

Immune Pharmaceuticals, Inc. (IMNP - OTC)

IMNP: Sitting On A Potential Blockbuster With Bertilimumab...

INITIATION

Current Recommendation	Buy
Prior Recommendation	N/A
Date of Last Change	02/28/2014
Current Price (03/10/14)	\$3.99
Target Price	\$9.00

We are initiating coverage of Immune Pharmaceuticals, Inc. (OTC: IMNP) with a Buy rating and a \$9.00 price target.

Immune is developing a first-in-class monoclonal antibody targeting eotaxin-1, a chemokine that has been implicated in a number of inflammatory diseases, including inflammatory bowel disease (IBD), bullous pemphigoid (BP) and severe asthma. The lead candidate bertilimumab is in Phase 2 trials for both IBD and BP. Biomarker based patient selection is a key differentiator for Bertilimumab and is expected to maximize its clinical value and reduce development risks.

SUMMARY DATA

52-Week High	\$5.10
52-Week Low	\$1.60
One-Year Return (%)	42.50
Beta	2.28
Average Daily Volume (sh)	28,782

Risk Level	Above Average
Type of Stock	Small-Growth
Industry	Med-Biomed/Gene

Shares Outstanding (mil)	13
Market Capitalization (\$mil)	\$53
Short Interest Ratio (days)	6.28
Institutional Ownership (%)	0
Insider Ownership (%)	2

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

ZACKS ESTIMATES

Revenue

(In millions of \$)

	Q1	Q2	Q3	Q4	Year
	(Mar)	(Jun)	(Sep)	(Dec)	(Dec)
2013	0 A	0 A	0 A	0 E	0 E
2014	0 E	0 E	0 E	0 E	0 E
2015					0 E
2016					0 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1	Q2	Q3	Q4	Year
	(Mar)	(Jun)	(Sep)	(Dec)	(Dec)
2013	-\$0.21 A	-\$0.21 A	\$0.11 A	-\$0.14 E	-\$0.46 E
2014	-\$0.15 E	-\$0.16 E	-\$0.18 E	-\$0.18 E	-\$0.68 E
2015					-\$0.05 E
2016					\$0.04 E

WHAT'S NEW

Initiating Coverage



We are initiating coverage of Immune Pharmaceuticals, Inc. (OTC: IMNP) with a Buy rating and a \$9 price target.

The company's lead candidate, bertilimumab, is in Phase 2 trials for both ulcerative colitis (UC) and bullous pemphigoid (BP), the later an orphan, autoimmune blistering skin disease. Bertilimumab is a first-in-class monoclonal antibody targeting eotaxin-1, a chemokine that selectively recruits eosinophils through chemotaxis and has been implicated in a number of inflammatory diseases, including inflammatory bowel disease (IBD), BP and asthma. We expect data from the ongoing Phase 2 trial in BP are expected around the middle of 2014, while data from the ongoing double-blind, placebo controlled Phase 2 trial in UC are expected in 2015.

The U.S. IBD market totaled approximately \$5 billion in 2012 and is expected to grow to \$9+ billion by 2017. UC is the most common form of IBD worldwide. Active disease is manifested as inflammation of the rectal mucosa that can spread to the rest of the colon. Symptoms include diarrhea, abdominal pain, fever, and weight loss. UC patients go through flares (periods of active disease and symptoms) and periods of remission (few to no symptoms). Serious complications are known to occur, and ultimately up to 20% of UC patients opt for colectomy (i.e., removal of the colon). This procedure is curative in most UC patients, however it is not a desirable outcome thus more and better treatment options are needed to treat this disease. The role of eosinophils and eotaxin-1 in UC has been shown through both animal models, where elimination of eotaxin-1 renders mice immune to the effects of a UC model, and in clinical data, where elevated eotaxin-1 levels have been shown in the sera of UC patients, with severity of disease correlating to the level of eotaxin-1. The role of eotaxin-1 in CD has also been evidenced in pre-clinical and clinical observational studies.

Immune Pharmaceuticals is also developing a next-generation antibody drug conjugate (ADC) platform (NanomAbs) that consists of chemotherapy-loaded nanoparticles bound by therapeutic antibodies. The antibodies specifically target the nanoparticles to tumor cells and initiate binding to the cell surface. After binding, the tumor cells take up the nanoparticles and the chemotherapy is released / activated inside the cell through a controlled release. This mechanism of action enhances the efficacy of the chemotherapeutic agent and could lead to a reduction in off-target effects. NanomAbs hold a number of distinct advantages over current ADCs such as the ability to deliver a larger payload of molecules, a wider array of compounds (e.g., chemotherapies, peptides, RNAi therapies) and controlled release of therapeutic. Ongoing pre-clinical studies are being conducted as a prelude to Phase 1 clinical trials, with the lead compound targeting pancreatic cancer through anti-ferritin antibodies attached to gemcitabine and paclitaxel loaded nanoparticles. The ADC market is expected to reach \$9 billion by 2023, thus representing an attractive opportunity for the company.

Immune's pipeline also includes AmiKet, a topical analgesic cream for the treatment of neuropathic pain, which is pain associated with damage to the peripheral nervous system. AmiKet has been extensively studied in the clinic in over 1,700 patients and has received Fast Track designation from the FDA for both chemotherapy-induced peripheral neuropathy (CIPN) and post-herpetic neuralgia (PHN). Immune Pharmaceuticals is actively seeking a partner to bring the program into a Phase 3 trial and eventually to market.

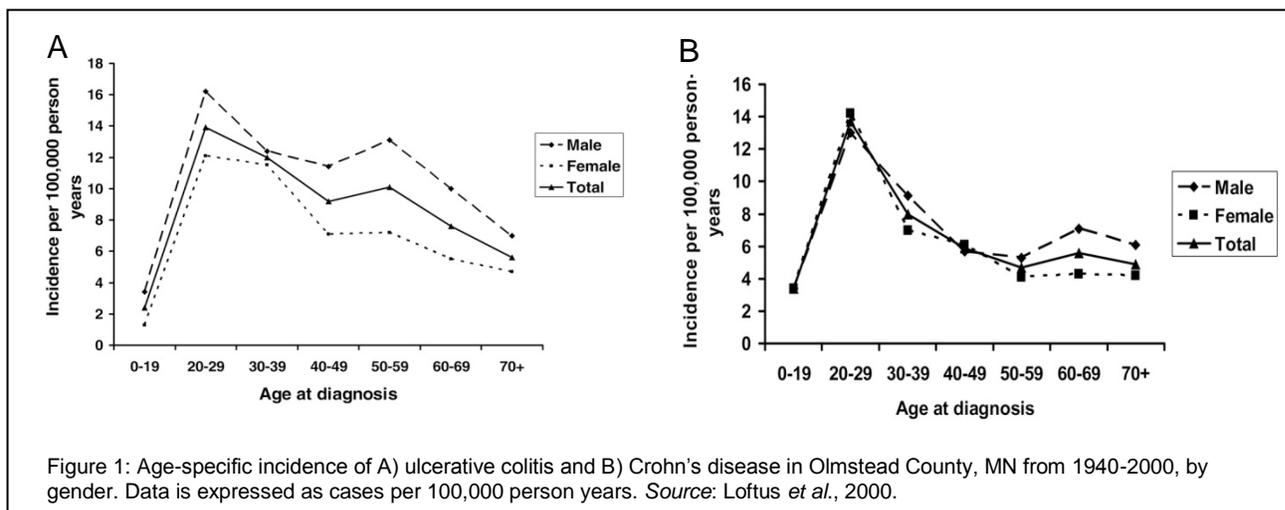
In August 2013, Immune completed a merger with EpiCept Corporation that allowed the formerly privately held biopharmaceutical company access to capital markets. The stock currently trades on the Nasdaq OMX First North Premier and on the OTCQX under the symbol IMNP. With recent \$11.6 million financing completed, we believe the company's financial position is solid. We expect an uplist to the NASDAQ exchange, a move that will increase liquidity and give added exposure to the company, within the next few months.

INVESTMENT THESIS

Inflammatory Bowel Disease

The Inflammatory Bowel Diseases (IBDs) are a group of chronic ailments that affect the intestinal tract. The two most prevalent IBDs are Crohn's Disease (CD) and Ulcerative Colitis (UC). CD is most likely to affect the ileum and colon, although it can affect any part of the intestinal tract from the mouth to the anus, often discontinuously. UC involves the rectum and may or may not affect other parts of the colon. The inflammation in CD is transmural, meaning it affects the entire colon wall as compared to UC where the inflammation typically only affects the mucosa. CD may also involve intestinal granulomas, strictures and fistulas while these are usually not found in UC. Smoking is a risk factor that affects CD and UC differently; smokers are more than twice as likely as non-smokers to suffer from CD, while smokers have a decreased risk of developing UC. No other risk factors have been associated with IBDs.

The first description of UC dates to the mid-1800s while CD was not described until 1932. IBDs are considered disorders of modern society as their prevalence in developed countries have been increasing since the mid-20th century (Danese and Fiocchi, 2011). Whether the low incidence in developing countries is due to a lack of awareness, confusion with infectious diseases causing diarrhea or truly a low incidence is unclear. IBDs occur most commonly in North America and Western Europe, while they are least common in Asia. In North America, epidemiological data suggests that between 7-46,000 new cases of UC are diagnosed each year with as many as 780,000 people suffering from the disease, while for CD approximately 10-47,000 individuals are diagnosed each year with as many as 630,000 people suffering from the disease (Loftus, 2004). The annual numbers of UC and CD diagnoses in Europe are very similar, with as many as 2.2 million people suffering from IBDs. There does appear to be a slight gender related difference in UC, with more females being diagnosed than males with little to no gender effect seen in CD. A long-term epidemiological study in Olmstead County, MN examined the incidence of IBDs and found that while IBDs may be diagnosed at any age, they are typically diagnosed in late adolescence or early adulthood (Figure 1, Loftus *et al.*, 2000).



Individuals of all races are affected by IBDs, with Caucasians the most likely to suffer from the diseases. There is no nationwide epidemiological data (incidence and prevalence) available on minorities with IBD. However, it has been shown that people of various ethnic groups who have immigrated to the United States from developing countries with a low incidence of IBDs have higher rates of the disease after settling in this country. This suggests that race is not a sole determining factor in IBD, and that there are likely environmental factors that contribute to its development.

IBDs are thought to arise through an improper inflammatory response to the host microbiome, with genetics playing a role in determining those most likely to develop the disease. Genetic studies have shown a familial clustering of cases and twin studies have further aided in establishing a role for certain genomic regions. Thus far, there are 47 genetic loci associated with UC, with 19 being specific for UC and 28 shared with CD. UC and CD are both so genetically heterogeneous, with each associated gene having such a small additive effect, that genetic screening is not currently utilized for assessing the risk of developing IBD.

Symptoms associated with IBDs vary from person to person and also whether the individual is currently suffering a flare (a time of active disease) or is in remission (when the disease is quiet with few or no symptoms). Bloody diarrhea with or without mucus is the hallmark of UC, while CD typically presents with fever, abdominal pain, and clinical signs of bowel obstruction or diarrhea. Other generalized symptoms include loss of appetite, fatigue and night sweats. Serious complications arising from IBDs can occur and include perforated bowel, toxic megacolon, fistula, abscess and nutritional deficiencies. Importantly, individuals suffering from IBD for greater than 8 years have an increased risk of developing colon cancer compared to the general population (Bergeron *et al.*, 2010). In addition to the physical symptoms associated with IBDs, there are also psychological complications to consider. Chronic illnesses are typically associated with a decreased quality of life and the symptoms and unpredictability associated with IBD flares can result in psychological issues such as depression and anxiety. In addition, the stress and worry associated with having IBD may in fact contribute to flare-ups.

...Current treatment options for IBD...

While there are no medical cures for IBD, certain medications have proven to be useful in controlling disease. The three main goals of IBD treatment are to induce remission as quickly as possible, maintain remission for as long a time period as possible, and improve the patient's quality of life. Factors such as severity and location of disease, past treatments, side effects and additional medical conditions the person is suffering from must all be considered in approach to treatment. Generalized therapy classes are as follows:

- ✓ Aminosalicylates: These compounds can be given orally, rectally or both, and interfere with the inflammatory response. They are effective in treating mild to moderate UC and can be utilized to both induce remission and as maintenance therapy. They have not been shown to be effective in treating CD.
- ✓ Corticosteroids: These agents have been used in the treatment of IBD for over 60 years. They are powerful anti-inflammatory and immunosuppressive agents and are given to those who fail to achieve remission on aminosalicylates. They are only recommended for short-term use and are not utilized for maintenance therapy due to their undesirable long-term side effects and toxicity.
- ✓ Immunomodulators: These drugs weaken the activity of the immune system that in turn reduces the inflammatory response. They are used in patients who do not respond to aminosalicylates or corticosteroids and who need to maintain remission in CD.
- ✓ Antibiotics: These compounds are frequently used as a first-line treatment for CD, particularly for those patients who have fistulas or recurrent abscesses. There is no data to indicate antibiotics are useful in treating UC.

