Life Science Digest

MD BECKER PARTNERS LLC

Life Science Digest is published by MD Becker Partners LLC, a boutique management and strategy consulting firm focusing on both public and private companies in the life sciences industry.

www.mdbpartners.com

Medical Advances May Help Improve Psoriasis Outcomes

Autoimmune diseases are a group of disorders in which the primary cause is an inflammatory reaction resulting from the body's own immune system attacking normal tissues. The inflammatory reactions may affect one of more organs or tissue types, which often include skin, blood vessels, connective tissues, endocrine glands, joints and muscles.

One such autoimmune disease is psoriasis, which is a chronic systemic immune-mediated disorder that is characterized by inflammatory skin and joint manifestations. According to the National Psoriasis Foundation, psoriasis is the most prevalent autoimmune disease in the U.S., affecting as many as 7.5 million Americans. According to the World Psoriasis Day consortium, 125 million people worldwide, or 2 to 3 percent of the total population, have psoriasis. Even though psoriasis affects a large number of people, this disease is not highlighted as frequently as other chronic diseases such as cancer, diabetes and Alzheimer's.

Causes of Psoriasis

Researchers have found nine gene mutations that may be involved in causing psoriasis. These mutations seem to largely affect T-helper cells. Among these mutations, psoriasis susceptibility locus 1 (PSORS1) on chromosome 6, within the major histocompatibility complex, and psoriasis susceptibility locus 2 (PSORS2) on chromosome 17q, appear to be major factors that can lead to psoriasis[1]. Not everyone who has these gene mutations gets psoriasis and there are several forms of psoriasis that people can develop. Scientists now believe that at least 10% of the general population inherits one or more of the genes that create a predisposition to psoriasis. Researchers believe the individual must receive a combination of different genes (a combination which is likely to be different for different people) that work together to cause psoriasis and the individual must then be exposed to specific factors that can trigger his/her particular combination of genes to cause disease[2].

The specific factors that play a role in causing psoriasis in people who have these gene mutations include certain environmental, physical, and chemical triggers. Examples include weather, stress, bacterial or viral infections, stress, and low levels of calcium. Certain medications that are also known to either worsen psoriasis or induce a flare-up are choroquine, ace inhibitors, beta-blockers, lithium and indocin.

Physical injury to the skin exacerbates psoriasis. Types of skin injuries that can trigger a psoriasis flare include abrasion, increased friction from clothing or skin rubbing against skin in folds (such as armpits), sunburn, viral rashes and drug rashes. Psoriasis may also be more severe in people with weakened immune systems.

Types of Psoriasis

There are five types of psoriasis. The most common form, plaque psoriasis, appears as raised, red patches covered with a silvery white buildup of dead skin cells. Approximately 80% of those who have psoriasis have this type and approximately 17% of psoriasis patients have moderate-to-severe plaque psoriasis[3].

Chronic plaque psoriasis can have a profound impact on a patient's life. The skin lesions associated with plaque psoriasis are associated with significant symptoms, such as itching, scaling and pain, which ultimately impact a patient's emotional, social, occupational and physical functioning[4]. The effects of chronic plaque psoriasis on patient's reduced health related quality of life are similar to those seen with

arthritis, hypertension, heart disease, diabetes and depression[5].

The four remaining types of psoriasis are:

- Erythrodermic: skin redness is very intense and covers a large area;
- Guttate: small pink red spots appear on the skin;
- Inverse: skin redness and irritation occurs in the armpits, groin and in overlapping skin; and
- Pustular: white blisters are surrounded by red, irritated skin.

Psoriasis can occur on any part of the body and is associated with other serious health conditions, such as diabetes, heart disease and depression.

Pathogenesis

Psoriasis is a disease of T cell dysregulation[6]. As early as the 1970s, T cells were hypothesized to induce and perpetuate psoriatic disease. However, more recently, the pathogenesis of psoriasis has been further defined, implicating a more complex immune cascade and identifying new disease modulators as potential therapeutic targets.

