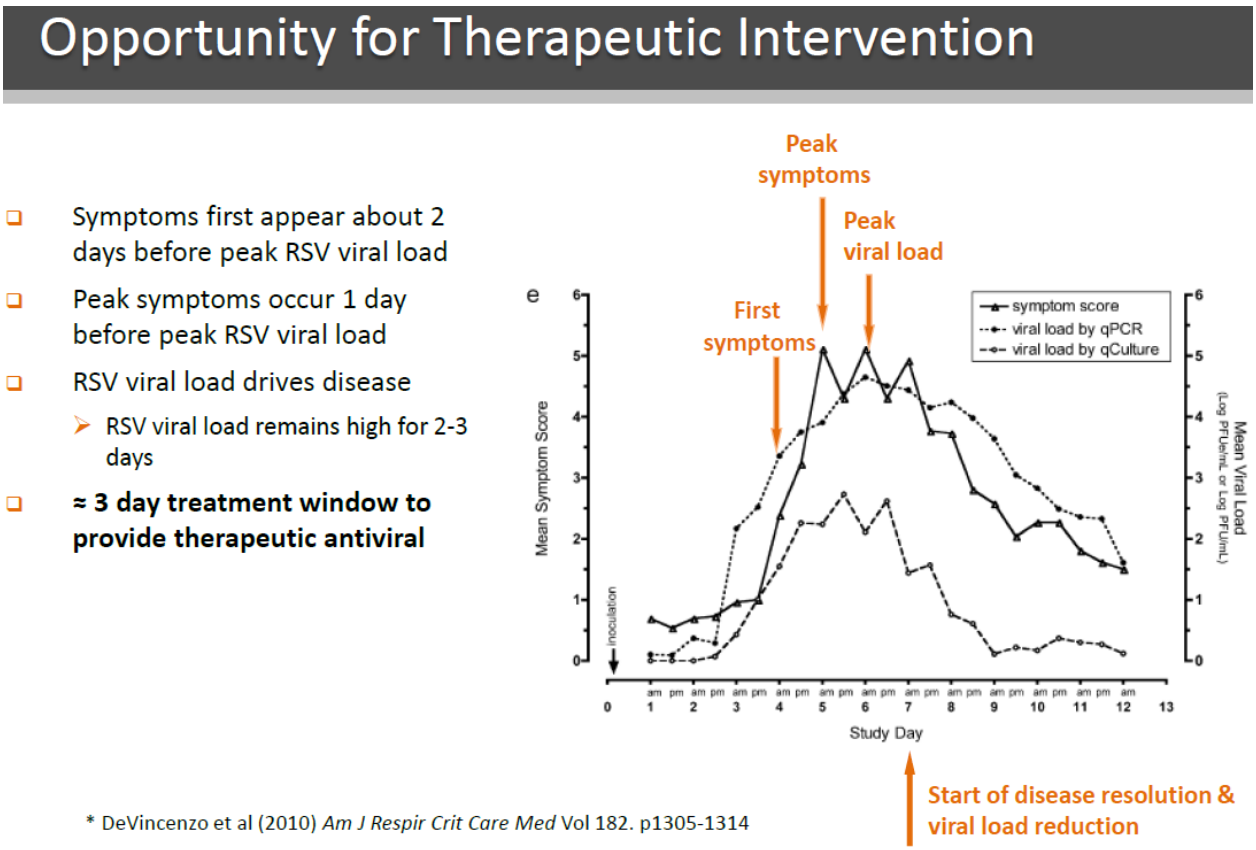
FDA approved treatment on the market: Only two drugs are currently available to either prevent or treat RSV infections. Antibody-based Synagis (palivizumab) is approved to prevent, not treat, RSV infections in premature infants, and its use is limited due to its high cost. Palivizumab neutralizes RSV and interferes with the fusion of the virus to the host (respiratory epithelial) cells. The American Academy of Pediatrics (AAP) approves the use of palivizumab for RSV prophylaxis even in high risk infants since it is well-tolerated. Synagis is injected intramuscularly once a month during the RSV season to prevent infection.

Valeant Pharmaceuticals' Virazole (Ribavarin) is currently the only therapy for treating serious RSV infections in infants with severe bronchiolitis and in immune-compromised patients daily for a period of 3-7 days. It is marketed as inhalation solution for treating of RSV infection in the U.S. However, its use is limited due to highly variable efficacy and toxicity risks and difficulty in the method of administration. Ribavirin requires long periods of nebulization, which implies it

[13] http://cdn.intechopen.com/pdfs-wm/24399.pdf

requires a specialist to administer the drug. The American Academy of Pediatrics does not recommend the routine use ribavirin for the treatment of bronchiolitis in children as there is not enough clinical evidence supporting its use.

Currently there are no treatment options available for patients who are highly susceptible to RSV infections. This indicates a potential commercial opportunity for Biota, despite being a new player in the market.



(Source: www.biotapharma.com)

Biota's molecule: The RSV genome encodes fusion F-protein to form the viral coat. The fusion of viral membrane with the cell membrane is mediated by the RSV F-protein. Biota is currently in Phase 1 development of a potent, non-cytotoxic and selective inhibitor that interferes with the earliest stage of infection by inhibiting the attachment and/or fusion of the virus to the host cell. Data from studies investigating the mechanism of BTA585 anti-viral activity, including analysis of RSV resistance mutants, support the conclusion that BTA585 inhibits the function of the RSV protein. BTA585 is equally active against both RSV A and B subtypes but has no known activity against other pathogenic viruses.

Clinical Trial:

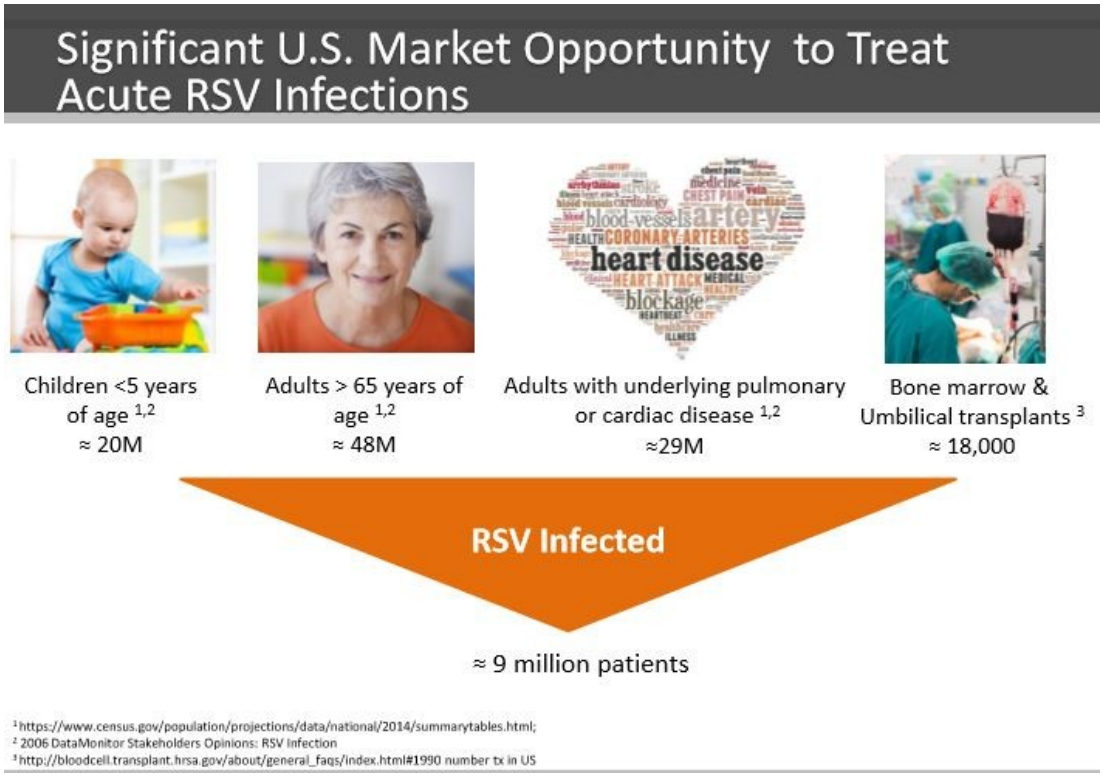
- ***Phase 1 study 1:*** In August 2015, the company commenced a randomized, placebo-controlled, Phase 1 single ascending dose ("SAD") clinical trial to evaluate the safety and pharmacokinetics ("PK") of BTA585 in fifty healthy volunteers. The Phase 1 SAD trial has five oral dose level cohorts: 50, 100, 200, 400 and 500 mg and includes an evaluation of the effect of food on the pharmacokinetics of BTA585. The 100 mg cohort included an evaluation of the effect of food on the pharmacokinetic profile of BTA585. Each of the dosing cohorts consisted of ten subjects; seven subjects that received BTA585 and three that received placebo. Results from this study demonstrated no serious adverse events. BTA585 was well tolerated at all dose levels and there were no drug-related clinically-significant changes in ECGs or clinical laboratory values. Pharmacokinetic data demonstrated that doses ≥ 100 mg achieved BTA585 plasma levels that exceeded the mean EC50 of RSV clinical isolates for 24 hours. The EC50 represents the concentration of drug that is required for 50% inhibition of viral replication in vitro. The BTA585 plasma concentration Cmax was rapidly achieved at approximately one hour following oral dosing and the half-life (T1/2) was approximately five to six hours. Additionally, dosing of BTA585 with a high fat meal did not adversely affect the pharmacokinetics of the drug.

- ***Phase 1 study 2:*** Biota commenced dosing in a Phase 1 multiple ascending dose (MAD) clinical trial during the fourth quarter of calendar year 2015 and results are expected in 1H 2016.

- ***Non-fusion inhibitor program:*** In addition to BTA585, the company has identified a series of potent RSV non-fusion inhibitors that could be a stand-alone treatment or potentially in combination therapy with BTA585 for the treatment of patients infected with RSV. The goal is to select a lead candidate from this program by mid-year 2016.

Market Opportunity: Lower respiratory tract infections caused by RSV accounted for more than 30 million cases globally. Of the total cases of infants having upper respiratory tract infections, about 30% of them develop lower respiratory tract infections. The healthcare cost for infants on average amounted to $20,000 per inpatient treatment and $3,500 for outpatient consultations. Consequently, the total annual healthcare costs exceed $600 million among children in the U.S. alone[13]. Additionally, evidence shows that adults with chronic pulmonary diseases and the elderly are prone to be affected by RSV. Recent studies indicate about 3% of pneumonia in adults are caused by RSV. In the U.S., RSV is associated with 18% of all respiratory illnesses in children <5 years, 20% of all hospitalizations, 18% of all emergency department visits, and 15% of all pediatric office visits[14]. According to published reports worldwide Synagis sales were ~ $1 billion in 2009.

Several RSV antiviral compounds have been identified in multiple preclinical studies. The F protein inhibitor GS-5806 has been evaluated in a Phase 1 safety study as well as in the human challenge model. Another small molecule inhibitor that interfere with RSV fusion through interaction with the F protein of RSV is VP-14637 (renamed MDT-637) and JNJ-2408068. The nanobody ALX-0171 is also in Phase 1 development[14].



(Source: www.biotapharma.com)

<u>Human Papillomavirus – Most Common Sexually Transmitted Infection (STI) In The U.S.</u>

Incidence: Any person who engages in a sexual activity with a person infected with HPV is prone to be affected by it. HPVs are non-enveloped DNA viruses that are known to cause lesions of the epithelium. HPV infection prompts viral replication that can give rise to anogenital warts, plantar warts and cervical cancer. In particular, HPV6 and 11 are non-cancer causing virus but account for about 90% of anogenital warts (condyloma)[15]. Condyloma is not life-threatening or

[14] J Infect Dis. (2015) 211 (suppl 1): S1-S20.
[15] http://www.cdc.gov/vaccines/pubs/pinkbook/hpv.html

debilitating, but causes severe social and psychological stress. The infection has an early onset (adolescence/young adults) and a high incidence rate but in most cases resolves spontaneously. In some persons, the infection is persistent, causing frequent recurrences or leads to cancer. Immunocompromised adults are prone to be infected by HPV. HPV 6 and 11 are also known to cause Recurrent Respiratory Papillomatosis (RRP), a rare orphan indication where benign tumors grow in the air passages leading from the nose and mouth into the lungs. The incidence of RRP ranges from 1.8 to 4.3 per 100,000 for adults and children, respectively. It is estimated that 15,000 surgical procedures are performed per year in the U.S., at a total cost of $150 million, and lifetime costs per individual patient can reach up to $470,000. In spite of the infection's high prevalence, no antiviral drug has been developed yet.

Preventive Care: Abstinence from any form of intimate contact is a sole guarantee to eliminate the possibility of being affected by HPV.

FDA approved treatment on the market: The current therapeutic strategies to treat HPVs are directed at the diseases associated with them as well as with the relief of their symptoms. Since HPVs cause tumors the therapeutic options are invasive (excisional), and more accessible to a surgeon than to the primary care practitioner. Despite several surgical treatment options including excision, cryotherapy, electrocautery, laser, as well as topical Podofilox solution or gel 0.5%, Imiquimod cream 5%, or sinecatechins ointment 15%) and combinational therapies being available, the infection remains unresolved in most cases. Current therapies are known to be suboptimal, having substantial local side effects (pain, itching, and inflammation), low clearance rates, and a high incidence of recurrence.

FDA approved Gardasil® (Merck), a vaccine introduced in 2006, protects against HPV 6, 11 16, and 18. It is approved for use in girls and women 9-26 years of age as well as in men in at least 85 countries. Gardasil has proteins that self-assemble into virus-like particles with the same size, appearance, and immunologic properties as of the L1 capsid protein in HPV. Gardisil is not infectious because it is devoid of HPV DNA.