Past research into the etiology of inflammation pointed to tumor necrosis factor-alpha (TNF- α) as an ideal target for IBD therapy based on its pro-inflammatory effects on a range of innate and adaptive immune functions. As a result, a number of pharmaceutical companies have developed TNF- α inhibitors in the form of monoclonal antibodies:

- Infliximab (J&J's Remicade®): Infliximab is a chimeric monoclonal antibody that is given as an intravenous (i.v.) infusion. Studies over the past 15 years in CD patients have shown that infliximab is effective in inducing remission, maintaining remission in treatment-refractory patients and preventing recurrence of disease in post-operative patients. Infliximab was approved for the treatment of CD in 1998 and for UC in 2005. With a cost of nearly \$24,000/yr, worldwide 2012 revenues for infliximab were \$6.1 billion with approximately 30% of revenues owing to IBD treatment. Infliximab will go off patent in the U.S. in 2018 and in Europe in 2015.
- Adalimumab (AbbVie's Humira®): Adalimumab is a fully-human monoclonal antibody that is given by subcutaneous injection. This treatment has been shown to induce remission, maintain remission, and can be utilized in patients who are refractory to infliximab. As it is a fully-human antibody, there is a decreased likelihood of developing antibodies to treatment, an effect that contributes to a decrease in effectiveness of infliximab. In addition, the subcutaneous route of administration provides a viable alternative to those patients who experience infusion reactions with infliximab. Adalimumab is the world's top selling drug, with 2012 revenues of \$9.3 billion with approximately one-quarter of revenues derived from IBD indications. Adalimumab patent coverage will expire in 2016.
- Certolizumab pegol (UCB's Cimzia®): Certolizumab pegol is differentiated from infliximab and adalimumab in that it is a humanized Fab antibody fragment attached to polyethylene glycol. The lack of an Fc domain means it does not induce complement activation, antibody-dependent cellular cytotoxicity or induction of apoptosis. Studies show that certolizumab pegol is efficacious in moderate to severe CD for both induction and maintenance of remission in patients who do not respond to standard therapy. Sales of certolizumab totaled \$640 million in 2012. The drug is under patent protection until 2024.

- *Golimumab (J&J's Simponi®)*: Golimumab is produced by Johnson and Johnson as the follow-on to infliximab. It is a fully human antibody derived from TNF- α immunized transgenic mice that express human IgGs. It was originally approved in 2009 for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. The FDA approved golimumab for the treatment of moderate to severe CD and UC in 2013. Sales of golimumab totaled \$607 million worldwide in 2012.

While rare, there are serious side effects related to the use of anti-TNF- α therapy. The FDA has issued a black box warning covering the entire class of TNF- α inhibitors related to an increased risk of opportunistic infections from *Legionella* and *Listeria*, fungal infections, and the re-emergence of active tuberculosis in patients with latent mycobacterium tuberculosis infection. There have also been reports of a rare blood cancer (hepatosplenic T-cell lymphoma), primarily in adolescents and young adults being treated for UC or CD with anti-TNF- α therapy along with azathioprine.

In addition to TNF- α , additional molecules are the targets of IBD biological therapies:

- *Natalizumab (Biogen's Tysabri®)*: Natalizumab is a humanized monoclonal antibody that targets integrin $\alpha 4$ and works by disrupting leukocyte adhesion to the endothelium and subsequent migration into the gut mucosa. Clinical trial results suggest that natalizumab is less effective than TNF- α targeted therapies and the increased risk of progressive multifocal leukoencephalopathy (PML) has minimized its use as a first-line monoclonal antibody treatment. As such, natalizumab has only limited use in IBD indications.
- *Vedolizumab (Takeda's Entyvio™)*: Vedolizumab targets integrin $\alpha 4\beta 7$ and blocks leukocyte trafficking to the gut in a selective manner, as opposed to the systemic effects of natalizumab. Importantly, there were no reported incidences of PML in Phase 3 trials of the compound. Vedolizumab was shown to be effective at inducing and maintaining remission in UC and CD and is currently under review by the FDA after receiving a positive recommendation from the Gastrointestinal Drug Advisory Committee in Dec. 2013.

While anti-TNF- α therapy has been successful for a large percentage of patients who are refractory to other conventional treatments, approximately 25-40% of patients who initially respond to anti-TNF- α therapy go on to develop severe side effects or have a loss of response to therapy over time. Infliximab is typically the first monoclonal antibody used in the course of treatment, both because it has been around the longest and clinical trial results show it to be the most effective of the TNF- α targeted therapies. Infliximab is a chimeric antibody, meaning that it is part mouse (30%) and part human (70%). Because of this, patients typically develop anti-infliximab antibodies against the "mouse" portion of the protein, and thus after some time these patients develop resistance to therapy due to its inactivation by the immune system.

Patients who develop resistance to infliximab typically transition to another anti-TNF- α therapy. Adalimumab was shown to be effective for patients who become refractory to infliximab even though they both target TNF- α . Typically, only patients who have severe disease and are refractory to anti-TNF- α therapies like infliximab and adalimumab will be put on natalizumab.

Takeda's vedolizumab has a number of attributes that could potentially lead to its use as a first-line treatment in both UC and CD. The first attribute is safety, with data from clinical trials of vedolizumab showing it to be a safe drug both in absolute terms and in comparison to anti-TNF- α therapies. The drug has been used to treat close to 3,000 patients in clinical trials. Takeda specifically enrolled a large number of patients in vedolizumab clinical studies due to the similarities between vedolizumab and natalizumab. Both biologics target integrins, and natalizumab has shown an increased risk of developing rare and often fatal viral infection known as Progressive multifocal leukoencephalopathy (PML). Takeda did its best to rule out the PML risk with vedolizumab. Another important safety issue that arose during clinical testing is that, in comparison to infliximab, there was an absence of injection site related adverse events in patients treated with vedolizumab, even though it is a similar intravenously injection. One last point in the comparison with infliximab is the lack of serious infections noted with vedolizumab, with 12.9% and 8.4% of patients reporting nasopharyngitis and upper respiratory tract infections, respectively, with none being life-threatening. This is in comparison to the clinical trials of Remicade, where 36% of patients developed infectious diseases with 5% of patients developing infections with a high mortality rate.

The efficacy data for vedolizumab was just as good if not better than seen with anti-TNF- α therapy. Data from the infliximab pivotal Phase 3 ACT-1 study showed a clinical remission rate of 35% at one year, with mucosal healing seen in 45% of patients. This is in comparison to a clinical remission rate of 45% at one year with 56% of patients exhibiting mucosal healing in the vedolizumab pivotal Phase 3 study. The improved efficacy coupled with fewer serious side effects signifies that vedolizumab could become the top selling IBD treatment shortly after its approval.

How vedolizumab, and other biological agents that treat UC and CD, will be positioned in the clinic will ultimately be determined in part by the FDA and EMA label, coupled with the position of pertinent guideline-issuing committees such as the American College of Gastroenterology.

There is a debate currently ongoing amongst gastroenterologists about the proper place for monoclonal antibodies in the hierarchy of medical therapies for IBD. The more conservative approach that most doctors have utilized is the so-called “step-up” approach, in which traditional therapies (aminosalicylates, corticosteroids and immunomodulators) are exhausted first before moving on to monoclonal antibody therapy (Figure 2). Recently, given the evidence that monoclonal antibody therapy is superior to traditional IBD therapies, is generally well-tolerated, and may reduce incidence of surgery, there is a movement by gastroenterologists toward so-called “top-down” therapy where monoclonal antibodies are utilized early in the disease course for moderate to severe disease.

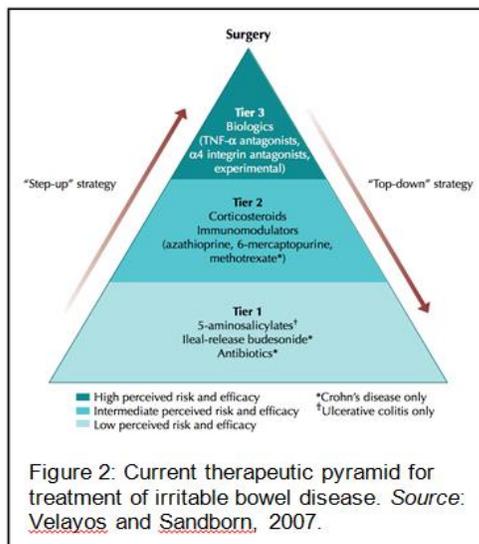


Figure 2: Current therapeutic pyramid for treatment of irritable bowel disease. Source: Velayos and Sandborn, 2007.

The conventional “step-up” therapy approach has not altered surgical rates for IBD patients even with the introduction of biological therapies. Thus, the hypothesis is that administering monoclonal antibody therapy early in the disease course could alter the natural history of the disease and reduce steroid dependency, surgery and promote mucosal healing.

Even with these treatment options, approximately 30% of UC and 80% of CD patients will go on to require surgery, typically after an extended period of time following initial diagnosis (> 20 years). For UC, the standard surgical option is removal of the colon and rectum with some patients eligible for an ileo pouch-anal anastomosis (IPAA), which precludes the necessity of an external bag for the collection of fecal waste. The type of surgery for CD depends on the reason for surgery and the location of the disease. Unlike UC, surgery does not cure CD, with 30% of patients experiencing a flare within 3 years after surgery and 60% having recurrence within 10 years.

...A New Hope...

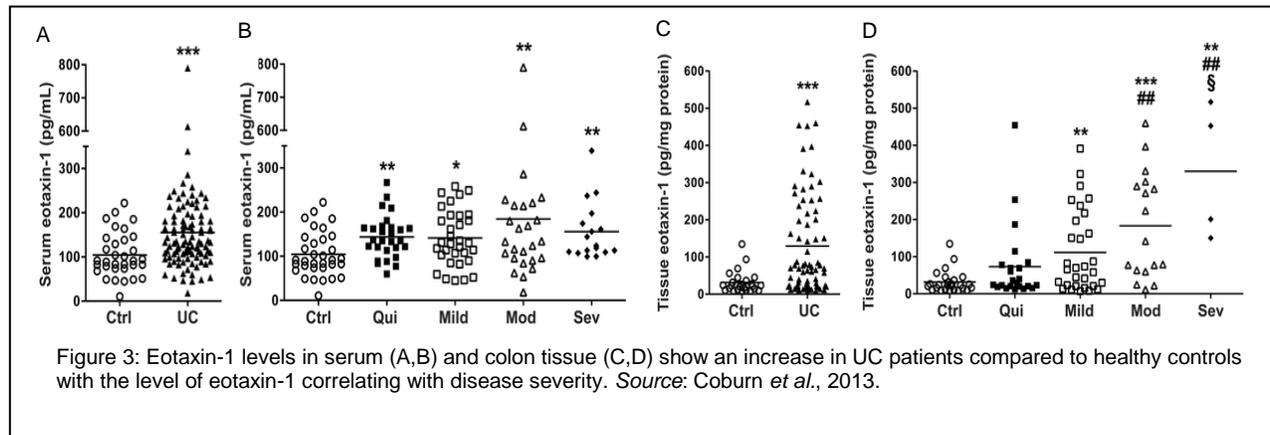
The inflammatory process involves a number of different cell types, including lymphocytes, macrophages, mast cells, neutrophils and eosinophils. Eosinophils are white blood cells responsible for combating parasitic infections along with regulating mechanisms associated with allergens and asthma. They produce a number of different cationic proteins, reactive oxygen species, enzymes, growth factors and cytokines. These agents make the eosinophil an effective weapon against invading pathogens; however, they also make it a nemesis in chronic inflammatory conditions such as asthma and IBD.

After developing in the bone marrow, most eosinophils reside within the lamina propria in the gastrointestinal tract and are believed to play an important role in host defense. Recruitment of GI eosinophils is regulated by the continued expression of eotaxin-1 (CCL11) (Garcia-Zepeda *et al.*, 1996), a potent eosinophil-specific chemotactic agent. The role of eotaxin-1 has been effectively shown from data acquired using eotaxin-1 deficient mice. Mice lacking eotaxin-1 show a marked reduction in the population of gastrointestinal eosinophils (Matthews *et al.*, 1998), a reduced eosinophil-associated inflammation and gastrointestinal pathology (Hogan *et al.*, 2001) and reduced colitis associated with reduced number of colonic eosinophils in a mouse model of UC (Ahrens *et al.*, 2008).