The cell-mediated adaptive immune response is primarily responsible for initiation and maintenance of the disease. While T-helper cell type 1 (Th1) cytokines, such as interferon-gamma (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), and IL-12 have long been implicated in the pathogenesis of psoriasis, new research demonstrates the role of T-helper cell type 17 (Th17) in the evolution of the disease[7]. Th17 cells are stimulated by IL-23 and produce many recently identified pro-inflammatory cytokines, such as IL-17 and IL-22, leading to the recruitment of neutrophils and dysregulation of keratinocytes seen in psoriasis[8]. IFN-γ functions synergistically with IL-17 to produce IL-6 and IL-8, which also act to recruit inflammatory cells such as neutrophils. Other studies have shown that Th1 cells can induce the production of Th17 cells through the production of chemokine (C-C motif) ligand-20, a cytokine chemoattractant for dendritic cells, lymphocytes such as Th17 cells, and neutrophils[9]. Further understanding of the role of IL-12 in the production of Th1 cells and its complex interaction within the IL-23/Th17 axis will provide a rationale for unique targeted therapies.

TNF-α, produced by both activated dendritic cells and T cells, including Th1, Th17, and T-helper cell type 22 (Th22), is often elevated in inflammatory conditions including psoriasis, as evidenced by increased levels found in the serum and blister fluid of patients with the disease. Gene studies have also demonstrated that when TNF-α interacts with IL-17, there is a corresponding increase in gene expression that correlates with the degree of inflammation[10].

Among the newest factors identified in the pathogenesis of psoriasis are IL-22 and IL-20, which share a common receptor complex (IL-22R1). IL-22 effects keratinocyte terminal differentiation, resulting in epidermal hyperplasia and acanthosis (a diffuse hyperplasia and thickening of the epidermis), the well known psoriatic phenotype. IL-20, produced by keratinocytes, further perpetuates epidermal hyperplasia, through activation of IL-22R1[11]. The IL-22R1 receptor appears to be a novel driver of inflammation through positive auto-regulatory loops. In clinical studies, elevated serum levels of IL-22 and IL-20 in psoriatic patients correlate with the Psoriasis Assessment Severity Index (PASI)[12].

Current Treatments

Despite the availability of topical, oral and biologic treatments, patients are still in need of new and alternative treatment options for psoriasis. Limitations of the existing oral and biological treatments include adverse events and reduction in effectiveness over time. The systemic medications, which include oral and injectable drugs, that are currently approved for the treatment of moderate and severe psoriasis include:

- Retinoids, such as Soriatane® (aciretin), an oral retinoid, which is a synthetic form of vitamin A
- Methotrexate
- Cyclosporine
- Hydroxyurea
- Immunomodulator drugs (biologics), such as Amevive® (alefacept), Enbrel® (etanercept), Remicade® (infliximab), Stelara® (ustekinumab), Humira® (adalimumab), and Simponi® (golimumab)
- Thioguanine

Limitations of Approved Biologicals

The approved biologicals for moderate-to-severe psoriasis offer significant improvements in therapeutic alternatives over the older systemic drugs. However, there are notable adverse events with the biologics

"Infections, including severe opportunistic infections and tuberculosis, are a noted risk with TNF-α antagonists, and all three approved agents have a black box warning."

approved for psoriasis and their efficacy has been shown to diminish over time.

For example, the safety of TNF-α antagonists has been demonstrated and justified by use of these agents in the treatment of rheumatoid arthritis (RA) and inflammatory bowel disease for more than a decade. Data from the psoriasis trials confirm these established drug profiles. Major organ toxicities associated with conventional systemic therapies are not observed with TNF-α antagonists, although hepatitis has been reported with the use of infliximab. Infections, including severe opportunistic infections and tuberculosis, are a noted risk, and three approved TNF-α antagonists (adalimumab, etanercept and infliximab) have a black box warning required by the U.S. Food and Drug Administration (FDA) concerning the development of serious infections, including tuberculosis and disseminated fungal diseases, such as coccidioides and histoplasmosis. Opportunistic infections have been reported, but many of the patients were treated concomitantly with other immuno-suppressive agents, which is typical of treatment for inflammatory bowel disease or rheumatoid arthritis, but far less common in the treatment of psoriasis, possibly limiting the potential for infection in this population. The FDA requested that the etanercept boxed warning and prescribing information be updated to include legionella, listeria, and blastomycosis as potential infectious risks.

