AmpliPhi Biosciences Corp. (APHB - OTC)

**APHB: Development of bacteriophage therapies continues...**

<table>
<thead>
<tr>
<th>Current Recommendation</th>
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<td>Prior Recommendation</td>
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<tr>
<td>Date of Last Change</td>
<td>08/04/2014</td>
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<td>Current Price (11/17/14)</td>
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<td>Target Price</td>
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**UPDATE**

On November 14, 2014, AmpliPhi Biosciences filed form 10-Q with results for the third quarter of 2014. Due to a non-cash gain on derivative liabilities the company reported net income of $19.3 million. Without the non-cash gain the company lost $4.9 million.

AmpliPhi exited the third quarter of 2014 with $9.8 million in cash and cash equivalents. Based on average cash burn of $3-$4 million per quarter, we estimate that the current cash balance will fund the company through the first quarter of 2015. We believe AmpliPhi has an exciting technology but we are maintaining a Neutral rating on the stock due to how early in development the company is with their lead products.

**SUMMARY DATA**

| 52-Week High | $0.66 |
| 52-Week Low  | $0.14 |
| One-Year Return (%) | -67.80 |
| Beta         | 0.81 |
| Average Daily Volume (sh) | 88,855 |
| Shares Outstanding (mil) | 187 |
| Market Capitalization ($mil) | $34 |
| Short Interest Ratio (days) | 0.01 |
| Institutional Ownership (%) | 6 |
| Insider Ownership (%) | 14 |

| Annual Cash Dividend | $0.00 |
| Dividend Yield (%)   | 0.00 |

**5-Yr. Historical Growth Rates**

| Sales (%) | N/A |
| Earnings Per Share (%) | N/A |
| Dividend (%) | N/A |

| P/E using TTM EPS | N/A |
| P/E using 2013 Estimate | N/A |
| P/E using 2014 Estimate | N/A |

**Risk Level**

Above Average

**Type of Stock**

Small-Growth

**Industry**

Med-Biomed/Gene

**ZACKS ESTIMATES**

**Revenue**

(In millions of $)

<table>
<thead>
<tr>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Year</th>
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<tr>
<td>(Mar)</td>
<td>(Jun)</td>
<td>(Sep)</td>
<td>(Dec)</td>
<td>(Dec)</td>
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<tr>
<td>2013</td>
<td>$0.02 A</td>
<td>0 A</td>
<td>$0.3 A</td>
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<td>2015</td>
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**Earnings per Share**

(EP is operating earnings before non-recurring items)

<table>
<thead>
<tr>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Year</th>
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<td>(Mar)</td>
<td>(Jun)</td>
<td>(Sep)</td>
<td>(Dec)</td>
<td>(Dec)</td>
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<tr>
<td>2013</td>
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<td>-$0.10 A</td>
<td>$0.08 A</td>
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<td>2015</td>
<td>0 E</td>
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<td>0 E</td>
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</tr>
<tr>
<td>2016</td>
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Financial Update

On November 14, 2014, AmpliPhi Biosciences (APHB) filed Form 10-Q with results for the third quarter of 2014. The company did not report any revenues in the current quarter. Due to a non-cash gain on derivative liabilities of $24.3 million the company reported net income of $19.3 million. AmpliPhi had research and development expenses of $1.8 million in the third quarter of 2014 compared to $1.1 million in the third quarter of 2013. The increase was mainly attributable to research and clinical development planning expenses for all of the company's product candidates. General and administrative expenses $1.6 million for the current quarter versus $1.2 million for the corresponding time period in 2013. The increase was mostly attributable to a $0.3 million accrual for payments to certain shareholders as required by the terms of the company's Series B Preferred Stock Purchase Agreement. In addition to R&D and G&A expenses, the company recorded a severance charge of $1.5 million related to severance-period compensation and benefits and stock-based compensation expense related to the acceleration of vested stock options related to the termination of the company's Chief Executive Officer during the quarter.

Cash burn for the third quarter of 2014 was $2.7 million. AmpliPhi exited the third quarter of 2014 with approximately $9.8 million. Based on operating burn of $2.7 million, $3.9 million, and $3.9 million for the previous three quarters we estimate that the company's cash should be sufficient to fund the company through the first quarter of 2015. Thus, the company will need to raise funds during the next six months.

AmpliPhi searching for a new CEO

On September 19, 2014, AmpliPhi announced that Philip J. Young stepped down from his role as President and CEO. In addition, the company announced that Chairman Jeremy Curnock Cook would serve as interim CEO and Wendy Johnson, a member of AmpliPhi's Board of Directors, would serve as interim COO, overseeing the company's operations until a new CEO is appointed.

Mr. Cook was responsible for identifying and managing the acquisition of the AmpliPhi phage technology into the company and has helped refine the therapeutic phage platform concept over the past five years as the company's Chairman. He has a background in microbiology and a successful track record of building biotech and technology companies as an investor and director for over the past 30 years.

Ms. Johnson, who joined AmpliPhi's Board of Directors earlier this year, has an extensive and successful career in investment and company building. She also has a background in microbiology and is highly experienced in regulatory affairs having served as Assistant Director with the Center for Devices and Radiological Health at the U.S. Food and Drug Administration for ten years prior to her commercial and investment career.
Bacteriophages, otherwise known as phages, are viruses that infect, replicate in, and kill bacteria. These viruses do not infect eukaryotic cells, and they are highly specific to one or a very limited number of bacterial species. In addition, as viruses they are only able to reproduce while infecting bacteria and cannot propagate themselves outside of a host. Over 5,500 bacteriophages have been examined by electron microscopy since 1959. They belong to 17 virus families and occur in over 154 bacterial genera (Ackermann, 2007). Bacteriophages come in many different shapes and sizes, with most (96%) having the same basic morphology: a head and a tail. The bacteriophage head is made up of protein that protects the nucleic acid genome, which can be either single-stranded (ss) or double-stranded (ds) ribonucleic acid (RNA) or deoxyribonucleic acid (DNA). The tail is a hollow structure through which the bacteriophage genome passes into the bacteria after the bacteriophage attaches to the host. Bacteriophages infect a host cell by first attaching to a specific receptor found on the bacteria’s surface. Each bacteriophage can typically bind just one or a few receptors, thus conferring their specificity and limiting the types of bacteria they can infect.

Bacteriophages are classified as either lytic or lysogenic, depending upon their life cycle. A lytic bacteriophage is one that can only replicate through breaking open (lysing) the bacterial host at the end of their life cycle. A lytic bacteriophage goes through three phases: an eclipse phase, an accumulation phase, and a release phase. The eclipse phase is where the bacteriophage genome takes over the host biosynthetic machinery to direct the production of bacteriophage proteins and nucleic acids. The accumulation phase is where the bacteriophage particles are assembled together and begin to accumulate inside the host. The release phase occurs after the accumulation of a number of bacteriophage particles and the lysis of the bacterium, which then releases the newly created bacteriophages that are then capable of finding a new host to infect. Upwards of 1,000 bacteriophages can be released per infected bacterium.

A lysogenic bacteriophage can multiple through either the lytic cycle or it can enter a dormancy period inside of the host. After infecting the host, the viral genome of a lysogenic bacteriophage is integrated into the host genome and is replicated and passed on to daughter cells. The cells containing a dormant phage are not harmed by its presence and the lysogenic state may last indefinitely. It is not until host conditions deteriorate that the virus then enters the reproductive cycle thereby creating hundreds of new bacteriophages and causing lysis of the cell.
...Bacteriophage Use Dates Back Almost A Century...

It has been almost 100 years since the initial discovery of bacteriophages. Frederick Twort, a bacteriologist from England, reported the discovery of what he described as “an acute infectious disease of micrococi” (Twort, 1915). Twort’s work was interrupted by World War I, but two years later a second microbiologist working independently, Félix d’Herelle, reported an “antagonistic microbe” that caused “death of the bacillus through complete lysis...” (d’Herelle, 1917). He first coined the term bacteriophage, derived from ‘bacteria’ and the Greek phagein, which means, “to devour”.

The potential of bacteriophages to treat microbial infections was recognized very shortly after their discovery. In 1919, d’Herelle reported the use of bacteriophages to cure four individuals of dysentery. In addition, he used bacteriophages to halt outbreaks of cholera in India and plague in Egypt. In India, d’Herelle reported data from three separate locations where patients were treated with and without bacteriophage. Among patients treated with anti-cholera bacteriophages, in the first location there were no deaths in 16 cases, in the second location there were 6 deaths out of 74 cases (8%) and in the third location 92 deaths in 684 cases (13.5%). This compares to 13 deaths in 33 cases (39%) in the first location, 78 deaths in 124 cases (63%) in the second and 114 deaths out of 685 cases (16.6%) in the third location in patients not treated with bacteriophages (Summers, 1991).

The first bacteriophage trials in the United States were conducted in 1923 at the Baylor College of Medicine, where they reported the use of bacteriophages to treat children suffering from dysentery. Two of the 20 children treated with bacteriophages died while five of twelve children not treated with bacteriophages died. While not a controlled clinical study like those that are performed in the present day, the scientists conducting the study noted that “bacteriophages hold enormous possibilities as a new weapon for fighting infectious diseases.”

These early successes were soon followed by clinical results that failed to match the early hype. Even though d’Herelle recognized early on that a given bacteriophage is only effective against the bacteria from which it was derived, by 1933 there were at least three commercially available bacteriophage specimens of either staphylococcus or bacillus origin for use against staphylococcus, bacillus or streptococcus infections. These preparations were met with very mixed results, as bacteriophages derived from one species are ineffective against an infection caused by a different bacterial species. In addition, shortcomings in experimental designs lead to uninterruptable results, as they often did not include proper diagnoses, the amount and spacing of doses and route of administration.

In 1934, a report was published in the Journal of the American Medical Association that reviewed more than 100 papers on bacteriophage therapy, with conclusions that were clearly not favorable (Eaton et al., 1934). Amongst other things, the report stated that d’Herelle’s theory that bacteriophages were bacterial viruses had not been conclusively proven and that the material was inanimate and most likely an enzyme. In addition, since it was not proven that bacteriophages were viruses, it wasn’t prudent to attribute a bacteriophage cultures effect on bacterial cultures “a vital property of the substance”. Of course, we now know these conclusions to be false, and that d’Herelle was correct in stating that bacteriophages were viruses. Regardless, the report was a major setback to bacteriophage research in Western countries and also had a negative impact on the enthusiasm of funding agencies to support therapeutic bacteriophage research.

Seven years after the Eaton report was published, a second unfavorable report was published as a sequel to the 1934 report (Krueger et al., 1941). The authors’ conclusions in this report were also incorrect, as they stated that bacteriophages were “a protein of high molecular weight and appears to be formed from a precursor originating within the bacterium”. These two negative articles, coupled with the introduction of antibiotics, effectively ended all major studies of bacteriophage therapy in the United States.