The vaccine is administered as a 3-dose series. The vaccine does not prevent infection but provides protection against the HPV types 16 and 18 which are associated with 70% of cervical cancers and 90% of external genital warts (6,11). Clinical efficacy for HPV4 against cervical disease was determined in two double-blind, placebo-controlled trials. The current indications of Gardasil are supported by a series of Phase 3 studies. Gardasil was shown to be 99% effective in preventing external genital warts. The vaccine, however, does not offer therapeutic effect on pre-existing HPV infections, genital warts or cervical lesions[15,**Error! Bookmark not defined.**].

Gardasil-9, approved in 2014 for girls/women aged 9-26 and boys/men aged 9-15 years of age, protects against 9 strains of HPV, including HPV6&9. This vaccine protects against five more HPV types including the ones prevented by the earlier version of Gardasil. Gardasil 9 accounted for ~80% of the total HPV sales in the US during 3Q15. The combined sales of Gardasil and Gardasil 9 reported 7% growth during 3Q15.

Biota's molecule: Biota hopes to improve the treatment paradigm for anogenital warts and RRP. In June 2015, Biota acquired Anaconda Pharma, a privately-held Paris-based biotechnology company for a total of $47 million which included upfront payment through issuance of 3.5 million shares of Biota common stock, $8 million in cash and additional contingent consideration of up to $30 million, based on the successful achievement of certain future clinical and regulatory milestones, plus a royalty. Their lead candidate, BTA074 (AP611074), is a novel, direct-acting antiviral against HPV6 and 11. The company is currently in the clinical stage development of its drug candidate for the topical treatment of condyloma.

HPV DNA replication process uses only two viral proteins, E1 and E2. E1 is a DNA helicase protein that possesses enzymatic activity which initiates HPV DNA replication. E2 is a sequence-specific DNA-binding protein that is responsible for regulating DNA transcription and replication. E2 acts as a catalyst to provide sequence specificity and helps form an assembly of E1 protein complexes, specifically at the origin (binding sites of E1 and E2)[16]. Biota has identified the antagonists of HPV proteins, E1 and E2, and their interaction with their cellular targets. Biota's molecule, the BTA074, disrupts the E1-E2 (protein-protein) interaction in a specific manner in vivo and inhibits HPV DNA replication in infected cells.

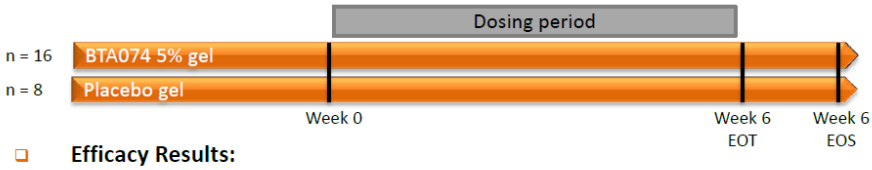
Clinical Trials using BTA074:

- ***Phase 2a study:*** Anaconda Pharma had completed a double-blind, placebo-controlled, randomized, Phase 2a clinical trial of BTA074 in November 2013. Subjects were directed to apply a 5% gel of BTA074 twice daily. The six-week study demonstrated a 38% reduction in the total condyloma area after treatment exhibiting a favorable local

[16] The Journal of Biological Chemistry, 2001, 276, 22426-22438.

skin tolerability profile. Since no patient terminated treatment before the end of the trial period, there were no study interruptions. Further, treatment with BTA074 produced a 56% overall response rate and a 38% reduction in mean baseline wart area.

- **Study Population:** Adult condyloma (anogenital warts) patients
- **Design:** Multi-center, randomized, double-blind, placebo-controlled
- **Primary Objectives:** Safety, tolerability, and partial or total clearance of baseline anogenital wart lesions at end of treatment (EOT)
- **Dosing:** twice daily for 6 weeks



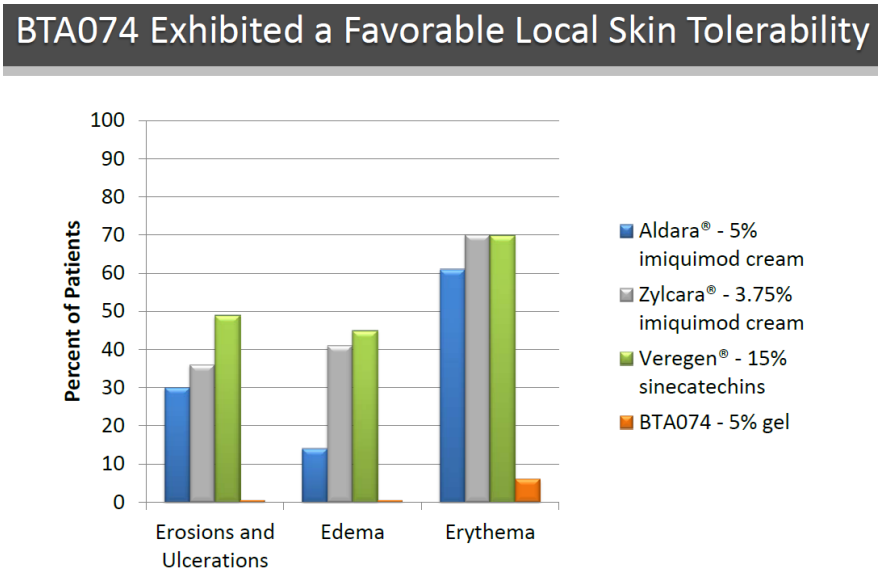
- **Efficacy Results:**

Assessment at End of Treatment	BTA074 5% gel	Placebo gel
Complete Clearance	13% (2/16)	25% (2/8)*
Partial Clearance >0 to <100 %	44% (7/16)	13% (1/8)
Overall Response Rate	56% (9/16)	38% (3/8)
Percent Reduction in Total Condyloma Area (mm^2)	38%	+123%

*Placebo clearance rates of <5% at 6 weeks were observed in Zyclara® and Veregen® Phase 3 pivotal trials in patients with anogenital warts