A large number of diseases are characterized by a marked accumulation of eosinophils (eosinophilia), including asthma, rhinitis, conjunctivitis, certain inflammatory diseases (including IBD) and some cancers (Giembycz and Lindsay, 1999). In addition to being associated with certain diseases, eosinophilia is also correlated with up-regulation of eotaxin-1, with a large accumulation of data showing eotaxin-1 involvement in asthma. Expression of eotaxin-1 is increased in the lungs of asthma patients compared to healthy controls, and this increase also correlates with eosinophil number (Taha *et al.*, 2001). In severe asthmatics, sputum eotaxin-1 level is correlated with disease severity (Dent *et al.*, 2004) as well as chronic impairment of lung function (Nakamura *et al.*, 1999).

The role that eosinophils and eotaxin-1 play in IBD has recently become a focus of intense research. In the early 2000's it was shown through two separate studies that IBD patients had elevated levels of eotaxin-1 in their serum compared to controls (Chen *et al.*, 2001; Mir *et al.*, 2002). In a group of pediatric UC patients, levels of eotaxin-1 messenger RNA (mRNA) in the rectosigmoid colon positively correlated with rectosigmoid eosinophil numbers. In addition, these colonic eosinophils appeared to be degranulating (activated), and the levels positively correlated with disease severity (Ahrens *et al.*, 2008).

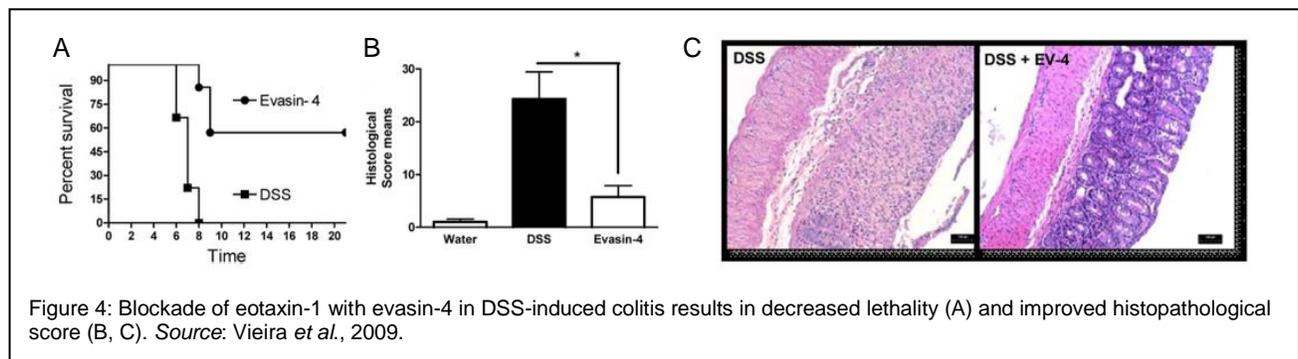
A recent study involving over 100 UC patients demonstrated that out of 42 serum analytes assayed, only eotaxin-1 and granulocyte-colony stimulating factor (G-CSF) were increased in the serum of UC patients compared to controls (Coburn *et al.*, 2013). The study further demonstrated that only eotaxin-1 was increased in all levels of active disease in both serum and tissue, and that tissue eotaxin-1 correlated with the Mayo Disease Activity Index (DAI) and with eosinophil counts (Figure 3). The authors of the study stated, "Our data implicate eotaxin-1 as an etiologic factor and therapeutic target in UC..."



Further examination of the role that eotaxins play in recruitment of eosinophils to the intestine in UC was determined through examination of rectal mRNA levels of eotaxin-1, 2 and 3 along with IL-5 (Lampinen *et al.*, 2013). Levels of eotaxin-1 were elevated in quiescent UC, while levels of all eotaxins were elevated in active UC. The level of eotaxin-1 expression positively correlated with eosinophil numbers and the number of intestinal myeloid cells correlated with eotaxin-1 and eosinophil level, suggesting that eotaxin-1 contributes to eosinophil rectal recruitment and the source of eotaxin-1 is intestinal myeloid cells.

The available data shows that, in addition to macrophages, mast cells, epithelial cells and endothelium, eosinophils and T-cells influxing inflamed tissue significantly contribute to eotaxin production and release, thus providing an autocrine mechanism involved in local recruitment of inflammatory cells during allergic reactions. **Hypothesis:** The ability to block eotaxin production should dampen this mechanism and decrease the inflammatory response.

The effect of eotaxin-1 on eosinophil function and its association with inflammatory conditions has lead several groups to examine the effect of neutralizing eotaxin-1 as a therapeutic option. One such study examined the effect of blocking eotaxin-1 in a mouse model of colitis induced by dextran sodium sulfate (DSS) (Vieira *et al.*, 2009). DSS is an intestinal irritant that causes a number of symptoms in mice similar to those seen in UC, including inflammation of the mucosa and infiltration by inflammatory cells including neutrophils, macrophages and eosinophils (Solomon *et al.*, 2010). Using the DSS model, it was found that 1) mice have an accumulation of eosinophils in the colon upon DSS-induced colitis, 2) preventing eosinophil infiltration (as observed in eosinophil deficient mice) prevents DSS-induced disease, pathological changes and lethality and 3) eosinophil influx is associated with local expression of eotaxin-1 and that blockade of eotaxin-1 decreased eosinophil influx, clinical disease, injury and death (Figure 4). In this study, eotaxin-1 was blocked through the use of evasin-4, a chemokine binding protein derived from tick saliva (Deruaz *et al.*, 2008), serving as a useful proof of principle that inhibiting eotaxin-1 could prove to be a valuable therapeutic option.



Therefore, **WE CONCLUDE** based upon the overwhelming amount of both pre-clinical and clinical data linking eotaxin-1 and eosinophilia to IBD, that a treatment specifically targeting eotaxin-1 is scientifically justified and would stand a good chance of showing clinical efficacy for the treatment of IBD.

Bertilimumab

Immune Pharmaceuticals is developing bertilimumab, a first-in-class fully human IgG4 monoclonal antibody targeted against eotaxin-1. The antibody was originally discovered by Cambridge Antibody Technology (CAT) using their fully human phage display library. The antibody (originally called CAT-213) binds to eotaxin-1 with very high affinity (~80 pM) and a series of experiments validated the specificity and activity of the antibody. Most importantly, ELISA analysis was conducted using a series of human cytokines and chemokines, including the functionally related eotaxin-2 and eotaxin-3 (Figure 5). The high sensitivity of the ELISA coupled with the high antigen coating concentrations and the lack of any cross-reactivity indicates that CAT-213 is highly specific to eotaxin-1. This high degree of specificity and affinity should decrease any off-target effects or toxicities due to cross-reactivity with other antigens.

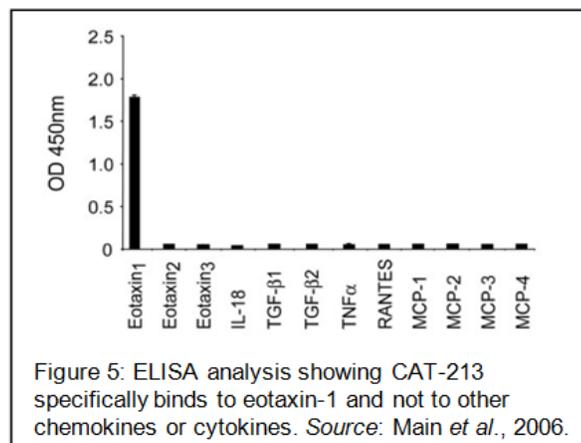


Figure 5: ELISA analysis showing CAT-213 specifically binds to eotaxin-1 and not to other chemokines or cytokines. Source: Main et al., 2006.

In 2007, CAT, later acquired by AstraZeneca Corp., announced they had granted an exclusive worldwide license for the development and commercialization of CAT-213 to iCo Therapeutics. Under the terms of the agreement, iCo agreed to pay CAT an upfront fee of \$400,000, and agreed to milestone payments for key clinical and regulatory achievements totaling \$7.0 million. Richard Mason, CAT's SVP Business and Commercial Operations commented at the time that "Following an internal review of our development priorities, CAT decided to out-license CAT-213." There were no other indications as for why CAT decided not to pursue development of bertilimumab. iCo stated that they planned to advance CAT-213 initially for the treatment of ocular allergies including allergic conjunctivitis.

In December 2010, iCo announced that they had granted Immune Pharmaceuticals an option to an exclusive license for the development and commercialization rights to the systemic uses of iCo-008 (bertilimumab), while retaining worldwide exclusive rights to all ocular applications. The option agreement came with a non-refundable \$1 million option fee creditable upon conversion to an upfront payment if executed to a full licensing agreement. This option was then **fully executed** in June 2011 whereby iCo received \$500,000 up-front with up to \$32.0 million in milestone payments plus royalties on net sales. In addition, iCo received 600,000 shares of Immune with an additional 200,000 warrants priced at \$0.95.

...Early clinical studies...

CAT conducted three separate clinical trials in the early 2000's to determine the pharmacokinetics, safety and effectiveness of CAT-213 in treating allergy, allergic rhinitis and conjunctivitis:

- **Phase 1:** The pharmacokinetics of CAT-213 was assessed in an ascending single dose, single-blind Phase 1 study. Twenty-five healthy male volunteers were administered 0.01, 0.1, 1, 5 and 10 mg kg⁻¹ intravenously over 30 min. No serious or adverse events were reported and the half-life of CAT-213 at the highest concentration was 8.4 days.
- **Phase 2:** A double-blind, placebo controlled study was undertaken to assess the effect of CAT-213 on allergen-induced rhinitis through i.v. or intranasal dosage 30 minutes prior to antigen exposure. A total of 52 patients with history of seasonal allergies were entered into the study. The primary endpoint was the reduction in nasal cross-sectional area as assessed by acoustic rhinometry. The results showed that CAT-213 administered intranasally attenuated the post allergen nasal obstruction for up to six hours, however there was no demonstrated effect on either peak nasal inspiratory flow or symptoms. The infiltration and activation of cells from nasal lavage samples were collected pre-dosing and 30, 60, 120, 360 and 480 minutes after allergen challenge, and a nasal biopsy was performed six hours post challenge. The results of the lavage showed a trend for reduction in eosinophils following treatment with CAT-213, though this effect was not statistically significant. For the biopsy, submucosal mast cells and submucosal eosinophil infiltrates were significantly decreased by intravenous and intranasal CAT-213 compared with placebo.

- Phase 1/2a: An allergen challenge study was carried out using a topically applied single dose of CAT-213 in patients with allergic conjunctivitis. CAT-213 did not have any effect on symptoms as analysis showed that allergen challenge did not provoke a large enough late-phase response involving eosinophils.

The early clinical trial results using CAT-213 were not particularly encouraging from an efficacy standpoint. However, while the total number of patients tested with the drug was limited (<150), CAT-213 was safe and well tolerated with no serious side effects reported. We believe that the lack of efficacy noted for CAT-213 is likely due to no selection criteria for patients with increased eotaxin-1 levels and is not necessarily due to the antibody itself.

Bertilimumab – Current Development Plans

Immune Pharmaceuticals has initiated a Phase 2 study of bertilimumab in UC. This randomized, double-blind, placebo-controlled, multi-center study will evaluate the clinical efficacy and pharmacokinetic profile of bertilimumab in patients with active moderate to severe UC. Importantly, key inclusion criteria include high eosinophilia, as confirmed by eotaxin-1 levels (≥ 100 pg/mL) from a colon biopsy. The primary endpoint is clinical response using the UC Mayo Clinic Index two weeks after final dosing. The study indicates that clinical response will be measured as a decrease in Mayo score from baseline of at least three points and at least 30%.

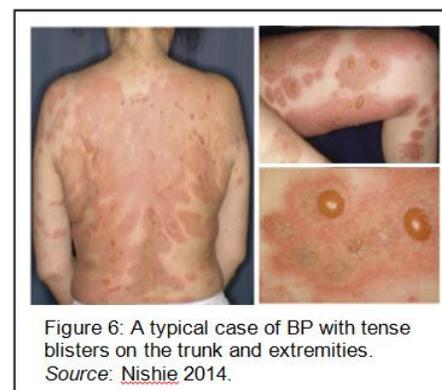
Secondary endpoints include mucosal injury, eotaxin-1 and eosinophil levels in the mucosa and clinical remission. Patients will be followed up until day 90 after initiation into the study. The trial was initiated in February 2013 with results expected in 2015.

A potential Phase 3 development strategy will be to position bertilimumab as a first-line personalized therapeutic option for moderate to severe UC patients with high eotaxin-1 levels. In order to achieve this, it will be necessary to show remission rates at least comparable (>30% decrease in Mayo score) to those seen in the Phase 3 trials of infliximab. In those studies, infliximab was shown to have a >65% clinical response rate at eight weeks, a >30% sustained response rate at one year, clinical remission >30% at one year and sustained remission of 20% at one year. Those two Phase 3 trials examined over 700 patients. Thus, for bertilimumab to be approved, it will likely take an equivalent number of trials, patients, and efficacy in patients with elevated eotaxin-1 levels.