...Antibiotics Render Bacteriophage Therapy Obsolete...

The age of antibiotics began in 1928 with the accidental discovery of penicillin by Sir Alexander Fleming, however due to the difficulty of isolating the antibiotic agent Fleming assumed that penicillin would not be important in human health. It wasn’t until 1940, when a pair of British scientists discovered how to isolate and concentrate penicillin that the mass production of the drug ensued. Use during World War II and the amazing effectiveness of penicillin in preventing soldier’s deaths from infections ushered in a time where antibiotics were cheap, widely available, and extremely effective against nearly all bacterial diseases. Because of this, antibiotics surpassed bacteriophages in their popularity and administration throughout most of the world.
In support of this, between 1966 and 1996, only 27 research papers dealing with bacteriophage therapy were published, with 19 of those from laboratories in Poland and Russia. Eastern Europe and Russia are the only areas of the world where research into bacteriophage therapy has never ceased, and where patients suffering from a host of bacterial infections have been treated for the past 80 years.

**...Antibiotic Resistance Opens Door Back Up For Bacteriophages...**

Sir Alexander Fleming first warned against the development of antibiotic resistant bacteria shortly after the widespread use of antibiotics began in the 1950’s. The rate of antibiotic resistant strains of bacteria has been growing rapidly since the 1980’s, with more than 70% of hospital acquired infections resistant to at least one of the drugs commonly used to treat them. Antibiotic resistance is fueled by the misuse and overuse of antibiotics in both the clinical and veterinary setting. It is estimated that a total of 23 x 10^6 kg of antibiotics are used annually in the U.S.; half of which is used for the treatment of disease in people with the other half reserved for agriculture and given to livestock animals (Harrison et al., 1998). The widespread use of antibiotics results in the survival and selection for organisms that harbor mechanisms for self-preservation, and with the ability of microorganisms to share genetic material these self-preserving principles are spreading rapidly and leading to an abundance of antibiotic-resistant microbes.

The Centers for Disease Control (CDC) published a report in 2013 on antibiotic resistance in the U.S. and the potential for catastrophic consequences if nothing is done to correct the problem. Each year, at least 2 million individuals in the U.S. contract a serious infection involving a bacterium that is resistant to one or more antibiotics, with at least 23,000 people dying each year as a result of antibiotic-resistant infections. In fact, methicillin-resistant *Staphylococcus aureus* (MRSA) infections in U.S. hospitals are responsible for more deaths than HIV/AIDS and tuberculosis combined (Klevens et al., 2006; Boucher et al., 2009). The rise of antibiotic resistance not only affects the ability to fight routine infections, but it also undermines the treatment of infectious diseases in patients with other diseases. A number of medical advancements were possible due to the ability to fight infections with antibiotics. These include joint replacements, organ transplants, cancer therapy, and the treatment of various chronic diseases.

**...A Clear Need For More Treatment Options...**

While pharmaceutical companies developed more than 20 new classes of antibiotics between the 1940’s and 1970’s, today there are limited compounds currently under development for highly resistant Gram-negative bacteria. There are a number of reasons for this, most importantly the lack of profitability in antibiotics. Typically, when a new antibiotic is approved, physicians hold it in reserve and save it for only the worst cases, rather than promptly prescribing it in an effort to stave off drug resistance, which ultimately hampers sales of the drugs. In 2008, the Infectious Disease Society of America confirmed that the world is in the midst of an emerging crisis of antibiotic resistant organisms. Failure to change the current course will likely mean a return to a “pre-antibiotic” era where patients die of routine infections and where many of our current medical treatments are no longer feasible. Given the economics surrounding antibiotic development and the misuse of the drugs that leads to bacterial resistance, many believe it is time for a new approach to treating bacterial infections, which bacteriophages are uniquely situated to do.

As mentioned previously, there is a lot of controversy surrounding the early work in bacteriophage therapy, which led to its rapid decline in use in the Western world. However, a resurgence of sorts occurred in the 1980’s following the seminal work of Smith et al. whereby they showed the ability of bacteriophage therapy to treat pathogenic *Escherichia coli* infections in a veterinary context (Smith et al., 1982). Much of the follow on work has been in animal models, with efficacious use of bacteriophage therapy shown against a range of experimental infections by *E. coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Enterococcus faecium* and *Vibrio vulnificus*.

There are very few reports of these pre-clinical animal models being used as a basis for human clinical testing. However, one such example is studies examining the efficacy of bacteriophages for the treatment of infections caused by *Klebsiella ozaenae*, *Klebsiella rhinoscleromatis scleromatis* and *Klebsiella pneumonia* (Bogovazova et al., 1991, Bogovazova et al., 1992). The bacteriophage preparations were reported to be safe and efficacious in treating infections in guinea pigs and mice, and from this they delineated the optimal bacteriophage concentrations and administration route for use in human volunteers. Their studies in 109 patients with *Klebsiella* infections showed the bacteriophage preparations to be effective (as reported by clinical improvements and bacterial clearance) with no toxicities noted.
The documented successes of bacteriophage therapy in Eastern Europe and Russia should probably be regarded as insufficient by Western standards; however, they should not be discounted entirely. Table 1 is adapted from a 2001 review by Sulakvelidze et al. of the major human bacteriophage therapy studies conducted in Poland and the former Soviet Union. Overall, there has been little primary publication of the enormous number of bacteriophage therapy studies conducted in these countries in English-language journals. This is in part due to the secrecy behind the Iron Curtain surrounding military applicable sciences, of which bacteriophage therapy is counted as it was utilized for the treatment of troops. In addition, bacteriophages were often utilized to treat otherwise incurable diseases and represented the standard of care long before the development of double-blinded, placebo controlled clinical trials. Thus, the standard type of medical documentation routinely performed in Western medicine was not utilized in these studies.

Table 1: Some of the Major Human Phage Therapy Studies Conducted in Poland and the Former Soviet Union

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>Infection(s)</th>
<th>Etiologic agent(s)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balasina et al. (7)</td>
<td>Bacterial dysentery</td>
<td>Shigella</td>
<td>Shigella phages were successfully used for prophylaxis of bacterial dysentery.</td>
</tr>
<tr>
<td>Bogdanov et al. (11)</td>
<td>Infections of skin and nasal mucosa</td>
<td>K. ozaenae, K. rhinoscleromatis, and K. pneumoniae</td>
<td>Adopted phages were reported to be effective in treating Klebsiella infections in all of the 104 patients.</td>
</tr>
<tr>
<td>Cato et al. (17)</td>
<td>Suppurative skin infections</td>
<td>Pseudomonas, Staphylococcus, Klebsiella, Proteus, and E. coli and Proteus</td>
<td>Thirty-one patients having chronically infected skin areas were treated orally and locally with phages. The success rate was 24%.</td>
</tr>
<tr>
<td>Jodziania et al. (18)</td>
<td>Lung and pleural infections</td>
<td>Staphylococcus, Streptococcus, E. coli, and Proteus</td>
<td>Phages were successfully used together with antibiotics to treat lung and pleural infections in 45 patients.</td>
</tr>
<tr>
<td>Kotova et al. (21)</td>
<td>Postoperative wound infections in cancer patients</td>
<td>Staphylococcus and Pseudomonas</td>
<td>A total of 131 cancer patients having post-surgical wound infections participated in the study. Of these, 65 patients received phages and the rest received antibiotics. Phase treatment was successful in 82% of the cases, and antibiotic treatment was successful in 62% of the cases.</td>
</tr>
<tr>
<td>Karpinski et al. (27)</td>
<td>Various infections</td>
<td>Staphylococcus, Klebsiella, E. coli, Pseudomonas, and Proteus</td>
<td>Immunocompetence of therapeutic phages was analyzed in 27 patients. The authors concluded that the phages' immunomodulation did not impair therapy.</td>
</tr>
<tr>
<td>Litvinova et al. (32)</td>
<td>Intestinal dysbacteriosis</td>
<td>E. coli and Proteus</td>
<td>Phages were successfully used together with bifidobacteria to treat antibiotic-associated dysbacteriosis in 500 low-birth-weight infants.</td>
</tr>
<tr>
<td>Melzhe et al. (33)</td>
<td>Lung and pleural infections</td>
<td>Staphylococcus</td>
<td>Phages were used to treat 223 patients having lung and pleural infections, and the results were compared to 117 cases where antibiotics were used. Full recovery was observed in 82% of the patients in the phage-treated group, as opposed to 61% of the patients in the antibiotic-treated group.</td>
</tr>
<tr>
<td>Milloniya and Vorontsova (39)</td>
<td>Bacterial dysentery and salmonellosis</td>
<td>Shigella and Salmonella</td>
<td>Bacteriophage therapy was represented in a combination of phages and antibiotics. Treatment of phages and antibiotics was reported to be effective in treating cases where antibiotics alone were ineffective.</td>
</tr>
<tr>
<td>Perepato et al. (40)</td>
<td>Inflammatory urologic diseases</td>
<td>Staphylococcus, E. coli, and Proteus</td>
<td>Adopted phages were used to treat acute and chronic urogenital inflammation in 67 patients. The efficacy of treatment was 92% (marked clinical improvements) and 82% (bacteriologic clearance).</td>
</tr>
<tr>
<td>Sikandar et al. Meisneriai (41)</td>
<td>Peritonitis, osteomyelitis, lung abscesses, and post-surgical wound infections</td>
<td>Staphylococcus, Strptococcus, and Proteus</td>
<td>Phages administered subeutaneously or through surgical drains in 236 patients having antibiotic-resistant infections eliminated the infections in 92% of the patients.</td>
</tr>
<tr>
<td>Sikandar et al. (46)</td>
<td>Infectious abscesses (chirotic, phlegmonous, dermolic, and conjunctivitis)</td>
<td>Staphylococcus, Streptococcus, E. coli, Proteus, enterococci, and P. aeruginosa</td>
<td>A total of 1,260 patients having infectious abscesses were treated with phages (930 patients), antibiotics (240 patients), or a combination of phages and antibiotics (96 patients). Clinical improvement was observed in 86%, 48%, and 66% of the cases, respectively.</td>
</tr>
<tr>
<td>Slopek et al. (50–58)</td>
<td>Gastrointestinal tract, skin, head, and neck infections</td>
<td>Staphylococcus, Pseudomonas, E. coli, Klebsiella, and Salmonella</td>
<td>A total of 350 patients were treated with phages. The overall success rate of phage treatment was 94%.</td>
</tr>
<tr>
<td>Strij et al. (67)</td>
<td>Cerebral meningitis</td>
<td>K. pneumoniae</td>
<td>Orally administered phages were used successfully to treat meningitis in a newborn (after antibiotic therapy failed).</td>
</tr>
<tr>
<td>Telkasher et al. (86)</td>
<td>Bacterial dysentery</td>
<td>E. coli and Proteus</td>
<td>Phages were used together with bifidobacteria to treat bacterial dysentery in 39 immunosuppressed leukemia patients. The superiority of treatment with phage-bifidobacteria over antibiotics was reported.</td>
</tr>
<tr>
<td>Weber-Dahnowa et al. (74)</td>
<td>Suppurative infections</td>
<td>Staphylococcus and various gram-negative bacteria</td>
<td>Orally administered phages were used successfully to treat 56 patients, and the phages were found to reach the patients' blood and urine.</td>
</tr>
<tr>
<td>Zhukova-Perepato et al. (77)</td>
<td>Suppurative surgical infections</td>
<td>Staphylococcus, Streptococcus, E. coli, and Proteus</td>
<td>The superiority of adapted phages (phages selected against bacterial strains isolated from individual patients) over commercial phage preparations was reported in treating 65 patients having suppurative infections.</td>
</tr>
</tbody>
</table>

Source: Sulakvelidze et al. 2001

In 2009, AmpliPhi's wholly owned subsidiary, Biocontrol, conducted what is believed to be the first double-blind placebo-controlled, randomized Phase 2 clinical trial of bacteriophage therapy for the treatment of chronic ear infections by antibiotic-resistant P. aeruginosa (Wright et al., 2009). Positive results were reported demonstrating decreased levels of P. aeruginosa in the ear and improvement of clinical conditions with a single input dose of 2.4 ng of bacteriophage preparation.