Treatment with TNF-α antagonists may slightly increase the risk of melanocytic and nonmelanocytic skin cancers, including squamous cell carcinoma, basal cell carcinoma, and cutaneous T cell lymphoma. The increased risk of lymphoma and other solid organ cancers is less clear. Studies have produced conflicting reports, have been underpowered to assess the risk of rare events, and have been tainted by the fact that patients with psoriatic disease are at an intrinsic increased risk of developing lymphoma[13].

Other reported events include development or worsening of both central and peripheral demyelinating diseases, drug-induced lupus-like syndromes, and worsening of congestive heart failure. Despite these safety concerns, meta-analyses of published trials conclude that the benefit of successful treatment is greater than the risk of serious events or toxicity.

The long-term effects of ustekinumab remain unknown, and much information will stem from post-marketing surveillance and additional long-term studies. Cumulative safety experience was analyzed through the pooling of safety data from the four Phase II and III psoriasis trials gathered over three years of treatment. Rates of serious infection during the placebo-controlled periods were similar between placebo (1.70) and ustekinumab 90 mg (1.97) groups, yet lower in the ustekinumab 45 mg group (0.49). The rates of non-melanoma skin cancer and other malignancies were consistent with the expected incidence in the general US population based on the Surveillance, Epidemiology, and End Results (SEER) database.

A major concern is the disproportionate number of major adverse cardiac events seen in the first 12 weeks of the Phase II trial of ustekinumab. Ultimately, it was determined that a high proportion of patients recruited into the trials had significant cardiovascular risk factors, such as obesity, smoking, high blood pressure, and diabetes[14]. However, significant concern about this issue prompted a retraction of the FDA approval for briakinumab (another humanized monoclonal antibody to the p40 subunit of IL-12 and IL-23), and clinical trials were stopped in the treatment of psoriasis.

A meta-analysis of randomized, placebo-controlled, double-blind, monotherapy studies evaluated cardiovascular outcomes for the anti-IL-12/23 agents (ustekinumab and briakinumab) and anti-TNF-α agents (adalimumab, etanercept, and infliximab). The primary outcome was a major adverse cardiac event during the placebo-controlled portion of the study. There were more major adverse cardiac events reported in patients who received active treatment with anti-IL-12/23 inhibitors than in the placebo group (10/3179 patients versus 0/1474 patients). These results lack statistical significance, suggesting that an increase in major adverse cardiac events during the early weeks of treatment may be due to an inherent disease risk in the psoriatic patient population[15,16].

Neutralizing human antichimeric antibodies have been reported to occur in approximately 16% of patients treated with infliximab[17]. These are neutralizing antibodies against the murine portion of infliximab and are thought to be responsible for the loss of sustainable treatment efficacy seen in patients treated long-term with infliximab. In contrast, antibodies to etanercept occur less often (approximately 3%) and are thought to be non-neutralizing[18]. Patients producing antibodies may experience decreased treatment efficacy with the cause being currently undefined. The presence of these antibodies is not only associated with a reduction in response to infliximab, but is also associated with the development of infusion reactions[19].

The major conclusion from a study comparing survival rates for three TNF-α inhibitors (adalimumab, etanercept, and infliximab) in patients with psoriasis vulgaris based on data from the Danish nationwide database DERM-BIO covering patients with psoriasis treated with a biologic agent is that the overall efficacy of anti-TNF-α drugs diminish with time, as envisaged by the progressive loss of patient adherence to treatment. The major reasons for stopping treatment were loss of efficacy (75%), followed by adverse events (12%). Infliximab had the best patient retention ability, with 70% of patients still being on the drug after four years of treatment[20]. Adalimumab and etanercept had significantly worse drug survival rates and there was no difference between these two drugs.

Product Pipeline

Products in development with different mechanisms of action than current treatments may help improve psoriasis patient outcomes. Due to the fact that a comprehensive review of the psoriasis landscape is beyond the scope of this article, the focus will be on systemic treatments, oral drugs, and injectable biologics that are in Phase II or Phase III clinical trials for the treatment of moderate-to-severe psoriasis.