Bullous Pemphigoid – An Orphan Autoimmune Disease Modulated by Eosinophils

Bullous Pemphigoid (BP) is an autoimmune blistering skin disease. It typically affects individuals aged >65 and is rarely seen in children. The prevalence of the disease is approximately 30 cases per million people per year, which represents approximately 30,000 new cases worldwide each year. Clinical features of the disease are tense blisters on the trunk and extremities associated with moderate to severe pruritus (Fig. 6).

Other symptoms include blisters in the mouth and redness and soreness of the eyes. European studies have reported first year mortality rates to be as high as 40%, however rates in the United States were reported to be lower (5-10%). Given the lack of current treatment options and the high associated mortality, there is a significant unmet medical need for better BP treatment options.

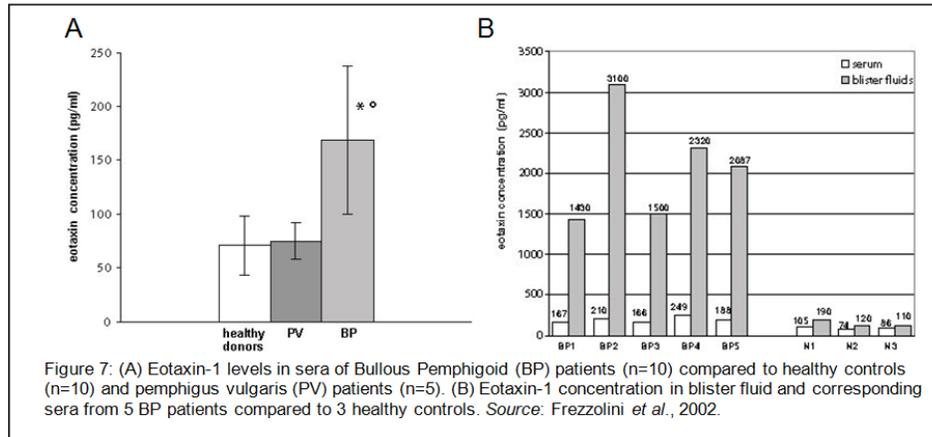


The immunological hallmark of the disease is the development of autoantibodies to two hemi-desmosomal components: transmembrane collagen XVII (BP180) and plakin family protein BP230. Of the two, collagen XVII (COL17) is thought to be the major auto-antigen. Binding of the autoantibodies in the skin leads to the induction of complement binding and the production of a wide array of cytokines and chemokines in mast cells, including the production of eotaxin-1. Eotaxin-1 then binds to CCR3, the main chemokine receptor expressed on eosinophils, which induces eosinophil migration to the skin.

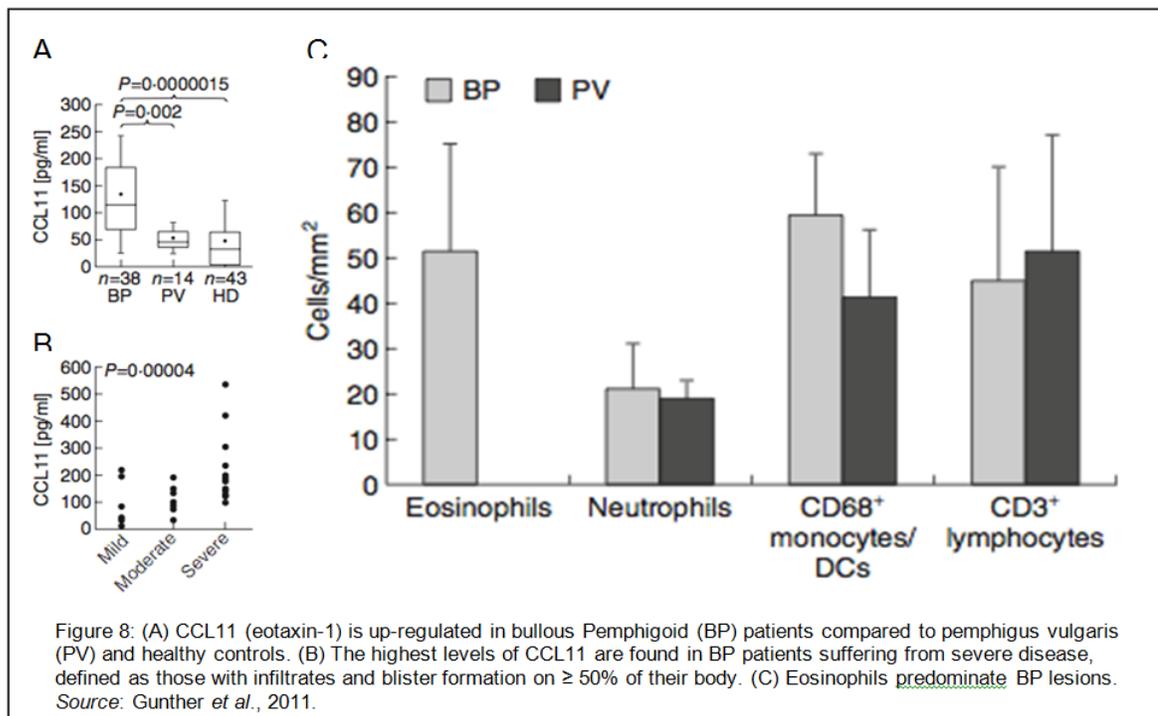
Once in the skin, the eosinophils release excess amounts of proteases that results in the major histopathological mark of BP, the formation of subepidermal blisters. The large scale production and release of cytokines and other inflammatory compounds from eosinophils has been widely reported in both the bullae and sera of patients with BP and is often related to disease activity..

...Eotaxin-1 is increased in BP patients...

Data from the early 2000's first showed the relationship between the levels of eotaxin-1 and eosinophilia in BP, similar to what has been shown in asthma and IBD. One study found an increased level of serum eotaxin-1 in BP patients compared to patients with pemphigus vulgaris (PV), a related skin disorder, and healthy controls (Fig. 7A) (Frezzolini *et al.*, 2002). In addition, the level of eotaxin-1 in blister fluids was found to be approximately 10-fold higher than in corresponding sera and when compared to blister fluid obtained from suction blisters from healthy volunteers (Fig. 7B). Interestingly, the authors of this study were unable to detect increased eotaxin-1 in the skin or the sera of PV patients, and they concluded "...this chemokine (eotaxin-1) may play a specific role in BP."



Results from an additional study also showed elevated levels of eotaxin-1 in blister fluid from BP patients, and the eotaxin-1 level, but not the level of IL-5, was strongly associated with tissue eosinophilia in BP (Wakugawa *et al.*, 2000). This corroborated with another small study from that year that also showed an increase in eotaxin-1 in blister fluid and sera of BP patients compared to healthy controls (Shrikhande *et al.*, 2000). More recently, a larger study examined the level of eotaxin-1 in BP patients and stratified the level of eotaxin-1 based on the severity of the disease and found the highest levels of eotaxin-1 were in patients suffering from severe disease (Fig. 8A, B) (Günther *et al.*, 2011). In addition, quantification of eosinophils in lesional tissue showed they were the predominant cell type in BP skin lesions and were not found in PV skin lesions (Fig. 8C).



This is a preponderance of evidence supporting the role of eotaxin-1 in the pathology of Bullous Pemphigoid. Therefore, **WE CONCLUDE** these data indicate that eotaxin-1 is involved in the dermal eosinophilia and pathogenesis of BP and thus is validated as a therapeutic target, suggesting bertilimumab could emerge as a novel treatment option for this disease.

...Current treatment options for BP...

There is no cure for BP, thus current treatment options are utilized to reduce the size of blisters and provide relief from what is typically severe itching. Commonly prescribed medications include corticosteroids to reduce inflammation and relieve itching and immuno-suppressants to get the immune response back under control. Mild disease is usually treated with topical corticosteroids, such as with clobetasol propionate cream. More severe disease is typically treated with oral prednisone. However, long-term use of corticosteroids like prednisone can cause serious complications, including diabetes, high blood pressure, elevated cholesterol and cataracts. This becomes a particularly important issue since the average age of patients who develop BP is approximately 65 and severe side effects can be especially problematic in this age group.

Azathioprine is typically added to prednisone treatment as it may lead to a reduction in corticosteroid dosing. Adverse effects of azathioprine include cytopenia, hepatitis, pancreatitis and an increased risk of infection. Other treatment options include cyclophosphamide, methotrexate and mycophenolate mofetil; however each of these medications can have severe side effects such as nausea, vomiting, leukopenia and hepatotoxicity. Patients with severe disease who do not respond to therapy are typically treated with plasmapheresis (the removal of large amounts of patient plasma to remove the autoantibodies) or intravenous immunoglobulin.

...Bullous Pemphigoid is an Orphan Disease...

As BP is only diagnosed in approximately 30,000 people worldwide each year, Immune is seeking orphan drug designation for bertilimumab for the treatment of BP. The Orphan Drug Act of 1983 was designed to provide financial incentives for and to reduce the costs associated with developing drugs for rare diseases and disorders. A “rare disease or disorder” is defined by the Act as affecting fewer than 200,000 Americans at the time of designation or one for which “there is no reasonable expectation that the cost of developing and making available in the United States...will be recovered from sales in the United States.” A sponsor must request that the FDA designate a drug currently under development for a “rare disease or condition” as an orphan drug, and if the FDA agrees that the drug and indication meet the criteria set forth in the Act, certain incentives become available including:

- ✓ The FDA must provide the sponsor with “written recommendations for the non-clinical and clinical investigations (based on the information available at the time of the request)... that would be necessary for approval of such drug for such disease or condition...”
- ✓ For a period of seven years post-approval, the FDA may not approve an application from a different sponsor for the “same drug” for the same disease or condition. For biological treatments, the FDA defines same drug to mean one that contains the “same principle molecular features.” The 7-year exclusivity period conferred by orphan drug status is important because patent protection and Hatch-Waxman data exclusivity have limited effectiveness in excluding competitors from introducing equivalent drugs with slightly different structures. An exception is provided by any change that leads to improved safety or efficacy.
- ✓ Grants and contracts are available to defray the costs of development. For 2013-17, the amount appropriated is \$30 million per year, which is a fairly modest sum but could make a significant difference for a small company such as Immune Pharmaceuticals.
- ✓ A tax credit in the amount of 50% of qualified clinical testing expenses is established by related legislation (Title 26 Part 1-28). The tax credits can be rolled forward by up to 15 years for companies that have no tax liability in the year in which expenses are occurred (e.g., pre-revenue biotech companies).
- ✓ Waiver of PDUFA fees. For 2014, these are \$2.17 million for full NDAs, a huge benefit for a company with limited financial resources.

Similar laws have been passed in other major markets such as Europe and Japan. In Europe, orphan drug status is not associated with tax breaks or subsidies at the European Union level, but the exclusivity period is longer at 10 years. In Japan, the exclusivity period is also 10 years, and takes special significance as the approval times are so long that many drugs are reaching the end of their patent life when finally approved.

Immune Pharmaceuticals has applied for orphan drug status for bertilimumab with the FDA and European Medicines Agency (EMA) and anticipates a positive decision during the first half of 2014. **We are confident** that orphan status will be granted for bertilimumab and believe that it is a prudent strategy to attempt to advance the compound as a potential first-line treatment for BP. Given the lack of efficacious treatments for BP and the novel mechanism of action of bertilimumab, we anticipate Immune to be able to justify a significant price for treatment and generate significant revenues even with the small treatable population.

...Next Steps In BP...

The Phase 2 trial for BP is a safety and efficacy trial that will involve administration of bertilimumab at onset of the study and two weeks later, with daily administration of medium-dose prednisone (30mg). The prednisone dose will be tapered down each week in patients responding to bertilimumab. Efficacy, as assessed by a clinical response – no new blisters and healing of existing blisters – will be evaluated at week four. Sparing of corticosteroids will be another important assessment. Positive results with no known safety issues will lead to a double-blind, placebo controlled Phase 3 trial. We estimate the size of this trial will be 60-80 patients. The primary endpoint of that trial would be disease control/remission as measured by a decrease in the number of blisters after three months of treatment. Secondary endpoints could include a reduction in hospitalization and morbidity, as well as lower use of corticosteroids. The trial could be completed by the middle of 2016 with a possible FDA approval in 2017.

The costs associated with developing a drug for an orphan indication are much lower than for a larger disease indication, thus we believe that Immune would be able to cover all development costs and retain all rights to sales of the drug in the United States for the treatment of BP. We foresee a larger pharmaceutical company taking control of the overseas rights in exchange for a percentage of sales. For an indication such as this, we anticipate a partnership deal bringing in \$25 million in upfront fees with an additional \$150 million in backend milestone payments plus royalties on sales outside the United States.

Market Potential for Bertilimumab

...In Ulcerative Colitis & Crohn's Disease...