While the trial was small (n=24), changes from baseline at the end of the trial in the test group (n=12) were statistically significant for both clinical condition (p=0.001) and bacterial load (p=0.016). Difference between test and control (n=12) groups was statistically significant on day 21 for bacterial count (p=0.0365). While encouraging, the results will need to be validated in larger well-controlled trials.
...Antibiotics vs. Bacteriophage Therapy...

While the worldwide market for antibiotics is extremely large, estimated to be approximately $40 billion in 2015, there is intense competition. Market share is determined by a number of characteristics, including a convenient dosage form, enhanced efficacy, reduced side effects, and/or a novel mechanism of action compared to the current treatment options. We believe that AmpliPhi's bacteriophage therapies hold many of these characteristics, and thus have a number of advantages over current antibiotic therapies. Advantages include:

✓ **Multiple modes of application:** Bacteriophage therapy has the potential to be utilized as 1) an inhalation for the treatment of lung infections, 2) as an orally ingested medication for the treatment of gastrointestinal infections and, 3) as a topical medication for the treatment of skin infections. This is especially important in the treatment of MRSA infections, as almost all antibiotics utilized for the treatment of MRSA infections have to be administered intravenously, while bacteriophage therapy could be applied as a topical wound dressing (through a hydrogel or cream) thus simplifying the treatment process for patients.

✓ **Less severe side effects:** All antibiotics have side effects, with the most common being gastrointestinal effects such as nausea, vomiting, and diarrhea. In addition, systemic complications including allergic reaction are common with antibiotics. Bacteriophages have been administered to humans for more than 80 years in Eastern Europe and the former Soviet Union 1) orally, in tablet and liquid formulation, 2) rectally, 3) locally (skin, eye, ear, nose, etc…), 4) as aerosols or intrapleural injections and, 5) intravenously, although to a lesser extent than the other methods. There have been virtually no reports of serious side effects associated with bacteriophage use. In addition, humans are constantly exposed to bacteriophages as non-polluted drinking water has been reported to have approximately $2 \times 10^8$ bacteriophages per mL (Bergh et al., 1989), and they are regularly consumed in foods.

✓ **Localized and highly specific effect:** Another drawback to antibiotic therapy is that the antibiotic effect is not specific, but rather it affects all bacteria inside the patient, including the beneficial microbiome that resides in the gut. Bacteriophage therapy is highly specific; in fact, most bacteriophages will only infect certain strains of a particular bacterial species. Treatment is analogous to a targeted cancer therapy vs. broad-scale chemotherapy; a laser-guided bacterial smart-bomb so to speak. This means that not only will the bacteriophages not affect other microorganisms residing in the patient, but that the treatment will localize at the site of the targeted infection.

✓ **Very low doses:** Since phages self-replicate, they can be administered in very low doses. They are outstanding at seeking out and targeting their bacterial host. During the accumulation phase, the number of bacteriophages can be increased by over 1000-fold. Once the host bacteria is lysed, newly created bacteriophages are capable of continuing the target-multiple-destroy cycle until all infecting bacterial have been eliminated. Picture a small Navy SEAL Team deep inside enemy territory that can move undetected, but then self-replicate 1000-fold when the battle begins. Pretty neat stuff!

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Source: AmpliPhi BioSciences Corp.
Can treat antibiotic-resistant strains: Antibiotic resistance is fast becoming a significant threat to human health and adds a significant burden to the U.S. healthcare system. Bacteriophages attack bacteria in a unique mechanism that is completely differentiated from antibiotics, thus they are even effective against multi-drug resistant bacterial strains offering an alternative therapeutic option for these difficult to treat infections.

Unique mechanism of action makes resistance less likely: While resistance to bacteriophage infection is known to occur, bacteriophages and bacteria have been co-evolving for millions of years, thus every time a bacterium develops a mutation that renders it immune to one type of bacteriophage, it is likely that the a different bacteriophage will subsequently evolve a new mechanism to allow for infection.

Given the preceding, WE CONCLUDE that there is a pressing need for alternative treatments for bacterial infections, and that bacteriophage therapy has enough supporting data to suggest that it could be both safe for human use and efficacious as a therapeutic agent, thus warranting the continued development of these novel antimicrobial treatments.

**AmpliPhage-001**

AmpliPhi is developing AmpliPhage-001 (“AP-001”) for the treatment of *Pseudomonas aeruginosa* infections in patients suffering from cystic fibrosis (CF), a population susceptible to chronic lung infections due to overgrowth of *P. aeruginosa* that leads to lung damage and eventually death.

...Background On Cystic Fibrosis...

Cystic Fibrosis (CF) is an autosomal recessive genetic disorder that affects close to 30,000 individuals in the U.S. and a total of 70,000 people worldwide. The hallmark of CF is a thick, sticky mucus build up in various organs throughout the body. Typically, mucus is a slippery, water substance produced by tissues that line organs and body cavities, such as the lungs and nose. However, due to abnormal sodium and chloride transport in the lungs, pancreas, liver, and digestive tract, patients suffering from CF have mucus that is thick and sticky and leads to blockages of the airways in the lungs and ducts in the pancreas (Boucher, 2004). The name refers to the characteristic scarring (fibrosis) and cyst formation seen in the pancreas.

CF is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR), a gene found on chromosome #7. The typical protein produced by the CFTR gene contains 1,480 amino acids, however in 70% of CF patients worldwide, and 90% of patients in the U.S., there is a loss of the amino acid phenylalanine at the 508th position on the protein (Bobadilla et al., 2002). This mutation, termed ΔF508 (Δ meaning deletion), causes the protein to fold improperly thus resulting in its degradation.

The CFTR protein is a chloride ion channel that is involved in creating sweat, digestive juices and mucus. When the protein is either not present or not functioning properly, there is a buildup of chloride ions inside the cells in the airway. While no one knows exactly how this leads to a buildup of thick mucus, one theory suggests that the malfunctioning CFTR protein leads to a paradoxical increase in sodium and chloride uptake, which in turn leads to increased water reabsorption, creating dehydrated and thick mucus.

The most serious complication associated with the disease is difficulty in breathing due to recurrent lung infections. Lung disease in patients with CF results from airway blockage and resulting inflammation. The build up of mucus is an ideal environment for bacteria to grow, and the inflammation and repeated infections result in injury and structural changes to the lungs. Early stages of the disease are characterized by excessive coughing, phlegm production and shortness of breath. These symptoms are exacerbated when the overgrowth of bacteria leads to pneumonia. *Staphylococcus aureus*, *Haemophilus influenza* and *Pseudomonas aeruginosa* are the three most common organisms that cause lung infections in CF patients (Figure 2).

The lungs of CF patients are colonized by bacteria starting at a very young age. The combination of bacterial growth and thick mucus leads to the production of bacterial microenvironments known as biofilms, which are an aggregate of microorganisms in which cells stick to each other and are embedded within a self-produced matrix of extracellular polymeric substance. Biofilms are difficult both for the immune system and for antibiotics to penetrate, thus leading to reduced treatment efficacy. Early in life, *S. aureus* and *H. influenzae* are the most common bacterial strains found in CF patients lungs. However, by the age of 18, 70% of CF patients will harbor *P. aeruginosa* (CFF 2012 Patient Registry Report). The spread of bacteria between CF patients is so common that they are routinely isolated from one another in a healthcare setting.
...**Current Treatment Options for CF...**

There is no cure for CF, and median survival in the U.S. is 38 years of age. However, there are several treatments available to alleviate symptoms of the disease. In fact, management of CF has improved remarkably in the last 70 years; while infants born with CF in the 1940’s were not expected to live much past their first birthday, infants born today with CF are likely to survive well into adulthood. The majority of CF-related morbidity and mortality is the result of chronic pulmonary sepsis, with the major pathogen in CF lung disease being *P. aeruginosa*. The following table list treatments that are typical for most CF patients at various stages of the disease:

### Table 2: Management of Cystic Fibrosis Lung Disease.

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Pulmonary status</th>
<th>Aim</th>
<th>Management</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Pneumonia</td>
<td>Mucus drainage; prevent infection; maintain good lung function</td>
<td>Segregation and coughing to prevent cross infection; airway clearance techniques (physiotherapy and adjuncts, mucolytics such as fl onError); hypotonic saline; prophylactic antibiotics (usually against Streptococcus most commonly Pseudomonas or co-annulosa in UK); influenza vaccination usually recommended; ciprofloxacin or co-amoxiclav.</td>
<td>Segregation of patients with organisms such as Boc or epidemic strains of <em>Ps</em> is common (practice more variable with regard to other strains of <em>Ps</em>, <em>Sin</em>, or <em>Hi</em>); for both ciprofloxacin and hypotonic saline evidence favours shorter to medium term benefit (as long term or survival data); prophylactic antibiotics decrease incidence of infection with <em>Ss</em> (long term benefit not well defined); increase in infection with <em>Ps</em> seen limited to trials including broad spectrum cephalosporins. Eradication achieved in 80-90%, but uncertain long term benefit.</td>
</tr>
<tr>
<td>Intermittent isolation of organisms</td>
<td>Eradication of infection</td>
<td>Suppression of bacterial load and thus limitation of inflammatory response</td>
<td>Depends on organism (<em>Ps</em> nebulised tobramycin or colistin)</td>
<td><em>Ps</em>: median term benefit, <em>Ss</em>: uncertain effects on survival; now, faster nebuliser devices (such as e-flow and Neb) available.</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Chronic infection with usual organisms (<em>Pn</em>, <em>Bc</em>, <em>Hi</em>)</td>
<td>Treat infective exacerbations</td>
<td>Oral or intravenous antibiotics appropriate for culture</td>
<td>Efficacy &amp; symptomatic use.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce inflammation</td>
<td>Iloprostenol; macrolide antibiotics (azithromycin)154</td>
<td>Iloprostenol: limited use in much of Europe26 (used more often in US); azithromycin: good evidence for short-term medium term benefit, but mechanism of action uncertain (anti-inflammatory properties thought likely); no evidence supporting a role for corticosteroids except in treating allergic bronchopulmonary aspergillosis.</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Davies et al. 2007