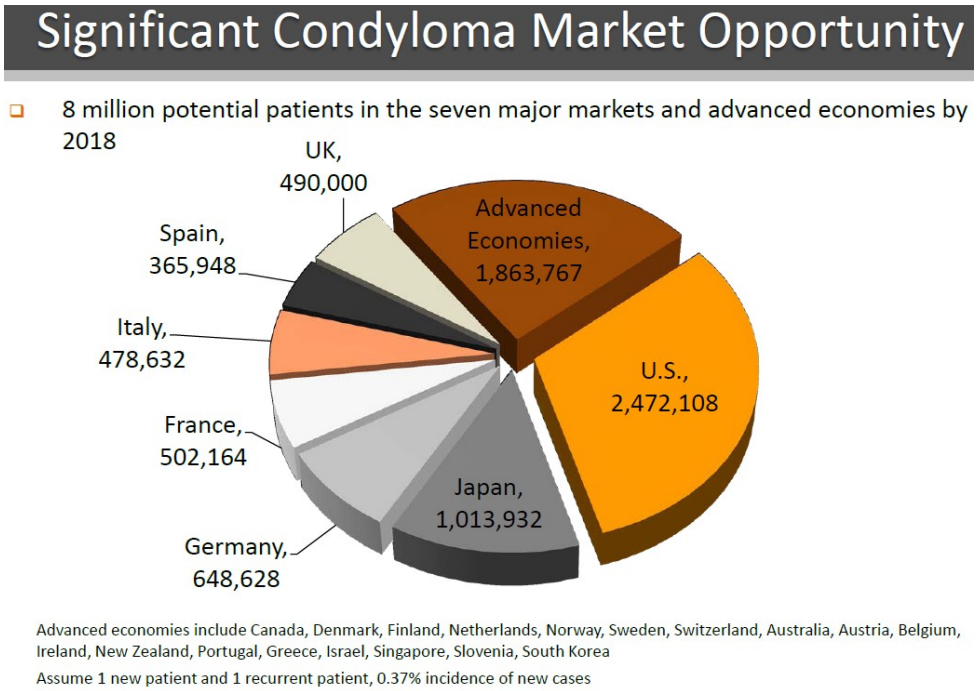
(Source: www.biotapharma.com)

- ***Phase 2 study – in process:*** The company plans on initiating a double-blind placebo-controlled, randomized, Phase 2 study in Q2 2016 to further validate BTA074's favorable local skin tolerability profile and antiviral activity. The primarily objective of which is to assess the safety, tolerability, pharmacokinetics and efficacy of the compound. Approximately 210 adult condyloma patients will be treated with topical applications of BTA074 (5% gel) twice daily for up to 16 weeks.



(Source: www.biotapharma.com)

Market Opportunity: There is significant market opportunity to treat condyloma as the virus has many diverse subtypes and has a high frequency of transmission sexually. There are more than 100 subtypes of HPV of which roughly forty



(Source: www.biotapharma.com)

infect the oral sites and anogenital areas. About 50–80% of sexually active adults acquire one or more types of HPV during their lifetimes, making HPV infection the most common STI. In the U.S., about

80 million persons are infected, and an estimated 14 million new HPV infections occur annually with half of these in persons 15-24 years[15]. Roughly 360,000 people in the U.S. get genital warts each year[17].
U.S. spends roughly more than $1.5 billion annually to treat HPV infections. Currently vaccines on the market cannot treat individuals who are already infected, prescription medications can only treat the symptoms and there are no over the counter medications for genital warts. Gardasil, Merck's prophylactic HPV vaccine was brought to market in 2006 and grossed over $200 million in the first year of launch in the U.S. alone. Gardasil is approved for girls/women in the age range of 10-23 years and administered by injection in three doses at 0, 2 and 6 months. The drug costs about $360 and had been approved for use in 86 countries; Gardasil brought in $1.5 billion in revenues during its peak market share.

Tamir Biotechnology is experimenting on an antiviral drug ranpirnase and claims that it can completely clear away the warts caused by HPV. A Phase 1/2 trial is planned for this year.

Biota's use of antiviral therapy for anogenital warts is a novel approach as compared to existing methods. BTA074 is the first compound in clinical development that directly interferes with HPV replication in infected cells. Based on favorable results obtained from Phase 2a study, Biota is planning to initiate another Phase 2 study shortly.
Another potential application of the BTA074 is against the orphan indication RRP, for which the company planning to have an oral formulation of the drug. As a treatment for a rare disease which has no alternate approved therapy, BTA074 could dictate a substantial premium pricing.

LANI – Fighting The Flu

Incidence: Seasonal influenza, or the flu, is an acute viral infection. There are three types of seasonal influenza – A, B and C, with types A or B occurring more frequently than C. Influenza virus causes destruction of airway epithelial cells. Fever, dry cough, sore throat, rummy nose, headache, muscle and joint pain, and a severe feeling of unwell characterize flu. Most people recover from flu symptoms within a week without requiring medical attention. However, flu can be fatal in people with high-risk profile including the young, elderly or chronically ill patients.

[17] http://www.cdc.gov/std/hpv/stdfact-hpv.htm

Flu is a seasonal epidemic mostly occurring during fall and winter annually and varies in severity. In the U.S., the peak of flu season occurs anywhere from late November through March. According to the World Health Organization (WHO), flu causes severe illness in roughly three to five million cases and about half a million deaths worldwide. According to CDC estimates, between 5% and 20% of U.S. residents get the flu. Roughly, 200k people are hospitalized on average for flu-related complications each year[18]. Although seasonal flu is associated with respiratory symptoms, avian flu involves the central nervous system, and gastrointestinal tract.

Preventive Care: A preventive measure against infection is primarily by immunization. However, the efficacy of flu vaccine decreases with age, and is dependent on how well the antigen in the vaccine matches the circulating virus. Vaccines are usually available only after pandemic outbreaks making patients vulnerable to the virus. Symptomatic relief from flu comprises of anti-pyeretics, rest and rehydration. Early treatment with antivirals is recommended to reduce the effect of symptoms.

FDA approved treatment on the market: The influenza virus encodes the neuraminidase (NA) enzymes to release itself from the host cell. The NA enzymes cleave the sialic acid residues off the cell surface, allowing the virus to exit the cell. Inhibition of the NA enzyme has proven to be a successful attempt in antiviral therapy, as characterized by drugs such as zanamavir (Relenza) and oseltamavir (tamiflu). These antivirals interfere with release of the flu virus from the infected cell, and result in the aggregation of virus particles at the surface of the host cell.

Biota's molecule: Biota's LANI is designed to be inhaled orally or nasally in order to bypass hepatic first-pass metabolism, offer quick onset of action along with low enzymatic activity so that it can be delivered directly in the lungs. This method of delivery is believed to offer efficient therapy as a large surface area with high blood circulation and high permeability rate is available for absorption of the drug. Currently approved influenza therapies are dosed twice a day for five days (Tamiflu). Biota's LANI is given as an inhaled dose, and differs from other flu drugs in that it requires just one dose to treat flu and a once-weekly dose to prevent flu.

LANI, the long-acting antiviral has shown to have in vitro NA-inhibitory activity against various influenza A and B viruses, as well as active against clinically relevant oseltamivir and peramivir resistant viruses (H1N1; H275Y) including avian flu. LANI seems to be more potent and effective than the existing treatments. A single intranasal dose of LANI exhibited efficacy similar to that of repeated doses of zanamivir or oseltamivir phosphate.