While difficult to pin down an exact number of patients diagnosed with UC, based upon the literature it appears to be approximately 750,000 individuals in the United States and another 1,000,000 patients in the rest of the world. Of those individuals, we model 50% of them having a moderate to severe flare up per year with 50% of those patients presenting with a high eotaxin-1 level. This represents 187,500 potential patients in the United States and 250,000 patients in the rest of the world per year.

We foresee bertilimumab as potentially coming before TNF- α therapy in patients with high eotaxin-1 levels, which would represent the first “personalized therapy” approach to treating UC. It is anticipated that vedolizumab will be priced at a premium of anti-TNF in the \$30,000 to \$40,000 range. We believe that bertilimumab will be priced similarly to Entyvio (vedolizumab). The product will be sold along with a companion diagnostic to test for high eotaxin-1 levels prior to treatment. Therefore, we believe that bertilimumab will be priced at approximately \$32,000 per year, putting it above the current prices of infliximab and adalimumab. We model a price of \$28,000 per year in the rest of the world. We model this level of pricing because a personalized therapeutic should command a higher price point than a standard biological treatment, and this price would be warranted if bertilimumab shows significant efficacy in two large Phase 3 clinical trials in a patient population selected based upon their eotaxin-1 levels.

We do not foresee Immune taking bertilimumab all the way to commercialization alone for the treatment of UC, but rather that positive results from the Phase 2 study will ignite interest from a partnering company. The significance of the results from the Phase 2 trial will dictate the type of deal that can be structured; however for our model we believe a deal worth approximately \$50 million upfront with backend milestone payments of \$400 million is possible for UC and CD.

We forecast bertilimumab being approved by the FDA for the treatment of UC in 2019 and for the treatment of CD in 2020. This is based on the availability of Phase 2 data in the 1st half of 2015, with two pivotal Phase 3 trials occurring from 2016-2018 with a BLA filed in 2018. With or without an eventual approval in CD, we see significant off-label use of bertilimumab in CD for patients with high eotaxin-1.

Distinct Mechanism of Action Differentiates Bertilimumab From Competitors

Addresses innate immunity with biomarker based patient selection

Property	Anti-eotaxin 1	Anti-CCR9	Anti-TNF	Anti-alpha 4 Integrins
Primary cellular target	Eosinophile	T-cells	Pleotropic resident and immune cells	T-cells
Adaptive immune system (memory)	No	Yes	No	Yes
Innate immune system (inflammatory quick responses)	Yes	No	Yes	No
Targets epithelial cell product	Yes	No	No	No
Targets soluble ligand	Yes	No	Yes	No
Targets receptor	No	Yes	No	Yes
Biomarker Strategy	Yes	No	No	No
Immunosuppressive effects	No	Likely	Yes	Yes

Source: Immune Pharmaceuticals, Inc.

...In Bullous Pemphigoid...

The market size for BP is very small, especially in the United States. With reported prevalence of only 35 cases per million people per year, that represents approximately 12,000 cases in the United States per year. The prevalence is slightly higher in the rest of the world, with approximately 20,000 cases reported each year. Just as in UC, bertilimumab will be utilized in a cohort of patients with high eotaxin-1 levels. This could differentiate it from current treatments of BP, as it could target the source of the disease and not just be utilized in a palliative setting.

We believe that premium pricing for bertilimumab in BP would be warranted based upon its distinct mechanism of action, thus for our model we have priced it at \$50,000 per year in the United States and \$40,000 per year in the rest of the world. We model 50% of BP patients as having severe disease with 75% of those patients also having a high eotaxin-1 level, meaning the total addressable market in the United States is approximately 4,500 individuals. Worldwide, our assumptions put the market size at approximately 7,500 individuals for a total addressable market close to 12,000 patients.

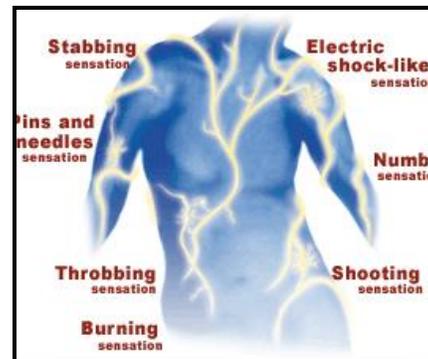
Assuming that bertilimumab is granted Orphan Drug status, we believe that Immune would be able to retain all rights to the drug in the United States with a partnering organization taking control of the rights overseas in exchange for a royalty on sales. We base this upon the fact that for an orphan disease the Phase 3 trials require much fewer patients, thus keeping costs significantly lower than for a typical Phase 3 study.

In addition, we believe that Immune will be able to partner with the International Pemphigus Pemphigoid Foundation for getting patients access to bertilimumab treatment. We forecast an FDA approval of bertilimumab for the treatment of BP in 2017. This is based upon a Phase 2 trial initiating in 2014, a Phase 3 trial in 2015 and filing of a BLA in 2016.

AmiKet: Treatment for Chemotherapy Induced Peripheral Neuropathy

Chemotherapy induced peripheral neuropathy (CIPN) is a severe dose-limiting toxicity associated with cancer chemotherapy and remains one of the major limitations in cancer treatment due to the lack of an effective treatment. The prevalence of CIPN ranges from 10-100% depending on the anticancer drug, dosage and methods of pain assessment.

CIPN symptoms range from a tingling or burning sensation in the hands and/or feet to muscle weakness, digestive problems and changes in blood pressure. Painful symptoms may persist well beyond the discontinuation of treatment resulting in a condition that is often more painful than the original cancer. While slow recovery of nerve damage may occur, often times it does not result in persistent pain.



Approximately 30-40% of chemotherapy patients develop peripheral neuropathy and experience symptoms of pain and sensory disturbances. This equates to approximately 15 million people just in the United States. When the pain is severe enough, a change in chemotherapeutic agent or discontinuation of chemotherapy all together is common, which in turn often leads to reduced effectiveness of treatment and a higher rate of disease relapse. Diagnosis of CIPN involves measurement of sensory and motor nerve conduction velocity, sensory nerve action potential and compound muscle action potential together with electromyography. Skin biopsy may or may not be utilized while nerve biopsy is rarely performed.

Anticancer agents most typically associated with CIPN are platinum agents (cisplatin/oxaliplatin), antitubulins (vincristine/paclitaxel), proteasome inhibitors (bortezomib) and thalidomide. These compounds are used to treat a range of cancer types and are typically utilized in combination therapies to enhance treatment efficacy. This in turn increases the risk of developing CIPN. The mechanism of induction for CIPN is different depending upon which agent is responsible, however they all to some degree affect specific peripheral nervous system structures to produce neuronopathy, axonopathy and/or myelinopathy that contribute to the pathogenesis of the disease.

Treatment of CIPN is given to alleviate the pain associated with the disease and depends upon the level of pain that the patient is experiencing. The symptoms are commonly managed in a similar manner to other types of nerve pain such as with a combination of physical therapy, acupuncture, and medications that includes nonsteroidal anti-inflammatory, steroids, antidepressants, anti-epileptics and opioids for severe pain. However, none of these medications have demonstrated true efficacy for treating CIPN and all of them carry their own side effects. The FDA has yet to approve any compounds for the treatment of CIPN.

AmiKet is a topical formulation of the FDA approved compounds amitriptyline (4%) and ketamine (2%). AmiKet has been extensively studied in a number of clinical trials and the combination of these two compounds has been shown to synergistically act to relieve CIPN at the local level through two separate mechanisms. Amitriptyline is a tricyclic antidepressant, a class of drugs that are considered the "gold standard" for neuropathic pain as they are the most effective and best-known drugs for this condition. While the exact mechanism of action for amitriptyline is uncertain, it is likely through interference with reuptake of serotonin and noradrenalin (Moore *et al.*, 2012). Ketamine is a noncompetitive NMDA receptor antagonist (Pachman *et al.*, 2011). Binding of ketamine to the NMDA receptor results in analgesia by preventing pain transmission in the spinal cord. It also inhibits the production of nitric oxide, a neurotransmitter involved in pain perception.

In April 2012, the FDA granted AmiKet Fast Track status for a Phase 3 trial for the treatment of CIPN. We believe positive results are likely to position AmiKet as a first-line treatment of CIPN. This represents a significant opportunity in an area of clear unmet medical need. Immune Pharmaceutical is actively pursuing out-licensing opportunities with a deal expected in the second half of 2014.

...Current neuropathy treatments...

There are no FDA approved medications for the treatment of CIPN, however there are medications available for the treatment of other neuropathy's that are sometimes prescribed off-label to CIPN patients. Pregabalin (Lyrica™) is the current standard of care for neuropathic pain as it has the broadest neuropathic pain label of all the marketed therapeutics. However, it is associated with a number of CNS-related side effects such as dizziness and sedation. Another leading neuropathic pain treatment is the anti-depressant duloxetine (Cymbalta™), however it has begun to face fierce competition from generic duloxetine as it has just recently come off patent. There has been a shift in recent years towards the use of transdermal patches that includes lidocaine (Lidoderm™). Lidoderm has dominated the topical neuropathic pain market since the 1990's. Sales of Lidoderm™ in 2012 totaled \$948 million.

AmiKet's topical ointment formulation offers a number of advantages to currently used medications, including a more versatile application method than the current patch formulations and a novel mechanism of action. The novel mechanism of action will be especially important to the large percentage of neuropathic pain patients who do not respond to current therapeutic options. Sales of the top seven neuropathic pain treatments totaled \$2.4 billion in 2010 with sales expected to grow to approximately \$3.6 billion by 2020. This increase in sales will be due to new drugs entering the marketplace as a number of the leading brands experience generic competition after expiration of patent coverage.

...AmiKet Clinical Data...

AmiKet has been studied in a total of five separate Phase 2 studies for the treatment of CIPN, post-herpetic neuralgia (PHN) and diabetic peripheral neuropathy (DPN). The three most recent trials are outlined below:

- **Phase 2 (CIPN).** In February 2011, Immune reported positive results from a Phase 2b trial evaluating the efficacy and safety of AmiKet in CIPN. The multi-center, double blind, randomized, placebo-controlled study was conducted by the National Cancer Institute (NCI)-funded Community Clinical Oncology Program. A total of 461 patients suffering from painful CIPN were enrolled in the six-week study. The results of the trial in the intent to treat (ITT) population demonstrated that the change in average daily neuropathy intensity scores in the AmiKet group achieved a statistically significant reduction in CIPN intensity versus placebo ($P < 0.001$), which was the trial's primary endpoint. Additionally, a pre-specified subgroup of the ITT population, those patients who previously received taxane chemotherapy, also showed a statistically significant reduction in average daily neuropathy intensity scores ($P = 0.034$). This subgroup constituted more than 50% of the ITT population. Secondary efficacy endpoints confirmed the superiority of AmiKet vs. placebo. Furthermore, the safety profile of AmiKet was comparable to placebo.
- **Phase 2 (PHN).** In January 2009, Immune reported positive results from a Phase 2b clinical trial of AmiKet in patients suffering from PHN. The trial was a randomized, double blind, placebo-controlled non-inferiority trial where patients were treated with AmiKet, gabapentin or placebo. A total of 360 patients were enrolled with the change in pain intensity as the first primary endpoint. The data demonstrated that AmiKet achieved statistically significant efficacy compared with placebo ($P = 0.026$). An additional primary endpoint, to demonstrate that AmiKet was not inferior to gabapentin in reducing pain, was also met. A key secondary endpoint measured in the trial from a responder analysis indicated that 63% of patients in the AmiKet treatment arm achieved a reduction in pain scores of at least 30%, significantly higher than that of patients in the placebo arm ($P = 0.033$). Top-line data results further indicated that AmiKet achieved a superior safety profile when compared with gabapentin, especially with regard to dizziness and somnolence. In January 2010, AmiKet received orphan drug protection for the treatment of PHN.
- **Phase 2 (DPN).** In February 2008, Immune reported encouraging results from a Phase 2 clinical study of AmiKet in patients suffering from DPN. The trial was a double blind, placebo-controlled study of AmiKet in 215 DPN patients. The data demonstrated that the primary endpoint, the difference in changes in pain intensity between AmiKet and placebo over the four-week duration of the trial, nearly reached statistical significance ($P = 0.0715$). Key secondary endpoints measured in the trial from a responder analysis indicate that 60% of patients in the AmiKet treatment arm achieved a reduction of pain scores of at least 30% compared with 48% of patients in the placebo arm ($P = 0.076$). In addition, 33% of patients in the AmiKet treatment arm achieved a reduction in pain scores of at least 50% compared with 21% of patients in the placebo arm ($P = 0.078$). Although this trial did not achieve statistical significance, all pain scores measured trended in favor of the AmiKet treated patients over the placebo group, indicative of an analgesic effect in this type of peripheral neuropathic pain.