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*Bc* = Burkholderia cepacia complex; *Ps* = Pseudomonas *aeruginosa*; *Ss* = Staphylococcus aureus; *Hi* = Haemophilus influenzae; *Sm* = Stenotrophomonas maltophilia; *Ax* = Alcaligenes xylosoxidans.
Antibiotics are the primary therapeutic agent for lung infections in CF patients, and in fact most CF patients are on some type of antibiotic at all times in an attempt to prevent development of pneumonia. Inhaled antibiotics are recommended as a maintenance therapy against chronic *P. aeruginosa* infections (Döring et al., 2000). While inhaled colistin was the main inhaled antibiotic for the past couple of decades, the introduction of nebulized tobramycin has yielded an improvement in lung function with reduced rates of exacerbations and hospitalizations (Ryan et al., 2011). The downside to this treatment is an increase in antibiotic resistant organisms, tinnitus, voice alterations, hemoptysis and cough. Long-term oral antibiotics are another treatment option, with studies showing patients on oral azithromycin for one year have improved lung function and reduced hospitalizations (Hansen et al., 2005).

There are a number of treatment options currently available for combating *P. aeruginosa* infections in CF patients, including some that have been recently approved:

- **Azithromycin**: This is a broad-spectrum antibiotic that has been shown to be effective in CF patients who harbor *P. aeruginosa* in their lungs. Azithromycin does not kill *P. aeruginosa*, but is thought to inhibit its growth and may also have anti-inflammatory effects. Generic versions of azithromycin tablets are available but the liquid suspension is only available from Pfizer under the name Zithromax®.

- **TOBI®**: An inhaled form of the antibiotic tobramycin that is approved for use in CF patients above the age of six. TOBI® has been shown to increase pulmonary function along with a significant reduction of *P. aeruginosa* in sputum. First approved by the FDA in 1997, it has been available as a generic since November 2013.

- **TOBI® Podhaler™**: Approved by the FDA in 2013, this is a non-nebulized formulation of tobramycin that delivers the drug into the patient's lungs via a pocket-sized dry powder inhaler and does not require the use of a nebulizer. According to Novartis, this saved patients approximately 13 hours per treatment cycle in a Phase 3 clinical study.

- **Cayston®**: Cayston® is an inhalation form of the antibiotic aztreonam, which Gilead received FDA approval for in 2010. Phase 3 results showed that Cayston® improved respiratory symptoms in CF patients with *P. aeruginosa* infections by approximately 10% over placebo-treated patients.

- **Colobreathe® Dry Powder Inhaler®**: Approved by the European Medicines Agency (EMA) in 2012, this device delivers a dry-powder formulation of colistimethate sodium via the Turbospin® inhaler, saving the patients approximately 30 minutes per dosage.

In addition, there are a number of products in various stages of clinical testing:

- **Arikace®**: Insmed is developing a liposomal formulation of amikacin designed for inhalation. Results from a Phase 3 trial of the drug in Europe and Canada showed it achieved its primary endpoint of non-inferiority to TOBI®. A Phase 3 extension study is currently ongoing. The drug has received orphan designation from the EMA, and a regulatory filing with the EMA and Health Canada is expected in mid-2014.

- **Aeroquin®**: Aeroquin® is an inhaled form of the antibiotic levoflaxin. It was compared to TOBI® in a Phase 3 trial that consisted of three 28-day treatment cycles. The primary endpoint of the trial, non-inferiority to TOBI® as measured by change in respiratory function, was met. Apatalis Pharma, Inc. is currently in discussions with the FDA regarding the results of the Phase 3 study.

- **Fosfomycin/Tobramycin for Inhalation (FTI)**: FTI is an inhalation formulation of the two antibiotics fosfomycin and tobramycin. Gilead achieved successful results in a Phase 2 trial evaluating the efficacy of FTI in CF patients with *P. aeruginosa* infections. CurX Pharmaceuticals licensed FTI from Gilead in Feb. 2014 and plans on initiating a Phase 3 trial for its continued development as a CF treatment.

- **KB001-A**: A monoclonal antibody being developed by KaloBios that targets the Type Three Secretion System (TTSS) of *P. aeruginosa*. The TTSS enables the bacteria to kill cells of the immune system, and it is thought that blocking TTSS will lead to a reduction in inflammatory cytokine release and a decrease in overall lung inflammation. The drug is currently in a Phase 2 trial for CF patients with *P. aeruginosa* infection.
All of the antibiotics listed above have similar side effects such as they can lead to the development of antibiotic resistant organisms and cause gastrointestinal side effects such as nausea, vomiting and diarrhea. In addition, none of the treatments listed above have been shown to eradicate chronic *P. aeruginosa* from the lungs of patients. Thus, there exists a serious unmet medical need in the treatment of *P. aeruginosa* infections in CF patients, especially for a treatment that could potentially eradicate the organism from the lungs of patients.

**...Kalydeco® & VX-809 / VX-661...**

Vertex Pharmaceuticals (Nasdaq: VRTX) is developing three compounds for the treatment of CF: Kalydeco®, VX-809 and VX-661. Kalydeco® (ivacaftor) is a drug approved for the treatment of CF in a certain subset of patients, specifically those that harbor the G551D mutation in the CFTR gene. This mutation results in the amino acid glycine (G) being substituted for aspartic acid (D) at position 551 of the CFTR protein and accounts for approximately 4-5% of all cases of CF. This mutation results in a nonfunctional CFTR protein on the cell surface that is unable to properly transport chloride ions across the cell membrane. The drug works by binding to the CFTR protein and improving the flow of chloride through the ion channel.

Kalydeco® is continuing to be tested in additional CF patient populations that harbor different mutations of the CFTR gene. In December 2013, Vertex announced that a Phase 3 trial examining the effect of Kalydeco® in CF patients harboring the R117H mutation had failed to meet its primary endpoint. This mutation accounts for approximately 2% of CF patients. In February 2014, Vertex announced that Kalydeco® was approved for treating patients harboring an additional eight mutations in the CFTR gene, with approximately 150 people in the U.S. having one of those mutations. Vertex reported $371.3 million in sales of Kalydeco® in 2013 and expects sales to be approximately $470-500 million in 2014.

VX-809 (lumacaftor) and VX-661 are being tested in patients who have the ΔF508 mutation. Lumacaftor and VX-661 belong to a class of compounds known as “correctors” that attempt to restore proper processing of the ΔF508 CFTR protein, preventing its degradation and allowing for its proper translocation to the cell membrane. Lumacaftor was tested in two Phase 3 clinical trials in combination with Kalydeco®. Both studies met their primary endpoint with statistically significant improvements in lung function. Vertex estimates that upon approval for use in patients who have the ΔF508 mutation, sales of Kalydeco® and VX-809 could top $6 billion a year. VX-661 is currently being tested both alone and in combination with Kalydeco® in a Phase 2 clinical trial.

**...A New Treatment Option...**

AP-001 is a mixture of bacteriophages that specifically target *P. aeruginosa*. To develop this product, AmpliPhi created a global “diversity” panel of relevant *P. aeruginosa* clinical isolates from CF clinics around the globe. Clinical isolates are bacteria cultured from infected patients. This diversity panel was screened against the company’s bacteriophage library that was isolated and characterized according to their proprietary discovery and development platform. Studies showed that a mixture of a few types of bacteriophages was able to effectively kill up to 100% of the targeted bacteria *in vitro*. Furthermore, the bacteriophage mix was selected to exhibit a high degree of “complementation,” defined as the number of bacteria targeted by more than one bacteriophage in the product. High complementation is an important factor in preventing bacteria from developing resistance to bacteriophage products.

A number of preclinical studies have been performed to test the effectiveness of AP-001 *in vivo*. One such study conducted at the Institut Pasteur demonstrated that the bacteriophage mixture was able to reach the lungs after oral administration in mice infected with *P. aeruginosa*. This is important, as it offers the added benefit of both oral and intravenous administration. The bacteriophage levels increased between two and six hours post-administration, showing that not only can bacteriophages reach the lungs after oral dosing, but also that they retain the ability to infect and multiply in target bacteria.

A study performed at the Institut Pasteur involved three groups of eight mice infected with a virulent strain of *P. aeruginosa* (containing a luminescent reporter gene) and treated with placebo (PBS), ciprofloxacin (an antibiotic), or AP-001. The model was optimized for the antibiotic used, thus full recovery of mice treated with the antibiotic was expected. Figure 3 shows the results of the study as measured by light intensity showing active *P. aeruginosa* infection. By hour 24, the surviving untreated animals (Group 1) were sacrificed as the infection had spread and in some cases had already proved lethal, whereas the two treatment groups (Group 2, AP-001; and Group 3, antibiotic) demonstrated effective reduction of the active infection.
In addition, it was shown that the bacteriophage mix effectively lowered the bacterial counts in the mouse lung comparable to antibiotic treatment. Lastly, the bacteriophages were shown to have replicated to a high level in the infected lung, indicative of biological activity. A separate in vivo study of P. aeruginosa infection of the mouse lung was undertaken whereby it was demonstrated that AP-001 reduced bacterial levels upon simultaneous administration and also when administered 24 hours post-bacterial infection using Pa01, a standard strain of P. aeruginosa (Figure 4).

![Figure 3: Preclinical Mouse Study](source)

**Figure 3: Preclinical Mouse Study**

In vivo data at 24h after simultaneous bacteria-phage administration (p<0.0001)

In vivo data at 48h with phage administered 24h post bacterial infection (p<0.0001)

**Fig 4: Preclinical Post-Infection data**

![Figure 4: Preclinical Post-Infection data](source)

**Market Opportunity & Development Plans**

The total CF population in the United States is estimated to be approximately 30,000 individuals, with another 40,000 people afflicted with the disease in the rest of the world. While a number of different organisms are known to cause lung infections in CF patients, P. aeruginosa is the most prevalent bacterial infection found in CF patients over 18 years of age, with approximately 70% of patients harboring the bacteria. These infections are known to be highly resistant to antibiotic treatment, and eradicating P. aeruginosa from patients' lungs once established is extremely difficult and very rarely occurs. Part of the reason for this is that P. aeruginosa acquires resistance to antibiotics very quickly. Another reason is the development of biofilms, which are organized structures of microorganisms that limit access of antibiotics to covered tissues. The thick, sticky mucus buildup associated with CF is the ideal environment for biofilm development.