Zanamivir (Relenza) is a neuraminidase inhibitor that prevents the release of flu virus from infected cells. Two puffs (10 mg) of the drug are delivered via an inhaler in adults and children ≥ 7 yr. Relenza is marketed by GlaxoSmithKline. Biota receives 7-10% royalties on global net sales of Relenza,

Inavir is the second generation influenza product, LANI, is a once-only inhaled dosing of laninamivir octanoate--and represents a significant advantage over the five-day, twice-daily dosing associated with the currently marketed neuraminidase inhibitors to treat influenza. The company has a world-wide license, to develop and commercialize a number of LANIs, including laninamivir octanoate. Biota has partnered with Daiichi-Sankyo (LANI is co-owned 50:50 by Biota and Daiichi Sankyo) outside of the U.S. and receives 4% royalties on commercial sales of LANI (Inavir) in Japan. Daiichi Sankyo, Japan's second largest pharmaceutical company, has close to 50% of all neuraminidase inhibitor sales in Japan (≈$135 million).

Clinical Trial: LANI was developed with the help of a contract worth $231.2 million from the U.S. Biomedical Advanced Research and Development Authority (BARDA), part of the Department of Health and Human Services. The BARDA contract was designed to fund and provide the company with all technical and clinical data and U.S. based manufacturing to support the filing of a U.S. new drug application (NDA) with the FDA for LANI. The BARDA contract commenced in March 2011 and terminated in May 2014.

- ***Phase 2 trial (IGLOO):*** A multi-national randomized, double-blind, placebo-controlled, parallel-arm Phase 2 trial was conducted to investigate the effects of LANI (IGLOO trial). The trial enrolled 636 subjects, randomized equally across the three treatment arms. The top-line data compared the safety and efficacy of both 40 mg and 80 mg doses of LANI with placebo, all delivered by a TwinCaps® inhaler in adults with symptomatic influenza A or B infection. The trial's primary end point was the difference in the median time to alleviation (reported to be mild or absent for greater than 24 hours) of all seven influenza symptoms (headache, feeling feverish, body aches and pains, fatigue, cough, sore throat and nasal congestion) and fever. Secondary end points include whether the use of

[18] http://www.cdc.gov/flu/faq/flu-season.htm

laninamivir octanoate reduces the incidence of secondary bacterial infections compared to placebo. Symptom data were collected through the influenza intensity and impact Flu-iiQ™ questionnaire.

Biota announced that the study failed to meet its primary endpoint of significantly reducing the median time to alleviation of influenza symptoms versus placebo. However, notable effects were seen in individual symptoms, the sub-set of systemic symptoms (headache, feeling feverish, body aches and pains, and fatigue) and a number of secondary endpoints. Subjects in the 40 mg cohort reported being symptom-free significantly earlier than placebo group (median time 58 hours and 72 hours, respectively, p=0.029). Patients in the 40 mg cohort also reported a significant reduction in the number of days they had severe symptoms (p=0.02) and in the number of secondary bacterial infections (p=0.013) as compared to placebo. In addition, patients in the 40 mg ($p < 0.001$) cohort also demonstrated a significant reduction in viral shedding on day 3 of the study compared to placebo as quantified by qRT-PCR. A statistically significant proportion of patients in both the 40 mg (p=0.002) and 80 mg (p=0.02) cohorts came out negative when tested for influenza culture on day 3 of the study as compared to placebo.

Market Opportunity: Although LANI failed to meet its primary end point in the IGLOO trial, management thinks that there are positive takeaways after analyzing the dataset. The company was encouraged by the overall reduction in the duration of severe symptoms as well as viral shedding in the group treated with 40mg of LANI. Biota has made a strategic decision to discontinue further development of LANI in the U.S. as time and cost related to additional trials and commercialization may not be viable from a commercial standpoint. Additionally, even if they were to conduct further trials and obtain marketing approval for LANI in the U.S., there may be significant limitations on its use.

Biota's management feels that at this point, even though the U.S. may not be an attainable market, the drug may still hold promise to gain approval in other large markets like Asia. The company, along with Daiichi Sankyo, intends to pursue a license agreement with a pharmaceutical company to advance the development and/or commercialize LANI in global regions outside Japan.

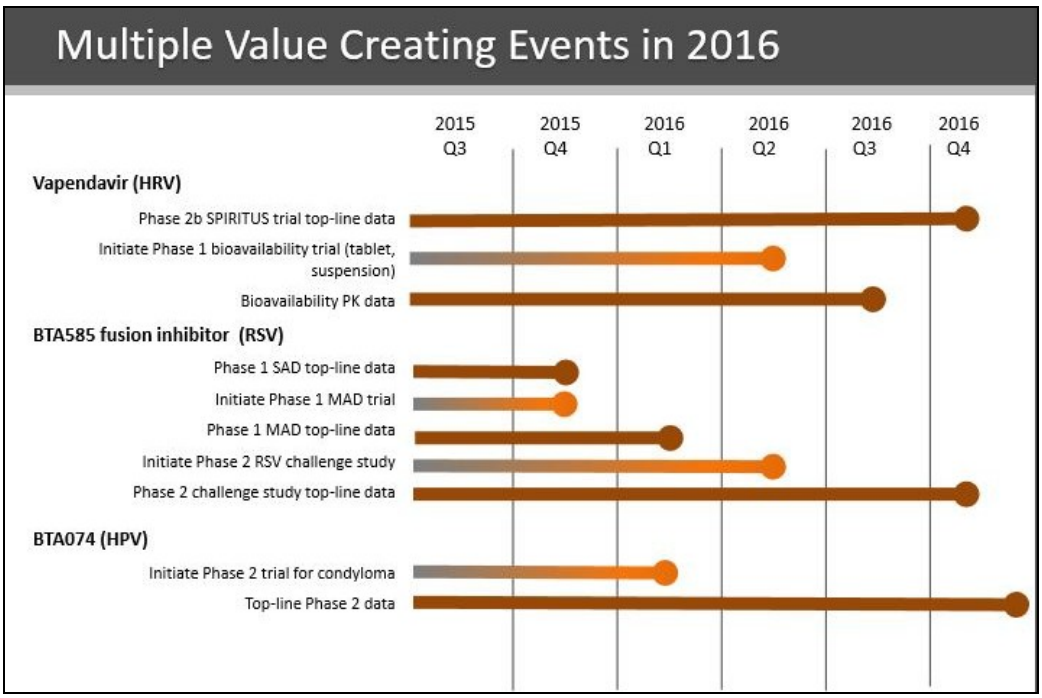
The outbreak of a new strain of virus is not unusual and can result in severe respiratory illness. In such a case of flu pandemic involving a new virus, demand for antiviral drugs can significantly increase. Under such circumstances where the demand is higher than anticipated, ~~there is a possible increase in revenues generated by~~ stockpiling LANI by governmental agencies across the globe may result in increase in revenue for Biota.

Both GSK and Roche market Relenza and Tamiflu, respectively, for the treatment of influenza. Tamiflu grossed more than $18 billion in sales revenues since its launch in 1999. However, these two antivirals have not resulted in significant sales, despite the high incidence of influenza across the major pharmaceutical markets. In the year ending June 2003, Tamiflu and Relenza only generated $159m and $7.2m, respectively. A number of factors, which contributed to the poor uptake of these compounds, such as poor availability of rapid and accurate diagnostics to determine viral etiology, low disease awareness and sub-optimal presentation rates would limit the uptake of antiviral therapies.