...Clear Regulatory Path...

We believe the positive results from the above Phase 2 studies support the advancement of AmiKet to a pivotal, registration-sized trial for CIPN. Immune's plan is to find an appropriate partner to advance AmiKet into Phase 3 development and commercialization. With the foundation from the Phase 2 results, we believe it should not be difficult for Immune to strike a lucrative deal with prospective partners and this could be closed later this year.

In 2012, Immune received further encouraging guidance for the Phase 3 clinical and nonclinical development and subsequent NDA filing of AmiKet based on the issuance of the final minutes of Immune's meeting with the FDA in December 2011. In the final meeting minutes the FDA acknowledged that painful symptoms due to CIPN represent a significant unmet medical need.

Further, the FDA waived several expensive and time consuming non-clinical toxicology studies, and indicated that a single four-arm factorial trial might suffice for regulatory approval if combined with other pivotal data in another neuropathy such as diabetic peripheral neuropathy.

The key element of the proposed Phase 3 clinical program is a 12-week, four-arm, factorial designed trial in CIPN that would seek to demonstrate AmiKet's superiority compared with placebo and with each of the component drugs of AmiKet, amitriptyline and ketamine. Immune intends to submit the protocol for this trial to the FDA via a Special Protocol Assessment (SPA). An additional two-arm efficacy study in another painful peripheral neuropathy may be performed as an alternative strategy to a second factorial-designed trial for the NDA filing, which could potentially lead to a broader label in the treatment of peripheral neuropathic pain.

The meeting minutes with the FDA included a summary of the nonclinical program requirements to file an NDA, which notably included only a single dermal carcinogenicity study. The dermal photo-irritation/toxicity assessment may be waived, provided dermal photo-irritation is assessed in the clinical program. A COMET assay (Single Cell Gel Electrophoresis to detect DNA damage) study is required prior to initiation of the long-term open label clinical safety study.

During the second quarter of 2012, Immune received written advice from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) concerning the clinical and nonclinical development and subsequent Marketing Authorization Approval (MAA) filing of AmiKet. In its written advice the CHMP recommended that the proposed clinical program consist of a single 12-week, four-arm, factorial-designed trial in CIPN that would seek to demonstrate AmiKet's superiority compared with placebo and with each of the component drugs of AmiKet, amitriptyline and ketamine. An additional two-arm efficacy study in CIPN or another neuropathy is required to complete the clinical requirements of the application. The advice provided a summary of the additional nonclinical program requirements to file an MAA, which included a 90-day dermal toxicity study in a non-rodent species, a dermal phototoxicity study in a rodent and an ocular toxicity study. The advice received from the CHMP is consistent with the guidance given to Immune by the FDA in January 2012, in which the FDA waived several expensive and time-consuming non-clinical toxicology studies, and indicated that a single four-arm factorial trial might suffice for regulatory approval if combined with other pivotal data in another neuropathy such as diabetic peripheral neuropathy.

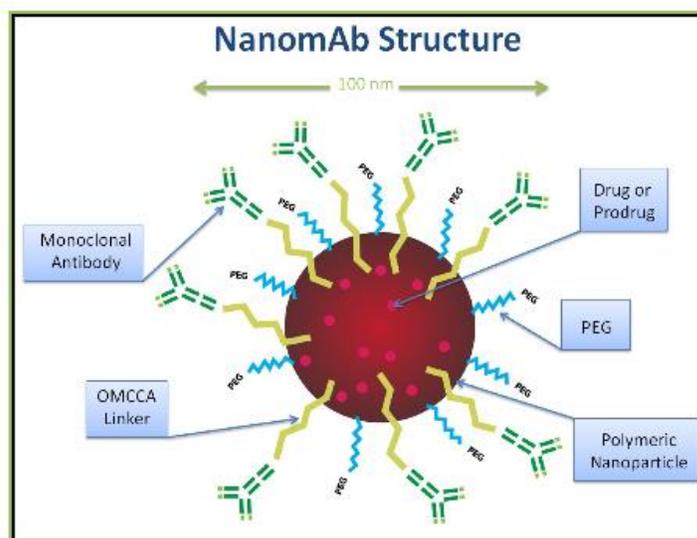
WE CONCLUDE the responses from both the FDA and CHMP on a path forward for AmiKet are positive. We see this as benefiting AmiKet's market opportunity and time to NDA or MAA filing. Besides the FDA already designating Orphan Drug designation to AmiKet for both CIPN and PHN, the agency also granted Immune Pharma Fast Track status in April 2012, and has agreed that a Special Protocol Assessment (SPA) would be available upon formal submission and agreement on the Phase 3 trial protocol in CIPN. This all helps facilitate the efforts to identify potential acquirers or strategic partners to advance AmiKet towards approval and commercialization.

NanomAbs: Ligand Conjugated Nanoparticles

Monoclonal antibodies (mAbs) have been a driving force in cancer treatment since their development over 30 years ago. However, as monoclonal antibodies can only target one antigen/pathway, cancer cells typically acquire resistance to them. One way to overcome this shortcoming is to conjugate a second cancer-killing compound (e.g., a chemotherapeutic agent) to the mAb that can target a second pathway, rendering both the antibody and the toxic agent more effective. These formulations are known as antibody-drug conjugates (ADCs) and are fast becoming a very intense focus in cancer research.

Immune Pharmaceuticals NanomAbs platform is an ADC technology that was licensed from The Hebrew University of Jerusalem. It is a four-component technology consisting of:

- 1) A PEGylated PLGA nanoparticle (PPN) that transports the toxic compounds,
- 2) A proprietary linker that connects the monoclonal antibody to the PPN,
- 3) A mAb, that serves to target a cancer-specific antigen,
- 4) A drug loaded within the PPN.



NanomAbs are considered a second-generation ADC and hold a number of advantages over traditional ADCs including:

- ✓ High payload – traditional ADCs are only able to carry an average of 4 toxic agents per antibody compared to up to 20,000 molecules per nanoparticle.
- ✓ Increased half-life – attaching PEG molecules to the outside of the nanoparticle extends circulation time and prevents clearance by immune cells.
- ✓ Diversity of delivered compounds – traditional ADCs can only carry chemotherapeutic agents while NanomAbs could theoretically deliver antisense drugs, peptides and multiple chemotherapeutics at once.

There are currently two ADCs that have been approved by the FDA, Adcetris (brentuximab vedotin; Seattle Genetics) and Kadcyla (ad-trastuzumab emtansine; Roche). In addition, there are multiple mid and late-stage products including CMC-544 (Pfizer), IMGN-901 (ImmunoGen), CDX-011 (Celldex Therapeutics) and SAR3419 (Sanofi). ADCs carry a premium price in the market, with brentuximab priced at over \$14,000 per dose, which equates to over \$100,000 per year. Ado-trastuzumab is similarly priced at \$9800 per month, a considerable premium to the \$4800 per month of trastuzumab alone.

Sales of Adcetris and Kadcyla totaled approximately \$200 million for the first 9 months of 2013. However, these drugs have only recently been approved and the ADC market is expected to be approximately \$9 billion by 2023 according to Roots Analysis Private Limited. The promise of ADC technology has led to a flurry of partnerships between larger companies looking to enter the ADC field and the smaller companies that hold the rights for ADC technologies. These partnerships typically include an upfront payment of between \$20-\$40 million and milestone payments totally approximately \$200 million.

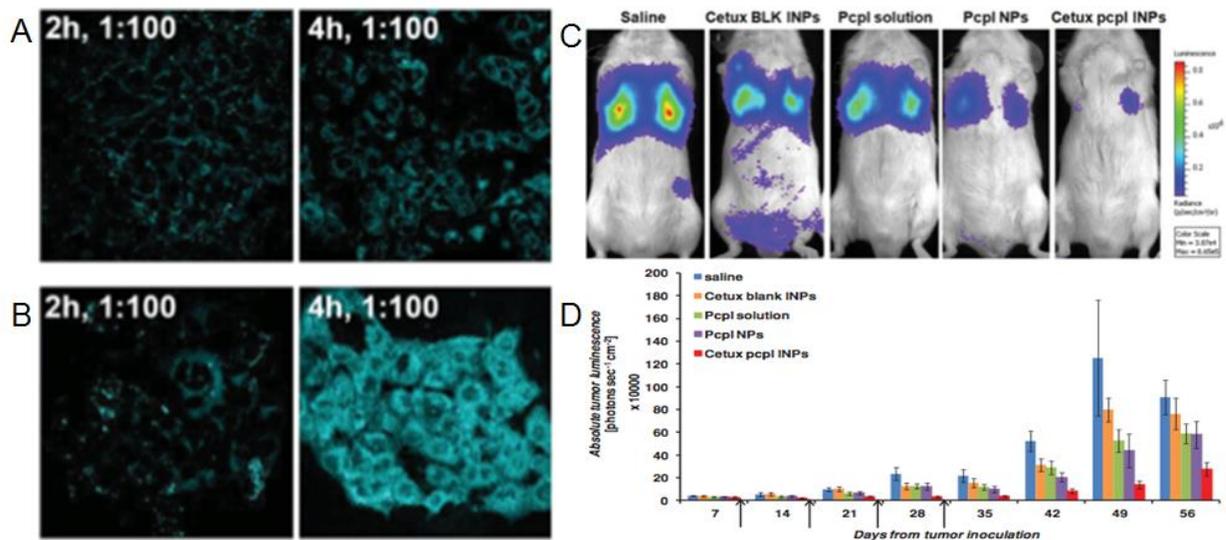


Figure 9: NanomAbs are taken up by cancer cells and lead to decreased tumor growth. Intracellular uptake of PNNs is shown using a fluorescently labeled PNN without cetuximab (A) or with cetuximab (B) following a 2-4 hr incubation. (C) Bioluminescent luciferase imaging assay of a lung cancer mouse model on day 42 with tumor size designated by the total luminescence intensity. (D) Quantification of longitudinal detection of tumors, with arrows indicating treatment schedule. Source: Karra *et al.*, 2013.

Immune Pharmaceuticals currently has three NanomAb products in pre-clinical development:

- ❖ ***NanomAbs for lung cancer.*** The epidermal growth factor receptor (EGFR) is a known driver of NSCLC. Thus, cetuximab, an EGFR-specific monoclonal antibody, was utilized as a targeting mechanism with the chemotherapeutic agent paclitaxel-palmitate. Binding of the anti-EGFR paclitaxel NanomAbs resulted in endocytosis and accumulation in the tumor cells (Figure 9) (Karra *et al.*, 2013). Using a lung cancer mouse model, they showed that mice treated with the anti-EGFR paclitaxel NanomAbs lived longer and had slower tumor growth compared to control mice.
- ❖ ***NanomAbs for prostate cancer.*** Overexpression of HER2 is a hallmark of a number of cancers, including breast and prostate cancers. Anti-HER2 NanomAbs loaded with paclitaxel palmitate were shown to bind and be taken up *in vitro* by two prostate cancer cell lines (Debotton *et al.*, 2008). In addition, the NanomAbs elicited a significant anti-tumor activity in a mouse model of metastatic prostate cancer compared to paclitaxel palmitate alone or paclitaxel loaded nanoparticles without anti-HER2 antibodies attached.
- ❖ ***NanomAbs for pancreatic cancer.*** Many cancer patients have an increased level of the iron-binding protein ferritin. Immune has acquired the rights to the intellectual property covering an anti-ferritin antibody, AMB8LK, which has shown marked affinity for specific tumor organs overexpressing ferritin (Sabbah *et al.*, 2007), and attached it to gemcitabine and paclitaxel loaded nanoparticles for pre-clinical studies. The AMB8LK labeled nanoparticles were shown to be taken up by the cancer cells where they exhibited cytotoxic effects. The rationale for using gemcitabine and paclitaxel is that the combination of these two chemotherapeutic agents was recently approved as a first-line treatment of pancreatic cancer.

Immune has announced that it plans to develop the AMB8LK coated nanoparticles for pancreatic cancer in-house while seeking licensing and partnership deals for additional indications. We anticipate an IND filing to begin Phase 1 studies in 2015 with any partnership deals signed within the next year involving a pre-clinical product to attract approximately \$5 million in upfront fees with \$50-100 million in milestone payments.

Successful completion of Phase 1 studies prior to a licensing/partnership deal would likely increase those numbers by a factor of 2-3x.

Intellectual Property

Immune holds or has acquired the rights to an assortment of intellectual property:

Bertilimumab: Immune acquired a license to the patent family covering bertilimumab that includes composition of matter patents and methods of obtaining eotaxin-1 binding antibodies. These patents expire in 2021, however approval by the FDA would grant bertilimumab data exclusivity for 12 years from the date of approval. While data exclusivity would keep generic drug makers from using Immune's clinical data to support an biosimilar submission, expiration of the patent would potentially allow another firm to conduct their own bioequivalence studies and clinical trials to support a generic drug application. Immune has filed in 2013 a patent covering anti-eotaxin mAbs for the treatment of IBD which would provide exclusivity until 2033. Bertilimumab will also benefit from orphan drug status for the treatment of bullous Pemphigoid which provides 7 years exclusivity in the US and 10 years in Europe.