While bacteriophages hold a number of advantages over antibiotics, two advantages that directly relate to the treatment of P. aeruginosa infections in CF patients are the fact that bacteriophages infect bacteria in a manner completely separate from how antibiotics exert their effect, and thus even antibiotic-resistant P. aeruginosa are potentially susceptible to bacteriophage treatment, and that bacteriophages can infect bacteria growing in biofilms. These two points mean that the total number of potential patients eligible for treatment with AP-001 will represent a sizable portion of the total CF patient population. We estimate this to be approximately 20,000 patients.
Inhaled tobramycin has been the first-line defense for *P. aeruginosa* infections in CF patients for a number of years, and this will likely continue with the recent introduction of TOBI® Podhaler™. Novartis reported sales of $387 million in 2013 for TOBI® and TOBI® Podhaler™. However, these numbers could be reduced going forward with the introduction of generic tobramycin in late 2013. Sales of Cayston® were $77 million in 2011, the last year for which Gilead gave detailed sales figures for that drug. Colobreathe® was first available for sale in the EU in April 2013, with sales of colistin and colomycin totaling $44.4 million in the United Kingdom in 2013.

AP-001 will not necessarily replace the aforementioned antibiotics, but could potentially be used alongside them. As mentioned previously, one of the advantages of bacteriophage therapy is that it is able to treat bacterial infections that involve a biofilm. One potential use of AP-001 is an adjunct therapy, whereby it is administered in conjunction with an antibiotic such that AP-001 breaks down the biofilm allowing the antibiotic greater access to the infected areas of the lung. Thus, AmpliPhi would not necessarily seek to take market share from the antibiotic therapies, but instead seek to form a niche market in the CF treatment space that complements and piggy-backs on already approved and commonly-used therapies.

AmpliPhi is planning to move the CF program into additional preclinical testing in preparation for a Phase 1/2 study to start in 2015. The Phase 1 portion of the study will be utilized to test whether the bacteriophage mixture can be safely administered to healthy volunteers. In addition, if no safety signal is observed, they will test for signs of efficacy in the Phase 2 portion of the study by testing for a decrease in bacterial counts in mild to moderate CF patients, which will set the stage for later-stage trials.

**AmpliPhage-002**

AmpliPhi is developing AmpliPhage-002 ("AP-002"), a bacteriophage mixture intended to effectively treat acute and chronic wound and skin infections caused by *Staphylococcus aureus*, including infections caused by methicillin-resistant strains of the same bacteria (MRSA).

...*Staphylococcus aureus*...

*Staphylococcus aureus* is a bacterium that is frequently found in the human respiratory tract and skin. Epidemiological studies have identified three cohorts of carriage in healthy subjects; approximately 20% of people are persistent carriers, 60% are intermittent carriers and 20% almost never harbor *S. aureus* (Kluytmans et al., 1997).

*S. aureus* is not always pathogenic; however, it is a common cause of skin infections, respiratory disease and food poisoning.

The pathogenicity of *S. aureus* is the result of several types of virulence factors. Different strains are capable of secreting several exotoxins, proteins expressed on the cell surface or secreted, which act to convert local host tissues into nutrients required for bacterial growth. The following are exotoxins produced by *S. aureus* that give rise to different diseases:

- **Pyrogenic toxin superantigens (PTSAgs):** These groups of exotoxins have superantigen activities, including the non-specific activation of large numbers of T-cells and subsequent overproduction of a large number of cytokines, which can induce toxic shock syndrome (TSS). Proteins classified in this group include toxic shock syndrome toxin-1 (TSST-1) and the staphylococcal enterotoxins. TSST-1 causes TSS by inducing the release of large amounts of the cytokines interleukin-1, interleukin-2 and tumour necrosis factor. Enterotoxins are potent emetics, and their ingestion causes a self-limiting severe gastroenteritis characterized by vomiting, diarrhea and abdominal pain. The toxins are quite stable, as they can remain active even after the contaminating bacteria have been killed and they can withstand boiling for a few minutes. While the total incidence is unknown, staphylococcal enterotoxins are thought to be the most common cause of food poisoning in the U.S.

- **Exfoliative toxins:** These proteins are excreted by *S. aureus* and cause detachment within the epidermal layer that manifests itself as staphylococcal scaled skin syndrome (SSSS). The disease is characterized by the formation of fluid filled blisters on the face and other intertriginous areas of the body. The disease is most common in children under 6 years of age and often occurs as epidemics in hospital nurseries. With proper treatment the prognosis of children with SSSS is excellent.
The treatment of choice for *S. aureus* is penicillin, however in most countries penicillin resistance is extremely common. Thus, first-line treatment for most *S. aureus* infections is a penicillinase-resistant β-lactam antibiotic such as oxacillin. Antibiotic resistance in *S. aureus* was uncommon when penicillin was first introduced; in fact the petri dish that Sir Alexander Fleming first observed the antibacterial activity of the *Penicillium* fungus was growing a culture of *S. aureus*. However, by 1950, 40% of *S. aureus* isolates were penicillin resistant and by 1960 the rate had grown to 80% (Chambers, 2001).

Resistance to penicillin is due to the activity of the enzyme penicillinase, which cleaves the β-lactam ring of the penicillin molecule. Penicillinase-resistant β-lactam antibiotics include methicillin, oxacillin and flucoxacillin. *S. aureus* strains that have acquired resistance to methicillin have an altered penicillin-binding protein (PBP2a) that has lower affinity for binding β-lactam antibiotics, thus rendering them ineffective. Strains that have acquired this resistance are referred to as methicillin-resistant *S. aureus* (MRSA).

**...MRSA Infections & Treatment Options...**

The U.S. CDC has grouped antibiotic resistant organisms by threat level: Urgent, Serious, or Concerning. MRSA is labeled with a threat level of Serious, with bacteria under this label being a serious concern and requiring prompt sustained action to ensure the problems associated with them do no grow. MRSA causes a range of illnesses including skin and wound infections, pneumonia and blood infections that cause sepsis. They are one of the most common hospital-acquired infections (HA-MRSA), and are typically associated with invasive procedures or devices, such as surgeries, intravenous lines, or artificial joints.

A second type of MRSA infection is one that afflicts otherwise healthy people and is known as community-associated MRSA (CA-MRSA). This type of infection often begins as a painful skin boil and is spread by skin-to-skin contact. At risk individuals have been identified and include high school wrestlers, child care workers, and people who live in crowded conditions.

MRSA infections can progress rapidly within 1-2 days of the initial symptoms appearing. After 3 days, MRSA can attack tissues in the body and become more difficult to treat. Approximately 75% of CA-MRSA infections are localized to the skin and soft tissue and are typically treated effectively. However, some CA-MRSA strains show enhanced virulence causing them to spread more rapidly through the body and causing more severe illnesses such as TSS and necrotizing pneumonia.

The Infectious Disease Society of America (ISDA) has published guidelines for the treatment of the most common clinical syndromes seen with children and adults infected with MRSA (Liu et al., 2011). One of the most common MRSA infections is of the skin and soft tissue (STTI). Primary treatment of STTI caused by CA-MRSA is an incision and drainage of the infected site. The use of antibiotics is based on a number of factors including how severe the disease is, whether there is rapid progression of cellulitis, any other comorbidities, if the abscess is in an area that is hard to drain and whether the patient is treated on an outpatient basis or while hospitalized.

Both CA-MRSA and HA-MRSA are resistant to the β-lactam antibiotics. Thus, treatment of MRSA infections is implemented using one of the following antibiotics:

- **Vancomycin**: This antibiotic is typically utilized as a “last-resort” treatment for MRSA infections as a means to prevent the development of resistance. However, vancomycin-resistant strains of *S. aureus* are beginning to emerge. Thus, newer antibiotics, such as those that follow, are typically being used in place of vancomycin.

- **Linezolid (Zyvox®)**: Approved for the treatment of STTI and pneumonia caused by MRSA. It is a bacteriostatic agent, meaning that it inhibits bacterial growth, as opposed to a bacteriocidal agent that kills bacteria. It is typically administered for short periods due to adverse side effects associated with long-term use, including bone marrow suppression and low platelet counts. It can be administered either intravenously (IV) or orally. The average cost for a one-week course of treatment is approximately $1,400.

- **Daptomycin (Cubicin®)**: This is a bacteriocidal agent with a unique mechanism of action in that it inserts into the cell membrane disrupting multiple aspects of bacterial cell membrane function. It is approved for the treatment of STTI but not pneumonia. It is administered intravenously once daily for 7 to 14 days. The average cost for daptomycin treatment is approximately $2,000.
- **Quinupristin/Dalfopristin (Synercid®):** This is a combination therapy consisting of two antibiotics that is administered IV twice daily. This medication is typically not utilized as a first-line treatment due to the side effects that are common with its use. A 10-day treatment course costs approximately $3,000.

- **Tigecycline (Tygacil®):** This is a tetracycline derivative that is given IV twice daily for 5-14 days. It has been shown to be at least as effective as vancomycin in treating STTI. The average cost for a two-week course of treatment is approximately $1,500.

- **Telavancin (Vibativ®):** This drug is a derivative of vancomycin approved by the FDA in 2009 for the treatment of STTI. It is administered IV once daily for 10-14 days. With a cost of approximately $180 per day, a typical two-week treatment course costs $2,500.

- **Ceftaroline fosamil (Teflaro®):** A cephalosporin antibiotic that is active against STTI caused by MRSA and first approved by the FDA in 2010. It is administered IV twice daily for 5-14 days. A full two-week treatment costs approximately $1,200.

Aside from linezolid, which does come in an oral dosage formulation, all of the other antibiotics listed must be administered intravenously. This is a serious drawback to treatment and makes treating patients on an outpatient basis difficult. The FDA recently approved a second-generation linezolid product, tedizolid, for the treatment of acute bacterial skin and skin structure infections. Tedizolid offers similar efficacy to linezolid with less-frequent dosing and the potential for less resistance due to the drugs bacteriocidal characteristics. However, as with other antibiotics, there are side effects for each of these medications that include nausea, diarrhea, abdominal pain, rash, dizziness and headache.