Seasonal flu is contagious, follows a mild course but can become serious and result in viral illness. Successfully inking government contracts around the globe for influenza product stockpiling will maximize the potential for Biota and provide non-dilutive capital to fund other infectious disease programs.

PIPELINE

We are anticipating a busy 2016 for Biota, with several planned milestones, which we believe will keep investors interested in the company. Data from the Phase 1 single ascending dose study involving BTA585 are expected before end of 2015. Top-line data from SPIRITUS Phase 2 study involving vapendavir is expected in early 2H 2016.



(Source:www.biotapharma.com)

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Compund	Patent Expiry	Extension(?)	Patent Extension
Relenza	July 2019 in Japan	Pending application (No. 08/737,141)	17 yrs from date of approval
LANI - structure	2017 in US, EU, Japan	no	
LANI-product	2021 in US, EU	no	
	2024 in Japan		
LANI-manufacture	2029 in Japan	no	
LANI-DPI	2027 in EU, Japan	no	
	2029 in US		
Vapendavir	Japan: 2021 + PTE - 2026 ; U.S.: PTE - 2022; PTA-2027; EU: SPL - 2026	Pending application for new formulation	U.S. - 2034
BTA074	2029 in US	yes	
BTA585	2024-2031	no	
BTA585-composition	2031		

The above table entails the patent on Biota's molecules and the methods. The commercial window for the molecules begin to expire from 2017 in the U.S. There are several patent extension applications that are pending. If the extensions on the patents are approved, this could potentially extend the commercial window even further.

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MANAGEMENT

Joseph Patti PhD
Chief Executive Officer & President
Dr. Patti joined the Company on November 12, 2012 and served as its Executive Vice President of Corporate Development and Strategy until October 1, 2014, when he was appointed as the Company's President and Chief Executive Officer. Prior to joining the Company, Dr. Patti co-founded Inhibitex, Inc. in 1998 and served as its Chief Scientific Officer and Senior Vice President of Research and Development from 2007 until it was acquired by Bristol Myers Squibb in February 2012. He also served as its Chief Scientific Officer and Vice President of Research and Development from 2005 to 2007 and as Vice President, Preclinical Development prior to that. Before co-founding Inhibitex in 1998, Dr. Patti was an Assistant Professor at Texas A&M's Institute of Biosciences and Technology and also served on the faculty at the University of Texas Health Science Center Graduate School of Biomedical Sciences. Dr. Patti is currently a director of SciStem Therapeutics, Inc., a privately-held company focused on developing cellular therapies for bone healing and musculoskeletal indications in both human and animal health. Dr. Patti was a director of Inhibitex from 1998 to 2005.
Dr. Patti received a B.S. in Microbiology from the University of Pittsburgh, an M.S.P.H. from the University of Miami, School of Medicine and a Ph.D. in Biochemistry from the University of Alabama at Birmingham.

Mark Colonnese
Chief Financial Officer & Executive Vice President
Previously, Mr. Colonnese served as the Chief Financial Officer of Stealth BioTherapeutics since November 2014 and as the Executive Vice President and Chief Financial Officer of Transgenomic Inc. from August 2012 to October 2014. Prior to that, he worked at Salutria Pharmaceuticals, LLC and at its predecessor company, AtheroGenics Inc., from 1999 to 2012, where he served in a number of executive roles, most recently as Executive Vice President, Commercial Operations and Chief Financial Officer . He has also held executive positions at Applied Analytical Industries and Schering-Plough, and served on the Board of Directors of Endeavor Pharmaceuticals, Inc.
Mr. Colonnese holds an M.B.A. Degree from Fairleigh Dickinson University and a B.S. magna cum laude from Ithaca College.

Peter Azzarello
Vice President, Finance
Mr. Azzarello served as VP Finance of Inhibitex, Inc., from November 2004 through January 2012 and interim CFO from February 2012 to September 2012. Previously, Mr Azzarello was Vice President of Financial Reporting at Netbank and prior to that he worked for Metavante, a division of Fidelity Information Services for several years.
Mr. Azzarello holds a Bachelor of Accounting and Finance from Florida Atlantic University and holds a Certified Public Accountant license.

John Vernachio PhD
Vice President, Preclinical Development
Dr. Vernachio served as Vice President for Research with the Arthritis Foundation in 2013. Prior to that, he served as Vice President of Biology for Inhibitex, Inc. from 1998 until 2012. From 1997 – 1998 Dr. Vernachio was Director of Life Sciences for Valentis, Inc. and from 1991 – 1997 served as Manager, Molecular Immunology for the Gene Therapy Unit of Baxter Healthcare.
Dr. Vernachio attended the University of Vermont where he earned a BS in Animal Science in 1984 and Johns Hopkins University School of Medicine where he completed a Ph.D. in biochemistry with a concentration in immunology and molecular biology in 1989. He completed his post-doctoral training in the Department of Immunology at The Research Institute of Scripps Clinic in San Diego in 1991.

Anna Novotney-Barry
Vice President of Clinical Development
Mrs. Novotney-Barry served as Vice President Clinical Development at Inhibitex, Inc. from March 2010 until August 2012, where compounds in clinical development included both small molecule anti-virals to treat Hepatitis C and Herpes Zoster as well as a monoclonal antibody directed at bacterial infection. Prior to Inhibitex, she held several global scientific and management positions within Clinical Development at UCB Pharma SA, including responsibility for leading clinical program development for certain monoclonal antibodies within the immunology therapeutic area. Earlier in her career which spans more than 25 years, she held a number of positions within Clinical Development or Drug Discovery at Solvay, Cryolife, and Searle.
Mrs. Novotney-Barry received a B.S. degree in Biology from the University of Illinois at Champaign-Urbana and M.S. degree in Immunology from Southern Illinois University at Edwardsville.

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Edward Lee PhD

Vice President, Chemistry, Manufacturing and Controls (CMC)

Dr. Edward R Lee was Vice President and Head of Chemical Development at Blend Therapeutics from April 2012 until November 2013, where novel platinum compounds and nanotechnology were combined to create innovative oncology therapies. Prior to that, he was Vice President and Head of Chemical Process Development at Genzyme Corporation. In a career spanning 22 years at Genzyme he was responsible for the development of small molecules and polymers to treat numerous diseases, including cystic fibrosis, multiple sclerosis and Gaucher Disease. Edward held a post-doctoral position at the University of Bern, Switzerland, from 1988 to1990, investigating vitamin B12 chemistry.
Dr. Lee received a BSc in Chemistry from the University of Warwick, UK and a PhD in Chemistry from the University of Warwick, UK

Uday Patel

Vice President, Regulatory Affairs

Mr. Patel has been a partner and key member of senior management and scientific project teams in successful start-ups to clinical stage organizations. Mr. Patel's background includes international experience in program management, clinical operations, regulatory affairs, analytical development and quality assurance. Most recently, he served as Vice President of Regulatory Affairs and Quality Assurance at Inhibitex, Inc. from 2010 to 2012. He was responsible for development and implementation of regulatory strategy for various clinical programs and management of QA tasks in clinical development of infectious disease therapies. Prior to joining Inhibitex, he was Vice President of Regulatory/Quality at Peptimmune from 2004 to 2010, responsible for execution of regulatory and quality initiatives focused on autoimmune indications and metabolic diseases.
Mr. Patel received a B.S. degree in Biochemistry from Suffolk University and Master of Liberal Arts (ALM) degree in Biology from Harvard University. Mr. Patel has received regulatory affairs certification (RAC) for US and EU from the regulatory affairs professionals' society (RAPS).