In addition, Immune has acquired a license from Lonza Sales AG to use, development, manufacture, market, and sell bertilimumab as it is produced through the use of Lonza's cell lines, vectors and know-how.

Amiket: Immune holds a patent for a formulation containing a combination of amitriptyline and ketamine used for the treatment of pain, which expires in 2021. In addition, Immune holds a license to patents covering topical use of tricyclic antidepressants and NMDA antagonists for treatment of pain. Under the Hatch Waxman patent restoration act, Immune is eligible for up to 5 additional years of protection in the US, while data exclusivity in EU is 10 years from approval.

NanomAbs: Immune acquired an exclusive license to the patents covering the NanomAbs technology from The Hebrew University of Jerusalem. The patents covering the technology have a range of expiration dates from 2026-2034.

AMB8LK: In March 2012, Immune acquired all patent rights related to the anti-ferritin mAb AMB8LK from MabLife. The patent family covering the use of anti-ferritin antibodies in the treatment of cancer expire in 2021, with the composition of matter patent covering an anti-ferritin mAb expiring in 2027.

Human Antibody Production Technology Platform: Immune has acquired all intellectual property related to mice producing human antibodies and a method of preparation of human antibodies. Through this platform, along with additional laboratory work, human immune system and specific cell lines are introduced in mice, enabling the mice to produce fully human mAbs. This technology is currently in patent prosecution.

Financial Position

On March 10, 2014, Immune Pharma announced a private placement with select group of investors raising gross proceeds of approximately \$11.6 million. The transaction included the offering of 11,700 units of 8% Series C Convertible Preferred Stock priced at \$1,000 per unit. Each unit is convertible into common stock at the lower of \$3.40 per share or 85% of the next future public offering plus a five-year warrant to purchase one-half of a share of common stock at the lower of \$4.25 per share or 125% of the next public offering and a five-year warrant to purchase one-half of a share of common stock at the lower of \$5.10 per share or 150% of the next public offering. The Purchasers include Daniel Teper, the Company's Chairman and Chief Executive Officer, and directors Daniel Kazado, Isaac Kobrin, Rene Lerer and David Sidransky (See [Form 8K](#) for more details).

We believe the current cash balance including this raise is sufficient to fund operations for the next several quarters. However, we are aware that the company's ultimate goal is to uplist the shares from the current OTCQX to the NASDAQ. Based on our analysis of the balance sheet, Immune current qualifies for an uplisting given the above transaction. We believe the company plans to move quickly over the next few months to list on the NASDAQ exchange. We believe this move will significantly increase liquidity and exposure for the company.

MANAGEMENT PROFILES

Dr. Daniel Teper – Chairman and Chief Executive Officer

Dr. Teper is the founder and CEO of Immune Pharmaceuticals. He was the Managing Director for North America at Bionest Partners, a global Strategy Consulting firm serving the pharmaceutical industry. He began his career at Sandoz (now Novartis) Global Headquarters in Basel. He became President, Global Operations at HAVAS Healthcare Worldwide, a leading marketing and communication group, where he helped launch multiple industry blockbusters. Dr. Teper was cofounder of Novagali, which was recently acquired by Santen. Dr. Teper holds a Doctor of Pharmacy degree from Paris XI University and an MBA from INSEAD.

Robert Cook – Senior Vice President and Chief Financial Officer

Mr. Cook was appointed as the CFO and Director of Immune Pharmaceuticals in August 2013. Mr. Cook previously served as the Interim Chief Executive Officer and Director since August 2012 and as the CFO and Senior Vice President, Finance and Administration since April 2004. Prior to joining Immune, Mr. Cook was Vice President, Finance and Chief Financial Officer of Pharms Corporation since January 1998 and became Executive Vice President of Pharms in February 2001. From May 1995 until his appointment as Pharms's Chief Financial Officer, he was a vice president in GE Capital's commercial finance subsidiary. Mr. Cook received his B.S. in International Finance from The American University in Washington, D.C.

Suzu Jones, Chief Business Development Officer

Ms. Jones is the Chief Business Development Officer. She is the Founder and Managing Partner of DNA Ink LLC, a life sciences business development and licensing firm in San Francisco, CA. Prior to starting her own firm, Ms. Jones spent 20 years at Genentech in Research, Product Development, and Business Development. Alongside her work with Immune, Ms. Jones is currently on the Board of Patrys, an Australian biotech company; and on the advisory boards of Stem CentRx and Biocision.

Dr. Simon Benita – Chair, Scientific Advisory Board

Dr. Benita is a Professor at The Hebrew University of Jerusalem and is the co-creator of NanomAbs. His research is focused on nano- and microparticulate drug delivery systems aimed at improving the therapeutic performance of active ingredients. He has published 144 research articles and 18 book chapters, edited 4 books and been issued 16 patents. Dr. Benita founded Novagali Pharma, which was acquired by Santen Co. in 2012. He is currently the Director of the Institute for Drug Research and Head of the School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem.

Dr. Mark Rothenberg – Co-Chair, Scientific Advisory Board

Dr. Rothenberg is the Director of Immunology and Allergy at the Center for Eosinophilic Diseases and a Professor of Medicine at Children's Hospital in Cincinnati, OH. Dr. Rothenberg completed his MD/PhD, Residency in Pediatrics and dual fellowships in Immunology and Hematology at Harvard Medical School. In 1996, he co-authored the landmark Nature Medicine publication on human eotaxin and eosinophils and has since published original experimental and clinical studies confirming the importance of eotaxin and eosinophil regulation in Inflammatory Bowel Disease and Severe Asthma.

Dr. David Sidransky – Vice Chairman

Dr. Sidransky is a renowned oncologist and research scientist named and profiled by TIME magazine in 2001 as one of the top physicians and scientists in America, recognized for his work with early detection of cancer. Since 1994, Dr. Sidransky has been the Director of the Head and Neck Cancer Research Division at Johns Hopkins University School of Medicine and Professor of Oncology, Otolaryngology, Cellular & Molecular Medicine, Urology, Genetics, and Pathology at Johns Hopkins University and Hospital. Dr. Sidransky is one of the most highly cited researchers in clinical and medical journals in the world, in the field of oncology during the past decade, with over 300 peer-reviewed publications. He has served as Vice Chairman of the Board of Directors. Dr. Sidransky is the recipient of a number of awards and honors, including the 1997 Sarstedt International Prize from the German Society of Clinical Chemistry, the 1998 Alton Ochsner Award Relating Smoking and Health by the American College of Chest Physicians, and the 2004 Richard and Hinda Rosenthal Award from the American Association of Cancer Research.

Dr. Isaac Korbin – Director

Dr. Isaac Korbin led worldwide clinical programs from Phase I development through to regulatory approval, marketing and launch for several major drugs. He spent 10 years at Roche Global Headquarters in Basel, Switzerland and in Nutley, New Jersey. He then joined Actelion Pharmaceuticals (SIX: ATLN) in September 1999 to build and lead its clinical development department. Dr. Korbin held the position of Head of Clinical Development till 2009, when he was appointed to Chief Medical Officer and Chairman of the Strategic and Portfolio Board. At Actelion, Dr. Korbin led the development of several large programs, including the regulatory approval of Tracleer, which supported a successful initial public offering on the Swiss Stock Exchange at a valuation of over CHF 1 billion within three years of the Company's formation. Dr. Korbin is Board certified in Internal Medicine and completed a Fulbright Fellowship at the Ochsner Foundation in New Orleans, Louisiana. Dr. Korbin was a Senior Lecturer and the Director of Pre-Clinical and Clinical Hypertension Research at Hadassah Hospital prior to joining Roche in 1989.

VALUATION AND RECOMMENDATION

We are initiating coverage of Immune Pharmaceuticals, Inc. (IMNP) with a Buy rating with a price target of \$9.

Our valuation is built upon the four key areas in Immune's pipeline: 1) bertilimumab in UC and CD, 2) bertilimumab in BP 3) partnering AmiKet 4) partnering NanomAbs. While bertilimumab will most likely be tested in additional indications where eosinophilia and high eotaxin-1 levels have been noted (i.e., severe asthma, Crohn's disease), we are not including additional FDA approved use in our model.

Bertilimumab has blockbuster potential as an IBD treatment

We believe that bertilimumab has blockbuster potential as a treatment for UC, although we do note that the drug is only in Phase 2 testing at this point, thus there is a high degree of uncertainty as to how the drug will ultimately fare in clinical testing. However, we are confident that bertilimumab will succeed based upon the following:

- 1) **High eotaxin-1 levels are associated with UC, and the severity of disease seems to directly correlate with the level of eotaxin-1 in both sera and tissue.** Beginning in the early 2000's it was noted that UC patients had elevated levels of eotaxin-1 in their sera. Follow-up studies performed all over the world by many different research groups have confirmed these initial results, and have further added that not only do sera eotaxin-1 levels correlate with UC, but also eotaxin-1 levels from colonic tissue.
- 2) **Animal data shows that an absence of eotaxin-1 leads to a decrease in eosinophilia and a marked decrease in disease in a model of UC.** Eotaxin-1 knock-out mice have a significant reduction in the population of gastrointestinal eosinophils, a reduced eosinophil-associated inflammation and gastrointestinal pathology and reduced colitis associated with reduced number of colonic eosinophils in a mouse model of UC.
- 3) **Blocking eotaxin-1 alters the disease pathogenesis in a mouse model of UC.** Using a chemokine binding protein isolated from tick saliva, researchers showed that blocking eotaxin-1 resulted in a reduction in the recruitment of eosinophils to the large intestine induced by DSS administration. This was accompanied by improvement in the clinical signs of colitis, weight loss and lethality rates.

Based upon the literature we estimate there to be approximately 1.5 million individuals in the U.S. and another 2.2 million patients in the rest of the world with IBD. Of those individuals, we model 50% of them having a moderate to severe flare up per year with 50% of those patients presenting with a high eotaxin-1 level. This represents 375,000 potential patients in the U.S. and 550,000 patients in the rest of the world per year. We see rapid uptake of bertilimumab in the target patient population (i.e., patients with high eotaxin-1 level) based upon its unique mechanism of action and personalized treatment approach. We forecast an initial 5% penetration in the target market the first year of approval, with a rapid increase in the number of treated patients peaking at 20% by 2025.

We believe that bertilimumab would be priced at approximately \$32,000 per year, putting it approximately 20% above the current price of infliximab and adalimumab. A personalized therapeutic would command a higher price point than a standard biological treatment, and this price would be further justified if bertilimumab showed great efficacy in two large Phase 3 clinical trials in a patient population selected based upon their eotaxin-1 levels.

We do not foresee Immune taking bertilimumab all the way to commercialization alone for the treatment of UC, but rather that positive results from the Phase 2 study will ignite interest from a partnering company. The significance of the results from the Phase 2 trial will dictate the type of deal that can be structured; however for our model we believe a deal worth approximately \$50 million upfront with backend milestone payments of \$400 million is possible for IBD with an estimated of a 15% royalty rate. We forecast bertilimumab being approved by the FDA for the treatment of UC in 2019 and CD in 2020. This is based on the availability of Phase 2 data in 2015, with two pivotal Phase 3 trials occurring from 2016-2018 with a BLA filed in the second half of 2018.

NPV → Under the above scenario, we believe bertilimumab for the treatment of IBD is worth: \$105 million

Treatment of BP is an underappreciated opportunity

We believe that bertilimumab could represent a paradigm shift in the treatment of BP as there is no cure and current treatment options are utilized to merely control symptoms. While the treatable patient population is small, we feel that targeting bertilimumab for the treatment of BP represents an underappreciated opportunity for the following reasons:

- 1) **BP is associated with an increased level of eotaxin-1 and eosinophilia.** Data has been collected for more than 10 years showing an increased level of eotaxin-1 in the sera and blister fluid of BP patients compared to both healthy controls and to patients suffering from PV, a related skin disorder. In addition, analysis of BP lesions showed eosinophils to be the predominant cell type, with very few eosinophils found in PV lesions. Thus, bertilimumab is likely to show clinical activity in this indication.
- 2) **Orphan drug designation will significantly decrease costs associated with developing bertilimumab as a BP treatment.** Immune has applied for orphan drug designation for bertilimumab in the treatment of BP and expects a positive reply during the first half of 2014. Orphan drug designation comes with a host of incentives, including written guidance from the FDA on clinical trial design, a smaller cohort of patients necessary for Phase 3 trials, grants and contracts are available to offset the cost of development and (perhaps most important for a company such as Immune) the waiver of PDUFA fees, which in 2014 cost \$2.1 million.
- 3) **Bertilimumab would quickly become the standard of care for BP patients.** While the total treatable BP population is small, we believe that clinical success would translate into bertilimumab quickly becoming the standard of care for BP patients, due to its unique and targeted mechanism of action.