### Market Opportunity & Development Plans...

AmpliPhi is developing AP-002 for the treatment of acute and chronic skin infections caused by *S. aureus*, including infections caused by MRSA. The total market for MRSA infections was estimated by Global Data to be more than $2.7 billion in 2007 with it forecast to grow to $3.5 billion by 2019. The CDC estimates that there are approximately 80,000 MRSA infections in the United States each year with over 11,000 deaths attributable to these infections. MRSA is the leading cause of hospital acquired infections and costs the U.S. healthcare system an estimated $3-4 billion each year and accounts for over 8 million additional hospital days. Pfizer recorded approximately $1.35 billion in Zyvox® sales in 2013. We estimate tedizolid sales will peak at $750 million worldwide, even with the expected patent expiration of linezolid in 2015.

One potential market for AP-002 could be with the U.S. Army. A study published in *Epidemiology & Infection* in 2010 tracked the monthly incidence of laboratory-confirmed MRSA from 2002-2007 in service members and trainees at Fort Benning, Georgia. The results of the study showed that by 2007 approximately 67% of the *S. aureus* strains analyzed were MRSA, with approximately 82% of those cases noted as CA-MRSA. Given the close living conditions at service bases and the high incidence of MRSA infections, members of the armed forces would seem to be a logical target population for treatment with AP-002.

AmpliPhi entered into a Collaborative Research and Development Agreement (CRADA) with the United States Army Medical Research and Material Command (USAMRMC) and the Walter Reed Army Institute of Research (WRAIR) that will focus on developing and commercializing bacteriophage therapeutics to treat *S. aureus, E. coli* and *P. aeruginosa* infections. In connection with the CRADA, AmpliPhi submitted a Pre-IND briefing package to the FDA to obtain their feedback on the Chemistry, Manufacturing and Controls (CMC) program and plans for the first human study with AP-002.

The company has recently completed construction on a wholly owned current good manufacturing practice (cGMP) facility in Ljubljana, Slovenia in order to produce bacteriophage product for clinical trials. The facility is approximately 4,000 sq. ft. and will be utilized to produce cGMP product through Phase 3 and initial commercialization. The facility recently passed a cGMP audit, which means that it is most likely to pass an FDA inspection. The Slovenian authorities will be conducting an inspection of the facility soon, and this inspection will be conducted according to EMA standards.

The FDA has endorsed the plan for progressing bacteriophage therapy to the clinic, specifically agreeing to AmpliPhi's manufacturing process, product specifications and the absence of any need for non-clinical toxicology to initiate the Phase 1 study. AmpliPhi plans to file an IND in the 4th quarter of 2014 and subsequently initiate a Phase 1 feasibility and safety study with AP-002 for the treatment of *S. aureus* no later than early 2015 followed by a
potential Phase 2 study of *S. aureus* wound infections. Ultimately, we see the development of AP-002 going the route of incorporation into a hydrogel or cream for topical administration. This administration would be particularly effective for skin infections and can be used in compliment to many of the oral or IV antibiotics noted above.

**AmpliPhage-004**

AmpliPhi is developing AmpliPhage-004 (“AP-004”) for the treatment of intestinal infections caused by *Clostridium difficile*, an organism that is part of some individuals normal gut flora, but can become an opportunistic infection after disruption to the normal flora, typically after taking a standard course of antibiotics. AP-004 is being developed in collaboration with the University of Leicester, which has yielded a proprietary mixture of bacteriophages that have greater than 90% coverage of clinically relevant strains of *C. difficile*.

...*Clostridium difficile*...

*Clostridium difficile* is a Gram-positive spore-forming bacterium that is best known for causing antibiotic-associated diarrhea. Some individuals harbor *C. difficile* as a normal part of their gut flora, however overgrowth of *C. difficile* and subsequent infection can occur when competing bacteria in the gut have been destroyed, as typically happens after a standard course of antibiotics. These infections typically occur in hospitalized or recently hospitalized patients who have been exposed to antibiotics. In addition, *C. difficile* can produce spores during times of stress, and these spores are capable of surviving extreme conditions such as high heat and household cleaners.

The CDC has designated *C. difficile* as an organism with a threat level of Urgent, with bacteria in this category representing an immediate public health threat that requires urgent and aggressive action. There are approximately 337,000 infections caused by *C. difficile* each year that result in 14,000 deaths. The number of deaths related to *C. difficile* infections increased 400% between 2000 and 2007, with more than 90% of deaths occurring in people aged 65 and older. In addition, *C. difficile* infections lead to $1 billion in excess health care costs each year. While antibiotic resistance is not yet a pressing concern with *C. difficile*, in 2000 a strain emerged that was resistant to fluoroquinolone antibiotics, which are commonly used to treat other infections.

Symptoms of *C. difficile* infection (CDI) are significant diarrhea, abdominal pain, fever and a distinctively foul stool odor. Pseudomembranous colitis (PMC) is the most severe form of the illness that results from a severe inflammatory response to *C. difficile* toxins. The pathogenicity of *C. difficile* is caused by multiple toxins, the best characterized of which are enterotoxin (*Clostridium difficile* Toxin-A) and cytotoxin (*Clostridium difficile* Toxin-B). The toxins are co-produced, with Toxin-A disrupting the cell cytoskeleton and Toxin-B activating signal transduction pathways of the immune system resulting in the diarrhea and inflammation associated with the illness. Treatment of CDI typically involves a course of antibiotics selected from one of the following:

- **Metronidazole** (Flagyl®): First-line treatment for mild to moderate CDI.
- **Vancomycin** (Vancocin®): Second-line treatment or first-line treatment for severe CDI.
- **Fidaxomicin** (DIFICIDE®): A narrow spectrum macrocyclic antibiotic that is non-systemic (minimally absorbed into the bloodstream), bactericidal and results in little disruption to the normal intestinal flora.

...*Market Opportunity & Development Plans*...

The market for *C. difficile* therapies exceeded $314 million in 2011 and is forecast to grow to more than $500 by 2019, according to Global Data. AmpliPhi has entered into collaboration with the University of Leicester to develop a bacteriophage therapy that targets and kills all toxin types of *C. difficile*. Researchers at the University of Leicester have identified bacteriophages that cover >90% of clinically relevant ribotypes and have >70% complementation.
The plan is to develop an orally administered bacteriophage treatment, which the company believes is well suited to treat CDI. The near term goal is to obtain non-clinical proof of principal data in two separate species by the end of 2014, initiate pre-IND meetings in the first half of 2015, and complete the cGMP production of Phase 1 material in 2015. This would allow for human clinical studies in late 2015. We are particularly intrigued by the potential for AP-004, specifically because CDI is listed as an urgent concern of the U.S. CDC and rapid diagnostic ELISA kits exist for detection of *C. difficile* infection in suspected individuals. We believe this facilitates use of a targeted phage therapy like AP-004.

**RISKS – Past & Current Drawbacks of Bacteriophage Therapy**

While bacteriophages have a number of properties that would seem to favor their clinical use, the fact remains that almost 100 years have passed since their initial discovery without their widespread prophylactic or therapeutic use throughout the world. A number of factors have contributed to this situation, including:

- **Failure to establish rigorous proof of clinical efficacy**: Throughout their development in Eastern Europe and the Soviet Union there were very few, if any, appropriately conducted, placebo-controlled studies. Ironically, it was d’Herelle himself who performed a great disservice to his ideas of bacteriophages as therapeutics by never performing clinical studies while including placebo groups of patients. Just recently, a double-blind, placebo-controlled Phase 2 study of a bacteriophage therapy was performed yielding positive results, suggesting that it is possible to show effectiveness of bacteriophage therapeutics in controlled clinical trials.

- **Bacteriophages have a narrow host range**: Due to their high specificity, a number of negative results have been obtained because of the failure to select the appropriate bacteriophages for the targeted bacterial species. In addition, bacteriophage therapy necessitates the identification of the exact infectious agent, which requires additional testing and delay in treating patients. The targeting of specific bacterial infections in select patient populations, such as *P. aeruginosa* infections in CF patients, will limit this drawback in drugs like AP-001. And, as noted above, rapid ELISA diagnostic kits exist for the detection of *C. difficile* infection, again lowering the hurdle for use of a drug like AP-004. However, new testing methodologies will likely need to be created in order to rapidly identify infectious strains to allow for the widespread adoption of bacteriophage treatments for other infectious bacteria.

- **Bacteriophages are rapidly cleared from circulation**: Reticuloendothelial system clearance of bacteriophages contributes to their rapid clearance from the circulation and could have hampered results of early trials. One way to address this problem would be to select for bacteriophages that have an increased ability to remain in circulation, such as was performed in mice (*Merril et al.*, 1996). Another way to circumvent this issue would be to administer the bacteriophages as close to the source of infection as possible (e.g., an inhaled product for lung infections, topical application for skin wounds, etc...).

- **Unclear regulatory pathway**: Due to their specificity, bacteriophage therapies can be thought of as personalized medicines, which could present difficulties with getting them approved by the FDA. Thus far, the FDA has essentially treated bacteriophage therapies similar to antibiotics, meaning that all components of a bacteriophage cocktail must go through individual clinical trials and the composition of the cocktails cannot be altered without re-approval (*Thiel, 2004*). However, there may be a regulatory precedent that could be applied to bacteriophage cocktails: rather than regulating them as drugs, the FDA could instead regulate them in a manner similar to an influenza vaccine. Each year, the influenza vaccine is reformulated, and instead of requiring new clinical trials the FDA just accepts the process by which the vaccine is produced. This type of regulatory model could be applied to bacteriophage cocktail treatments, whereby instead of requiring separate trials for each component of the cocktail, the FDA could instead set stringent guidelines on the process by which the cocktails are produced. This could remove a significant hurdle to getting bacteriophage therapies through the regulatory process and speed the production of novel therapeutic applications.
Intellectual Property

AmpliPhi holds or has exclusive rights to five U.S. and foreign patents, each expiring on various dates between 2024 and 2029. These patents relate to the therapeutic use of bacteriophages, bacteriophage compositions, the sequential use of bacteriophages with conventional antibiotics, genetic sequence variations, biofilm disrupting agents and methods to reduce antibiotic resistance.

- **US 7,775,856** and national patents within the EU deriving from PCT WO2004062677: Bacteriophage for the treatment of bacterial biofilms. Through an existing license from the United Kingdom Health Protection Agency, AmpliPhi has exclusive rights to develop and exploit technologies related to the use of bacteriophages in combination with biofilm-disrupting agents in treating biofilm infections (such as those seen in CF patients with *P. aeruginosa* infections). The U.S. patent expires on December 5, 2026 while the patent granted in the E.U. expires on January 12, 2024. The license agreement with the United Kingdom Health Protection Agency requires milestone payments up to £10,000 per product and single-digit royalties on the sale of products produced using this technology.