REGULATORY PATHWAY

Once clinical trials complete with favorable results, the next obvious step is to apply for an NDA. The "Breakthrough Therapy" designation was formulated by the FDA under Section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) of July 2012. This status is intended to accelerate the availability of new therapies to patients with serious conditions, when the existing therapies are unsatisfactory. FDA defines the expedited program as one that addresses an unmet medical need in the treatment of a serious condition. In the regulation a condition is interpreted as serious when, "…if left untreated, will progress to a more severe one". The eligibility criterion for the drug to qualify in the expedited program is that "…a product intended to prevent a serious condition or reduce the likelihood that the condition will progress to a more serious condition".

Patients, both adults and children having asthma and/or COPD experience frequent exacerbations that rapidly cause a decline in lung functionality resulting in high mortality. Vapendavir is being developed to address asthma and COPD exacerbations. Preliminary clinical studies (Phase 1/2) have shown evidence indicating vapendavir significantly lowered upper respiratory symptoms early in the illness. Vapendavir recipients also had significant improvements in secondary outcomes including higher peak expiratory flow rates on day 5 and reduced overall use of asthma relief medications. Vapendavir was also well-tolerated with no adverse events, reduced the incidence of infection and had a significant reduction in mean viral load. These results from the antiviral's effect raise the possibility that an appropriate dose might be able to provide pronounced clinical benefit. Consequently, we think vapendavir has the potential to qualify for the "breakthrough therapy" designation.

As per the FDA, companies developing antivirals had the most requests for this designation between the years 2012-2014 and 41% of the requests were granted[19]. The review process should take roughly two months from the date of application as opposed to ten months in a standard review procedure. Typically it is recommended by the FDA to submit a request for this designation by the end of Phase 2 meeting, which would be sometime in 2H 2016. We think the company could potentially gain this approval if the primary end point is met in the SPIRITUS trial.

[19] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM447162.pdf

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VALUATION AND RECOMMENDATION

We are initiating coverage on Biota Pharma (NASDAQ: BOTA) with a Buy rating and a price target of $4.50/share. We consider two possible scenarios for valuing Biota; if Biota were to sell vapendavir outright to a large pharma company or out-license the marketing rights alone. Under both scenarios we assume that the only product that comes to market is vapendavir. Vapendavir is currently going through mid-stage clinical trials.If data demonstrates significance in safety and efficacy, we believe there is potential opportunity for vapendavir to gain sizable market share given the limitations of the currently approved therapies for asthma and COPD exacerbation in the market.

Infectious disease portfolios have recently become an acquisition target for large pharma. HBM Partners' M&A report revealed that acquired companies developing antivirals for infectious diseases were acquired for an average 90%+ premium to their market value prior to the take-out announcement. One such exceptional deal was the sale of the VC-backed company, Alios BioPharma, involved in developing novel anti-virals, to Johnson & Johnson for $1.75 billion in 2014. Alios' portfolio of potential therapeutics for viral infections included an orally administered antiviral therapy for the treatment of infants with RSV. Venture capitalists invested $75 million in Alios but received more than 20x from this deal[20]. In another transaction, Roche acquired Anadys Pharma for roughly $230 million (a 256% premium over its prior day closing price of $1.04) in an all-cash deal in 2011. Anadys developed direct acting antivirals for the treatment of hepatitis C virus (HCV) infection.

If Biota sells vapendavir: We use forecasted revenues to derive an estimated value for the company which we can use as a guide for what an acquiring company would reasonably be expected pay for vapendavir. Our derived valuation takes into consideration that the molecule is still in mid-stage clinical development and the related risk that it fails in late-stage testing. We believe that our valuation represents a floor on what pharma companies would be willing to pay given their ability to leverage their existing infrastructure and gain greater market share than what BOTA may achieve.

Here are reasons why we think vapendavir may transform from a molecule to a successful product.

- Vapendavir has shown promising results in proof-of-concept studies. From the single/multiple dose escalation studies, vapendavir showed no dose limiting toxicities. In the drug interaction study, vapendavir demonstrated as being a weak-moderate inducer of a metabolizing enzyme implying that the molecule was not extensively or exclusively metabolized. In the bioavailability study vapendavir demonstrated 60% absorption. When Advair was orally dosed the systemic bioavailability of the drug was negligible (< 1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, when delivered to the lung it was systemically absorbed. Vapendavir proved to be ~10 times more active than pleconaril and was predicted to have a longer half-life and oral bioavailability[21]. In all of the Phase 1 studies vapendavir was well-tolerated with no adverse events. In a Phase 2a challenge study vapendavir showed statistical significant improvement in reducing the incidence of infection and viral shedding in volunteers who were experimentally infected with a rogue strain of HRV. In Phase 2b studies vapendavir demonstrated excellent tolerability and proved that the antiviral response limited the infection to the upper respiratory airways. Thus far, from the Phase 1/2 studies conducted, vapendavir has demonstrated a desirable clinical pharmacology profile with high bioavailability, linear pharmacokinetic profile, remained unaffected by concomitant medications, and was not exclusively metabolized. On the basis of these findings, another Phase 2 dose-ranging study is currently on-going in a selected group of HRV positive patients to confirm vapendavir's safety and efficacy profile.

- Patients prefer medications that are convenient to administer, have infrequent dosing routines as well as a rapid onset of effect. Phase 2 studies demonstrated improvement from the third day of treatment with vapendavir. Currently vapendavir is being tested for a once daily dosing for one week in HRV infected patients in the SPIRITUS trial.

DCF MODEL: We have built a financial model using a discounted cash flow (DCF) analysis to derive a fair value for Biota Pharma. Our forecasted revenue is based on the assumption that Biota markets the drug on their own. We incorporate a risk discount to capture the potential that the compound fails to gain U.S. regulatory approval. We have the following inputs to the model:

[20] http://www.hbmpartners.com/wAssets/docs/industry-reports/HBM-Pharma-Biotech-MA-Report-2014.pdf
[21] J Med Chem 2003;46:3181–3184.

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- Approximately 7% of the adult population in the U.S. has asthma, of which 50% have COPD and asthma exacerbations (Source: CDC.gov). Similarly 8.3% of children develop asthma of which 38% have exacerbations. Based on these statistics our estimated total HRV target population aggregates to around 10 million.