BP is an orphan disease, and we estimate that there are only 12,000 cases or so per year in the United States, based upon epidemiological data putting the prevalence at anywhere between 30-40 cases per million people per year. In addition, there are approximately 20,000 cases of BP in the rest of the world per year. We estimate that 50% of BP patients will be suffering from severe disease, and of these 75% will have high eotaxin-1 levels thus making them eligible for bertilimumab therapy. This equates to a treatable population of 4,500 patients in the United States and 7,500 in the rest of the world. We believe an effective treatment of BP would command premium pricing, and we have modeled it to cost \$50,000 per year initially in the United States and \$40,000 per year in the rest of the world.

NPV → Under the above scenario, we believe bertilimumab for the treatment of BP is worth: \$35 million

AmiKet partnership likely to happen in 2014

Immune has previously stated a desire to have a licensing deal in place for AmiKet by the end of 2014. We see this as a large market opportunity, with a drug that has been granted both Orphan Disease designation and U.S. FDA Fast Track status. Partnering AmiKet will have a positive impact on the company in a number of ways, including bringing in a much needed infusion of cash in the form of an upfront payment that we estimate could be approximately \$10 million with back end milestones worth approximately \$50 million. The neuropathic pain market represents a \$2 billion market opportunity, and we believe that AmiKet's novel mechanism of action, ease of application and excellent safety profile are representative of a \$400-500 million drug.

NPV → Under the above scenario, we believe AmiKet for the treatment of CIPN is worth: \$25 million

NanomAbs represent an exciting possibility in cancer treatment

Immune has indicated that they will be developing anti-ferritin NanomAbs with monoclonal antibody AMB8LK in-house and will look to forge partnerships for various other indications. Given the wide array of indications that NanomAbs could be targeted against, it is difficult to come up with a valuation for the technology based on what market it is likely to enter. However, we can estimate what a potential partnership deal would be worth based upon previous deals with similar products. Merrimack Pharmaceuticals is developing MM-398, a nanotherapeutic consisting of the chemotherapeutic agent irinotecan encapsulated in a liposomal sphere. Just before Phase 2 data was released in June 2011, Merrimack acquired the European and Asian rights to MM-398 from PharmaEngine, Inc. in exchange for a \$10 million up-front payment, \$80 million in development and regulatory milestone payments and \$130 million in sales milestone payments. Any deal structured in regards to rights to NanomAbs would likely be of similar value, with \$10-20 million up-front and \$150-200 million in back end milestone related payments.

NPV → Under the above scenario, we believe the NanomAbs portfolio and technology is worth: \$15 million

Immune Pharma: Sum-Of-Parts Analysis	
<i>Bertilimumab in IBD</i>	\$105 Million
<i>Bertilimumab in BP</i>	\$35 Million ^A
<i>AmiKet</i>	\$25 Million
<i>NanomAbs</i>	\$15 Million
<i>Cash & Investments</i>	\$11 Million ^B
<i>Operating Burn</i>	(\$10.0 Million)
Total Firm Value	\$180 Million
<i>Fully Diluted Shares</i>	20.0 Million ^C
Target Price	~\$9.00 / Share

A = Assumes Orphan Drug designation granted in U.S. & EU
B = Includes recent financing on March 3, 2014
C = Includes Basic shares + all outstanding stock options and reasonable warrants

Risks To Consider

The biggest risk in investing in Immune Pharmaceuticals at this stage is the potential failure of bertilimumab for the treatment of UC (or CD) or in BP. Above we calculated a fair-value for the company at roughly \$180 million, which assume an operating burn of approximately \$25 million over the next few years. Approximately \$140 million of that value (before operating burn) is associated with probability-adjusted net present value calculations on bertilimumab. The failure of bertilimumab in IBD or BP would have a profoundly negative impact on the shares. Although we see AmiKet and NanomAbs as nice secondary drivers for the stock, removal of bertilimumab from investment story would cause us to downgrade our rating and slash our price target dramatically.

We believe the company's goal is to uplist to the NASDAQ in the next few months, which would put a larger secondary public offering perhaps sometime this summer. Although we are big fans of the Immune story and believe the shares are dramatically under-valued at today's price, we cannot predict with certainty that the market will value Immune Pharma shares high enough by this summer that a larger secondary public offering will not be highly dilutive to existing shareholders.

Despite the recent \$11.6 million financing, we believe that Immune Pharmaceuticals will require substantially more cash to fund operations to cash flow positive. In the end, we believe securing additional cash to develop bertilimumab to Phase 3 for UC/CD or BP will be a significant value-creating event for the company, but we caution investors that we may have to revise our price target and financial model if the company enters into a large public offering this summer. At this time, we do not expect significant downward revision to our target unless terms of the public offering dramatically disappoint. We suspect that the momentum created in the shares by uplisting to the NASDAQ will be more than sufficient to cancel out any angst on a secondary offering.

PROJECTED FINANCIALS

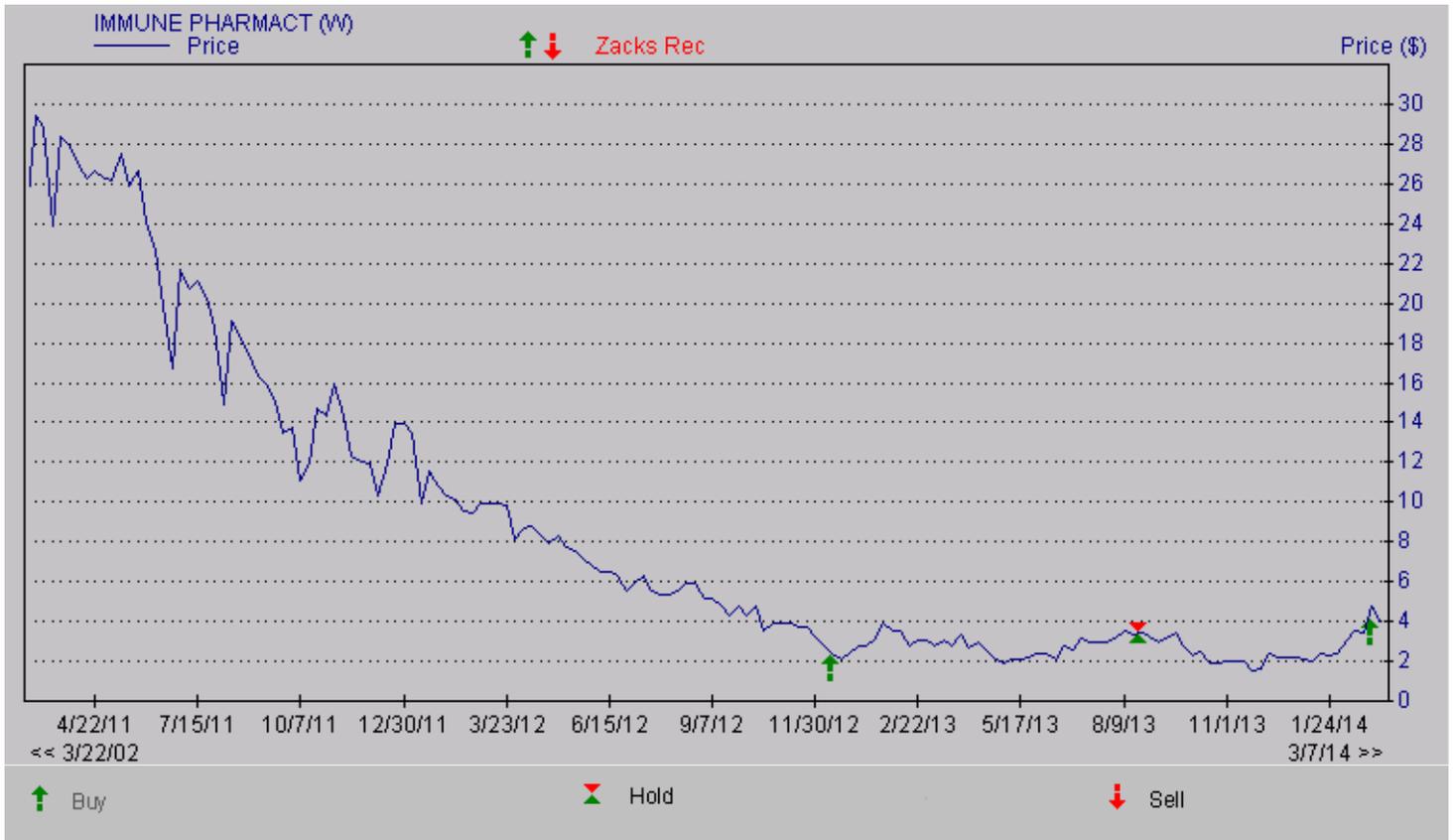
Immune Pharmaceuticals, Inc. Income Statement

Immune Pharma	2012 A	Q1 A	Q2 A	Q3 A	Q4 E	2013 E	Q1 E	Q2 E	Q3 E	Q4 E	2014 E	2015 E	2016 E
Bertilimumab	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$5.0	\$5.0
<i>YOY Growth</i>	-	-	-	-	-	-	-	-	-	-	-	-	-
AmiKet	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$5.0
<i>YOY Growth</i>	-	-	-	-	-	-	-	-	-	-	-	-	-
NanoMAbs	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$5.0	\$5.0
<i>YOY Growth</i>	-	-	-	-	-	-	-	-	-	-	-	-	-
Total Revenues	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$10.0	\$15.0
<i>YOY Growth</i>	-	-	-	-	-	-	-	-	-	-	-	-	-
Cost of Sales	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
<i>Product Gross Margin</i>	-	-	-	-	-	-	-	-	-	-	-	-	-
General & Administration	\$3.3	\$1.1	\$1.1	\$1.0	\$1.2	\$4.4	\$1.4	\$1.4	\$1.5	\$1.5	\$5.8	\$6.0	\$6.5
Research & Development	\$3.1	\$0.8	\$0.8	\$1.0	\$1.4	\$3.9	\$1.6	\$1.9	\$2.1	\$2.3	\$7.9	\$9.0	\$12.5
Other Operating Expenses	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Operating Income	(\$6.4)	(\$1.9)	(\$1.9)	(\$2.0)	(\$2.6)	(\$8.3)	(\$3.0)	(\$3.3)	(\$3.6)	(\$3.8)	(\$13.7)	(\$5.0)	(\$4.0)
<i>Operating Margin</i>	-	-	-	-	-	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	(\$3.5)	(\$0.1)	(\$0.1)	\$3.6	\$1.0	\$4.4	\$1.0	\$1.0	\$1.0	\$1.0	\$4.0	\$5.0	\$6.0
Pre-Tax Income	(\$9.9)	(\$2.0)	(\$2.0)	\$1.6	(\$1.6)	(\$3.9)	(\$2.0)	(\$2.3)	(\$2.6)	(\$2.8)	(\$9.7)	\$0.0	\$2.0
Income Taxes Paid	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
<i>Tax Rate</i>	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Deemed Dividends	\$0.0	\$0.2	\$0.2	\$0.4	\$0.3	\$1.2	\$0.3	\$0.3	\$0.3	\$0.3	\$1.0	\$1.0	\$1.0
Net Income	(\$9.9)	(\$2.2)	(\$2.2)	\$1.2	(\$1.9)	(\$5.1)	(\$2.3)	(\$2.6)	(\$2.9)	(\$3.1)	(\$10.7)	(\$1.0)	\$1.0
<i>Net Margin</i>	-	-	-	-	-	-	-	-	-	-	-	-	-
Reported EPS	(\$1.81)	(\$0.21)	(\$0.21)	\$0.11	(\$0.14)	(\$0.46)	(\$0.15)	(\$0.16)	(\$0.18)	(\$0.18)	(\$0.68)	(\$0.05)	\$0.04
<i>YOY Growth</i>	-	-	-	-	-	-	-	-	-	-	\$0.47	(\$0.67)	(\$1.06)
Basic Shares Outstanding	5.5	10.3	10.3	10.3	13.2	11.0	15.0	15.5	16.0	16.5	15.8	20.0	25.0

Source: Zacks Investment Research, Inc.

Jason Napodano, CFA

HISTORICAL ZACKS RECOMMENDATIONS



DISCLOSURES

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Buy/Outperform: The analyst expects that the subject company will outperform the broader U.S. equity market over the next one to two quarters.
Hold/Neutral: The analyst expects that the company will perform in line with the broader U.S. equity market over the next one to two quarters.
Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

The current distribution is as follows: Buy/Outperform- 16.5%, Hold/Neutral- 77.7%, Sell/Underperform – 5.1%. Data is as of midnight on the business day immediately prior to this publication.