- **US 7,807,149; US 8105,579; US 8388,946; continuing application and national filings deriving from PCT WO2005009451: Bacteriophage containing therapeutic agents.** Biocontrol Limited was granted three U.S. patents and a further continuing application is pending, whereby the granted patents relate to therapeutic, sequential use of bacteriophages in combination with conventional antibiotics, to bacteriophage compositions and to the uses of bacteriophages. The continuation application relates to genetic sequences variation associated with the protected agents. The expiration dates for the three granted patents are March 18, 2027, July 23, 2024, and July 23, 2024. The national application in Australia was granted as AU2004258731 and has an expiration date of July 23, 2024.

- **US 8475,787: continuing application and national filings derived from PCT WO2008110840: Beneficial effects of bacteriophage treatment.** Biocontrol Limited was granted a U.S. patent related to bacteriophage-induced induction of antibiotic sensitivity for *P. aeruginosa*. This patent has an expiration date of March 21, 2029. The continuation application has been filed related to other bacterial species. The national application in Australia was granted as AU 2008224651 and expires on March 7, 2028.
Collaborations

1. **Exclusive Channel Collaboration with Intrexon:** On March 29, 2013, AmpliPhi entered into the Exclusive Channel Collaboration (ECC) with Intrexon (NYSE: XON) in which AmpliPhi has access to Intrexon’s technologies directed towards the research, development and commercialization of new bacteriophage-based therapies to target specific antibiotic-resistant infections. Intrexon is a publicly held biotechnology company focused on the industrial engineering of synthetic biology.

According to Intrexon, the company’s advanced bioindustrial engineering platform enables Better DNA™ technology by combining DNA control systems with corresponding advancements in modular transgene design, assembly and optimization to enable unprecedented control over the function and output of living cells. On April 27, 2013, pursuant to the ECC, Intrexon received 24,000,000 shares of AmpliPhi’s common stock as an upfront technology access fee, which represented approximately 26% of the outstanding shares at the time of the transaction. In addition, Intrexon may receive up to $7.5 million in aggregate milestone payments for each product, payable either in cash or equity upon the achievement of certain events, and is entitled to tiered royalties in the upper-single digits on net product sales for products developed under the ECC.

2. **Global R&D Agreement with U.S. Army:** In June 2013, AmpliPhi entered into a CRADA with the USAMRMC and the WRAIR. The CRADA will focus on developing bacteriophage therapeutics to treat at least three types of infections: *S. aureus*, *E. coli* and *P. aeruginosa*. AmpliPhi plans to manufacture Phase 1 and Phase 2 batches of AP-002 at the cGMP Walter Reed Bioprocessing facility in Bethesda, MD and then conduct clinical trials at various sites throughout the world in collaboration with the U.S. Army. Under terms of the agreement, AmpliPhi will retain global regulatory ownership and commercial rights to all products developed under the agreement with the USAMRMC gaining access rights to any products developed.

3. **University of Leicester Development Agreements:** On April 24, 2013, AmpliPhi entered into the “April Collaboration Agreement” and on September 5, 2013 they entered into the “Leicester License Agreement” with the University of Leicester to develop a bacteriophage therapy for *C. difficile* infections. AmpliPhi also entered into the “August Collaboration Agreement” with the University of Leicester and the University of Glasgow, whereby the University of Glasgow will carry out certain animal model development work. Under terms of the agreements, collectively referred to as the Leicester Development Agreements, AmpliPhi will fund *in vitro* work at the University of Leicester and *in vivo* animal model work at the University of Glasgow. In addition, AmpliPhi is licensing related patents, materials and know-how from the University of Leicester for the development of a bacteriophage therapeutic to resolve *C. difficile* infections.
**Legacy Programs**

AmpliPhi has a number of legacy programs (shown below) that are no longer under development by the company, thus we have not included any economics on these products in our model because the company has outlicensed the technology and royalties associated with them.

**UniQure:** In December 2006 a sub-license was granted by Targeted Genetics Corporation, now AmpliPhi, to Amsterdam Molecular Therapeutics, now UniQure (Nasdaq: QURE), related to “AAV1 Vector” technology and the treatment of lipoprotein lipase deficiency (LPLD) for an upfront payment of $1.75 million.

UniQure has developed Glybera® for the treatment of LPLD and received marketing authorization from the European Commission in October 2012. This is the first approved gene therapy in the Western world. UniQure expects to launch Glybera® commercially in the first half of 2014 through a collaboration with Chiesi Farmaceutici.

UniQure estimates that there are 400 to 500 patients in Europe eligible to receive Glybera and it is estimated to cost $1.6 million per treatment. Approval of Glybera® included the stipulation that patients are only eligible to receive one treatment in their lifetime, putting the total sales of the drug in the E.U. at approximately $600 million. The potential market size for Glybera® is similar in the U.S.

**Celladon:** In 2009, Targeted Genetics Corporation, now AmpliPhi, licensed its adeno-associated virus (AAV) vector serotype and manufacturing capabilities to Celladon Corporation (Nasdaq: CLDN) and manufactured clinical supplies of MYDICAR®, a genetically-targeted enzyme replacement therapy for advanced heart failure patients. MYDICAR® is currently being tested in a Phase 2b trial with results expected in the first half of 2015.

**Genzyme:** In 2009, certain assets associated with AAV vector technology, including manufacturing technologies, patents, know-how and manufacturing-related equipment were sold to Genzyme Corporation (now a subsidiary of Sanofi, NYSE: SNY). Genzyme also received a license to use certain technology and materials necessary for manufacturing AAV vectors.
MANAGEMENT PROFILES

Jeremy Curnock Cook – Interim Chief Executive Officer and Chairman of the Board
Mr. Curnock Cook has served as a member of the company's board of directors since July 1995 and as chairman of the board of directors since February 1998. Mr. Curnock Cook has served as Chairman of International Bioscience Managers Limited, a corporate and investment advisory firm since 2000, and also currently serves as Managing Director of Bioscience Managers Pty Ltd, a medical sciences fund manager. From 1987 to 2000, Mr. Curnock Cook was a director of Rothschild Asset Management Limited, a corporate and investment advisory company, and was responsible for the Rothschild Bioscience Unit. Mr. Curnock Cook founded the International Biochemicals Group in 1975, which was sold to Royal Dutch Shell in 1985, where he served as managing director until 1987. Mr. Curnock Cook holds a M.A. in natural sciences from Trinity College, Dublin. He also serves as a member of the board of Avita Medical Ltd, Nexus6 Ltd, SeaDragon Ltd.

David Bosher – Interim Chief Financial Officer
On June 30, 2014, AmpliPhi Biosciences Corporation appointed David Bosher to serve as the company's interim Chief Financial Officer. Since October 1, 2013, Mr. Bosher is serving as Managing Director for Fahrenheit Advisors, a consulting and financial services company based in Richmond, Virginia. Prior to joining Fahrenheit, Mr. Bosher served from 2006 to 2013 as Senior Vice President and Chief Financial Officer of Snagajob.com, Inc., a leading human capital services and hourly employment network for job seekers and employers, headquartered in Richmond, Virginia. Prior to Snagajob, he served from 2001 to 2006 as Senior Vice President and Chief Financial Officer of Payerpath, Inc. a U.S.-based healthcare revenue cycle management software company based in Richmond, Virginia. From 1988 to 2001, Mr. Bosher served in various senior finance roles with Cadmus Communications Corporation (NMS: CDMS) and was Cadmus’ Senior Vice President and Chief Financial Officer from 1999 to 2001. His work experience also includes having served as Director of Corporate Accounting at a major publicly traded pharmaceutical firm and as senior audit professional with a large regional public accounting firm. Mr. Bosher received a B.S. in Business, with a major in Accounting, and a Masters in Business Administration, from the University of Richmond.

David Harper, Ph.D. – Chief Scientific Officer
Dr. Harper has served as the Chief Scientific Officer at AmpliPhi since the January 2011 acquisition of Biocontrol Ltd. by Targeted Genetics Corporation. Prior to joining AmpliPhi, Dr. Harper served as Chief Scientific Officer of Biocontrol, which he founded in 1997, from 2002 to 2011. He previously served as leader of the herpes virus research group in the Department of Virology at St. Bartholomew's Medical School, joining the faculty in 1991 as a Lecturer in Molecular Virology. Dr. Harper received his B.Sc. in microbiology and virology at the University of Warwick and his Ph.D. at the University of Newcastle-upon-Tyne, studying viral genetics. He carried out post-doctoral work at St. Bartholomew's Medical School in London and at the University of Iowa.

Baxter F. Phillips III – Vice President, Corporate Strategy and Business Development
Mr. Baxter has served as the Vice President, Corporate Strategy and Business Development at AmpliPhi since October 2013. From 2011 to 2013, Mr. Phillips served as Director, Business Development at Depomed, Inc., a commercially engaged specialty pharmaceutical company developing and commercializing products to treat pain and other central nervous system conditions. Prior to Depomed, Mr. Phillips served as Senior Director, Corporate Development at Osteologix, Inc., a global biopharmaceutical company, from 2007 to 2011. Prior to Osteologix, Mr. Phillips served in a number of senior research, corporate and sales and marketing positions at Insmed Inc., a publicly traded biotechnology company, from 1998 to 2007. Mr. Phillips has a B.S. in Biology from Hampden-Sydney College and an MBA from The Mason School of Business at the College of William and Mary.
VALUATION AND RECOMMENDATION

We are initiating coverage of AmpliPhi Biosciences Corporation (APHB) with a 'Neutral' rating and a price target of $0.45. We have constructed a sum-of-parts valuation based on the three programs currently being developed by the company, which we discuss in detail below.

We like the AmpliPhi story, and believe that bacteriophage therapy is a novel means by which to combat antibiotic resistant bacteria (e.g., MRSA) as well as difficult to treat infections (e.g., *P. aeruginosa* in CF patients and *C. difficile* infections). However, there are a couple of issues outstanding as of this moment that are preventing us from assigning a 'Buy' rating, and instead we are advising investors to put AmpliPhi on their radar screens as additional information/data is presented by the company in the future.

**AmpliPhage-001 could represent a paradigm shift in the treatment of CF *P. aeruginosa* infections**

Cystic fibrosis patients are at an increased risk for developing recurrent lung infections due to the build up of excess mucus as a result of the disease. This increased mucus is the ideal environment for bacteria to thrive in, and the recurrent lung infections and inflammation associated with these infections results in injury and structural changes to the lungs.

Bacterial colonization begins in CF patients from a very young age. The combination of bacterial growth and thick mucus leads to the production of bacterial microenvironments known as biofilms, which are an aggregate of microorganisms in which cells stick to each other and are embedded within a self-produced matrix of extracellular polymeric substance. Biofilms are difficult both for the immune system and for antibiotics to penetrate, thus leading to reduced treatment efficacy with eradication of *P. aeruginosa* from patients’ lungs once established being extremely difficult and very rarely occurring.