- Vapendavir Phase 2 effectiveness study commenced in February 2015 and is expected to complete by mid-2016. If the results turn out favorable, it could lead to a Phase 3 study in 2016-2017, a U.S. NDA filing in 2018, and potential launch in 2019. Historical data suggests that the chance of a compound in Phase 2 clinical trial successfully completing Phase 2 and Phase 3 trials, and obtaining NDA approval is roughly 30%[22]. We weight our cash flows by a factor of 0.3 to account for a 30% probability of successful product launch.

- We assume vapendavir will cost approximately $300-$350 per patient at the time of launch in 2019. This is consistent with other HRV drugs. Although vaccines are available for individuals with blunted immunity, there are no antivirals in the current market that have the capability to attenuate the infection by reducing the severity and duration of the illness. Rapid viral adaptation renders many treatments with existing drugs ineffective which offers the opportunity for vapendavir to gain substantial market share by displacing current drugs on the market. Given that Advair enjoyed close to 30% market share during its peak, we assume that Biota can achieve 25% peak market share by 2029, which would yield peak U.S. sales around $0.6 billion.

- We are using a 15% discount rate in our model. We forecast cash flows from revenue until vapendavir's patent expires. Vapendavir's patent expires in 2021 and if the patent (related to a free-base form of vapendavir) is extended as per the Hatch-Waxman Act then we expect coverage, and related revenue, to continue through 2034.

- At this time we are paying particular attention to vapendavir and remain cautiously optimistic that it could be launched sometime in the 2018 – 2019 timeframe. Although RSV and HPV present a significant opportunity and Biota's molecules currently in Phase1/2 clinical developmental stages appear attractive, we are not including BTA585 and BTA074 in our valuation. We remain speculative on the potential success of the trials. If and when they are launched it could prompt an upward revision to our forecast.

If Biota out-licenses vapendavir: We believe that if Phase 2 data yields strong results, Biota may attract interest from potential partners. We think a post-Phase 2 partnership deal for vapendavir could yield $100 to $150 million (roughly half the firm value) upfront, additional development, regulatory and commercial milestones and ~10% net sales royalties ($12 to $15 million). This is similar to the transaction between Biocryst Pharma and CSL Ltd.

The company receives royalties of 10% and 4% of net sales of Relenza and Inavir, respectively. This revenue stream, albeit small, provides Biota with meaningful cash flow to continue development of other products in their pipeline. If Relenza patent claims are ultimately issued, Biota will receive royalties from net sales of Relenza® in the U.S. for an additional 17 years from the date of allowance. We have included the revenue from the steady royalty stream from both Relenza and Inavir in our valuation.

The value for Biota derived from our model represents more than 100% upside from today's trading price.

[22] http://www.fdareview.org/approval_process.shtml

CONCLUDING THOUGHTS

Three years ago, Biota Pharmaceuticals was trading over $4.00 per share. Since then it has fallen almost 50% to $1.97 per share.

Biota's cash burn of roughly $3 million per quarter is likely to continue at this rate as Phase 1/2 trials with all of their molecules are underway. If favorable results are obtained from Phase 2 trials the company may plan pre-NDA meeting with the FDA to commence Phase 3 trials for vapendavir. Drugs in areas of high unmet need, such as asthma and COPD, may be considered for expedited approval but the go/no-go decision relies heavily on trial results. At this time, we estimate the Phase 2 trial may be fully enrolled in Q2 2016 with data available during the early part of 2H 2016. We think a best-case scenario may be that the trials complete in 2017, an NDA could be filed in 2018 and approval of vapendavir comes by 2019. However, any delays in trial completions will correspondingly push back the timelines for product launch. We estimate that the cash balance of $57.2 million (cash, cash equivalents and short term investments) as of Q1 2015, is sufficient to continue the company's operations until 2017.

We include Biota's current cash balance and an estimated $80 million in CapEx in our valuation. Using a 15% discount rate, FCF amounting to 60% of revenues and 43 million shares outstanding (on a fully diluted basis) we arrive at an NPV of $135 million ($3.14/share) for vapendavir.

Additionally, we believe the existing LANI partnerships with Glaxo and Daiichi is worth another $62 million in value, or $1.44 per share. We arrive at this value by calculating the NPV of our projected royalty revenues from Relenza and Inavir. Sum of the parts values Biota at $197 million or approximately $4.50/share.

Potential Risks to our thesis:

Patent Expiration: Relenza® patent portfolio is scheduled to expire in July 2019 in Japan. GSK has agreed to pay royalties on the net sales of Relenza® in the U.S. as long as the patent appeal (08/737,141) remains pending. If the appeal is rejected the company will cease to receive royalty revenues from the net sales of Relenza® in the U.S.

Clinical Trials Fail To Meet End-point: While we do not believe that this is likely to occur we cannot entirely rule out the possibility that the studies fail to demonstrate safety or efficacy in the targeted population. This would likely have a large negative impact on the stock and we would have meaningful downward revisions to our valuation.

Biota cannot out-license rights /sell vapendavir for a reasonable price: Although we have forecasted substantial vapendavir revenue , there could be a wide range of value on the price the potential acquiring company would be willing to pay for the licensing deal or acquisition.

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PROJECTED INCOME STATEMENT

Biota Pharma	2015 E	Q1 A	Q2 E	Q3 E	Q4 E	2016 E	2017 E	2018 E
Total Revenues	**$24.6**	**$1.7**	**$7.0**	**$6.2**	**$2.7**	**$17.6**	**$18.1**	**$18.7**
CoGS	$3.6	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	$21.0	$1.7	$7.0	$6.2	$2.7	$17.6	$18.1	$18.7
Product Gross Margin	-	-	-	-	-	-	-	-
R&D	$37.4	$5.5	$5.8	$6.3	$6.5	$24.1	$28.0	$33.0
G&A	$9.4	$2.2	$2.5	$2.4	$2.2	$9.3	$9.6	$9.9
ForEx (gain)/loss	$6.5	$0.7	$0.0	$0.0	$0.0	$0.7	$0.0	$0.0
Loss on disposal of Assets	$0.2	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($19.5)	($6.7)	($1.3)	($2.5)	($6.0)	($16.5)	($19.5)	($24.2)
Operating Margin	-	-	-	-	-	-	-	-
Interest Income	$0.30	$0.10	$0.10	$0.10	$0.10	$0.40	$0.40	$0.40
Pre-Tax Income	($19.2)	($6.6)	($1.2)	($2.4)	($5.9)	($16.1)	($19.1)	($23.8)
Tax Benefit	$0.1	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
Net Income	($19.1)	($6.6)	($1.2)	($2.4)	($5.9)	($16.1)	($19.1)	($23.8)
Reported EPS	**($0.54)**	**($0.17)**	**($0.03)**	**($0.06)**	**($0.15)**	**($0.42)**	**($0.46)**	**($0.54)**
Shares Outstanding	35.4	38.6	38.6	38.6	38.6	38.6	41.0	44.0

Source: Zacks Investment Research *Anita Dushyanth, PhD*

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