While bacteriophages hold a number of advantages over antibiotics, two advantages that directly relate to the treatment of *P. aeruginosa* infections in CF patients are the fact that bacteriophages infect bacteria in a manner completely separate from how antibiotics exert their effect, and thus even antibiotic-resistant *P. aeruginosa* are potentially susceptible to bacteriophage treatment, and that bacteriophages can infect bacteria growing in biofilms. These two points mean that the total number of potential patients eligible for treatment with AP-001 will represent a sizable portion of the total CF patient population.

There are a number of antibiotic treatments currently available to CF patients. AmpliPhage-001 will not necessarily replace the antibiotics, but could potentially be used alongside them. As mentioned previously, one of the advantages of bacteriophage therapy is that it is able to treat bacterial infections that involve a biofilm. One potential use of AmpliPhage-001 is an adjunct therapy, whereby it is administered in conjunction with an antibiotic such that AmpliPhage-001 breaks down the biofilm allowing the antibiotic greater access to the infected areas of the lung. Thus, AmpliPhi would not necessarily seek to take market share from the antibiotic therapies, but instead seek to form a niche market in the CF treatment space that complements and piggybacks on already approved and commonly used therapies.

The literature suggests there are approximately 30,000 CF patients in the U.S. and another 40,000 in the rest of the world. For our model, we estimate that approximately 70% of CF patients will develop a *P. aeruginosa* infection that could be treated by AmpliPhage-001, which is approximately 21,000 patients per year. We forecast an initial 3% penetration in the market the first year of approval with a peak market share of 15%, although this number could be adjusted much higher if AmpliPhage-001 leads to complete eradication of *P. aeruginosa* in patients' lungs.

We believe that Phase 1/2 testing of AmpliPhage-001 will start in 2015 and we model the filing of an NDA in 2019 with approval in 2020. We believe that AmpliPhage-001 will command a premium price due to the orphan indication and highly specific mechanism of action and we have modeled the price at $50,000 per treatment. This price would be further justified if AmpliPhage-001 were to show enhanced efficacy in late stage trials in the ability to completely eliminate *P. aeruginosa* from the lungs.
At this juncture we are modeling for AmpliPhi to retain U.S. rights and sign a licensing deal for rights to the rest of the world. Given the limited quantities of drug required for treatment coupled with the low cost of production, we are forecasting a 60% net margin rate for U.S. sales. We forecast a licensing deal to be worth approximately $15 million upfront with backend milestone payments of $50 million and an estimated royalty rate of 15%.

NPV ➔ Under the above scenario, we believe AmpliPhage-001 is worth: $56 million.

**AmpliPhage-002 represents a novel treatment option for MRSA infections**

The U.S. CDC has labeled MRSA with a threat level of Serious, meaning that infections caused by MRSA are a serious concern and requiring prompt sustained action to ensure the problems associated with them do no grow. This means that novel treatment therapeutics are needed, as the problem of antibiotic resistance continues to grow each year. MRSA is the leading cause of hospital acquired infections and costs the U.S. healthcare system an estimated $3-4 billion each year and accounts for over 8 million additional hospital days. The total market for MRSA infections was estimated by Global Data to be more than $2.7 billion in 2007 with it forecast to grow to $3.5 billion by 2019.

There is an intense amount of competition in infectious diseases, with a number of marketed antibiotics that target infections, including those caused by MRSA. However, one potential large market for AmpliPhage-002 could be with the U.S. Army. A study published in Epidemiology & Infection in 2010 showed that by 2007 approximately 67% of the *S. aureus* strains analyzed at Fort Benning, GA were MRSA, with approximately 82% of those cases noted as CA-MRSA. Given the close living conditions at service bases and the high incidence of MRSA infections, members of the armed forces would seem to be a logical target population for treatment with AmpliPhage-002.

Successful results with AmpliPhage-002 coupled with the high incidence of MRSA infections seen on military bases could lead to AmpliPhage-002 being a first line treatment for skin infections seen in the military. Given the current collaboration between the U.S. government and AmpliPhi, this is something for investors to keep a close eye on as AmpliPhage-002 moves into the clinic.

For our model, we estimate there were approximately 35 million treatment days for MRSA infections in 2013, with approximately half of those due to skin infections. We have modeled for AmpliPhage-002 to cost $300 per day, which puts it in line with other currently available branded antibiotics. The slight premium could be justified by the unique mechanism of action compared to other antibiotics, which would help alleviate the problem of antibiotic resistance.

The FDA has endorsed the plan for progressing AmpliPhage-002 into clinical trials, specifically agreeing to AmpliPhi’s manufacturing process, product specifications, and the absence of any need for non-clinical toxicology to initiate the Phase 1 study. AmpliPhi plans to file an IND in the 4th quarter of 2014 and subsequently initiate a Phase 1 feasibility and safety study with AmpliPhage-002 for the treatment of *S. aureus* no later than early 2015 followed by a potential Phase 2 study of *S. aureus* wound infections. We forecast an NDA filing in 2019 with FDA approval in 2020. We forecast an initial 1% market penetration with a peak market share of 5%.

NPV ➔ Under the above scenario, we believe AmpliPhage-002 is worth: $55 million.

**AmpliPhage-004 could garner a significant percentage of *C. difficile* market**

*Clostridium difficile* is a Gram-positive spore-forming bacterium that is best known for causing antibiotic-associated diarrhea. These infections typically occur in hospitalized or recently hospitalized patients who have been exposed to antibiotics and result in significant diarrhea, abdominal pain, fever and a distinctively foul stool odor.

The CDC has designated *C. difficile* as an organism with a threat level of Urgent, with bacteria in this category representing an immediate public health threat that requires urgent and aggressive action. There are approximately 337,000 infections caused by *C. difficile* each year that result in 14,000 deaths. The number of deaths related to *C. difficile* infections increased 400% between 2000 and 2007, with more than 90% of deaths occurring in people aged 65 and older. In addition, *C. difficile* infections lead to $1 billion in excess health care costs each year. The market for *C. difficile* therapies exceeded $314 million in 2011 and is forecast to grow to more than $500 by 2019, according to Global Data.
AmpliPhi’s plan is to develop an orally administered bacteriophage treatment, which the company believes is well suited to treat *C. difficile* infections. The near term goal is to obtain non-clinical proof of principal data in two separate species by the end of 2014, initiate pre-IND meetings in the first half of 2015, and complete the cGMP production of Phase 1 material in 2015. This would allow for human clinical studies in late 2015. We are particularly intrigued by the potential for AmpliPhage-004, specifically because *C. difficile* infections are listed as an urgent concern of the U.S. CDC and rapid diagnostic ELISA kits exist for detection of *C. difficile* infection in suspected individuals. We believe this facilitates use of a targeted phage therapy like AmpliPhage-004.

We forecast an initial 2% market penetration but due to the ease of confirming a *C. difficile* infection coupled with the targeted mechanism of action we believe peak market penetration could be 20%. We are forecasting for AmpliPhage-004 to be price at $5,000 per treatment course, which is a premium to currently available treatment options, but we believe warranted based on the high specificity of the treatment. We forecast an NDA filing in 2020 with approval in 2021.

**NPV ➔** Under the above scenario, we believe AmpliPhage-004 is worth: $55 million.

**AmpliPhi Biosciences is a company to put on your watch list**

Our model indicates that AmpliPhi is worth approximately $0.45 per share, and while this is a slight premium to the current share price, there are a couple of issues that we would like to see resolved before we can assign a ‘Buy’ rating.

1) **Uplist to the NYSE:** The company had hoped to be uplisted to the NYSE during the second quarter of 2014, however there has been a delay in getting the S-1 registration statement effective as the SEC has raised issues regarding the treatment of certain non-cash charges related to how the company is handling the accounting surrounding certain derivatives. In speaking with management, they have indicated that they believe all the issues raised by the SEC have been resolved and that the uplisting to the NYSE will commence in the fourth quarter of 2014.

2) **Reverse split:** In connection with the uplisting, the company is planning to perform a reverse split to reach the required minimum listing price. This will also lower the diluted outstanding share count, as it currently stands close to 335 million when counting all preferred stock, options, and warrants. As it is not uncommon for share prices to fall right after a reverse split, after these two events happen we will re-evaluate our rating based on the stock's performance.

3) **No products in the clinic yet:** The company will not be initiating their first clinical trial until early 2015 when they hope to begin proof of concept studies for both AmpliPhi-002 and AmpliPhi-001. The pre-clinical data for AmpliPhi-001 looks impressive, and there seems to be a large number of published data supporting the use of bacteriophages in humans. However, there have not been many controlled clinical studies of bacteriophages in humans, and thus we would like to see some positive clinical data before we can recommend the shares.
## AmpliPhi Biosciences Corporation
### Income Statement

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<td>$0.000</td>
<td>$0.000</td>
<td>$0.000</td>
<td>$1.510</td>
<td>$0.000</td>
<td>$0.000</td>
<td>$0.000</td>
<td>$0.000</td>
</tr>
<tr>
<td><strong>Operating Margin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-Operating Expenses (Net)</strong></td>
<td>($43.425)</td>
<td>($7.558)</td>
<td>$19.120</td>
<td>$24.241</td>
<td>$0.000</td>
<td>$35.803</td>
<td>$0.000</td>
<td>$0.000</td>
</tr>
<tr>
<td><strong>Pre-Tax Income</strong></td>
<td>($55.861)</td>
<td>($10.144)</td>
<td>$15.403</td>
<td>$19.295</td>
<td>($3.100)</td>
<td>$22.964</td>
<td>($12.500)</td>
<td>($14.000)</td>
</tr>
<tr>
<td><strong>Income Taxes Paid</strong></td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td><strong>Tax Rate</strong></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Deemed Dividends</strong></td>
<td>$8.464</td>
<td>$8.464</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td><strong>Net Income</strong></td>
<td>($64.325)</td>
<td>($18.608)</td>
<td>$15.403</td>
<td>$19.295</td>
<td>($3.100)</td>
<td>$22.964</td>
<td>($12.500)</td>
<td>($14.000)</td>
</tr>
<tr>
<td><strong>Net Margin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reported EPS</strong></td>
<td>($0.64)</td>
<td>($0.10)</td>
<td>$0.08</td>
<td>$0.10</td>
<td>($0.02)</td>
<td>$0.12</td>
<td>($0.06)</td>
<td>($0.06)</td>
</tr>
<tr>
<td><strong>YOY Growth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Basic Shares Outstanding</strong></td>
<td>101.2</td>
<td>182.5</td>
<td>183.6</td>
<td>187.2</td>
<td>205.0</td>
<td>189.6</td>
<td>220.0</td>
<td>250.0</td>
</tr>
</tbody>
</table>

Source: Zacks Investment Research, Inc. Jason Napodano, CFA
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