Phosphodiesterase 4 (PDE4) Inhibition

Apremilast (CC-10004)

One of the next oral systemic drugs for treatment of moderate-to-severe psoriasis that is expected to be submitted for FDA approval is Celgene Corporation's (NASDAQ: CELG) aprelimast, an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) and a thalidomide analog. Aprelimast is currently the subject of two large, pivotal global studies (ESTEEM 1 and 2) in more than 1,200 patients with moderate-to-severe psoriasis with data expected by the end of 2012.

Celgene has announced that the company plans to submit a new drug application (NDA) for aprelimast in psoriatic arthritis (PsA) during the first quarter of 2013. A supplemental NDA (sNDA) submission for psoriasis is expected to follow in the second half of 2013. A combined Marketing Authorization Application (MAA) submission in Europe is also planned for the second half of 2013.

Apremilast is a PDE-4 inhibitor that results in inhibition of cyclic adenosine monophosphate (cAMP) in leukocytes and exerts anti-inflammatory effects by reducing cytokine transcription and further inflammatory responses such as neutrophil degranulation, chemotaxis and adhesion to endothelial cells. PDE4 is a cAMP-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, IL-23, and other inflammatory cytokines. Elevation of cAMP also increases anti-inflammatory cytokines such as IL-10.

ESTEEM 1 (NCT01994219) and ESTEEM 2 (NCT01232283) are Phase III, multi-center, randomized, double-blind, placebo-controlled, efficacy and safety studies of apremilast in subjects with moderate-to-severe plaque psoriasis. Primary endpoint is the proportion of subjects achieving at least a 75% reduction from baseline PASI score (PASI-75) at week 16. ESTEEM 1 and ESTEEM 2 include 844 patients and 413 patients, respectively. ESTEEM 1 has two additional secondary outcome measures: population-based pharmacokinetic estimate of systemic exposure of apremilast and to explore the relationship of apremilast exposure with efficacy and safety endpoints.

In the Phase IIb (PSOR-005), multi-center, randomized, placebo-controlled, dose-ranging study, patients (aged ≥18 years) with moderate-to-severe psoriasis were randomly assigned (in a 1:1:1:1 ratio) to receive oral placebo or 10, 20, or 30mg of apremilast twice daily at 35 U.S. and Canadian sites. The primary endpoint was the proportion of patients achieving at least PASI-75 at week 16. Apremilast 10mg did not differ significantly from placebo in achievement of the endpoint. For both apremilast 20mg and apremilast 30mg, the differences from placebo were significant. Most adverse events (96%) were mild or moderate, including nausea, upper respiratory tract infection, diarrhea, nasopharyngitis, headache, arthralgia (placebo), gastroenteritis, or dyspepsia. Apremilast, given orally at 20 or 30 mg twice daily, appears to be efficacious, safe, and tolerable for patients with moderate-to-severe plaque psoriasis[21].

Kinase Inhibitors

Tofacitinib

Pfizer Inc.'s (NYSE: PFE) tofacitinib (formerly designated CP-690,550) is an oral Janus kinase (JAK) inhibitor. It is being studied at a dose of 5mg or 10mg orally twice daily. Phase III trials for plaque psoriasis with tofacitinib compared with placebo are expected to collect final data for analysis in the first half of 2013 with a long-term safety study being completed in May 2017.

"The major adverse effects of tofacitinib appear to be consequences of blocking cytokine signaling and seemingly not related to off-target effects."

Tofacitinib is also being evaluated at a dose of 5mg or 10mg orally twice daily compared with Enbrel (etanercept) 50mg subcutaneously twice weekly for plaque psoriasis. Final data from this trial are anticipated to be completed in 2012[22].

Tofacitinib was one of the first JAK inhibitors to enter the clinic. It inhibits JAK3 and JAK1 and, to a lesser extent, JAK2, but has little effect on TYK2. Consequently, tofacitinib potently inhibits cγc cytokines but also blocks IFN-γ, IL-6 and, to a lesser extent, IL-12 and IL-23[23]. Functionally, tofacitinib affects both innate and adaptive immune responses by inhibiting pathogenic Th17 cells and Th1 and Th2 cell differentiation[24].

In a Phase IIb trial dose-ranging study for the treatment of psoriasis in 197 patients, 25%, 40.8% and 66.7% of those taking 2, 5 and 15mg of tofacitinib twice daily achieved a PASI-75 response compared to 2% of placebo-treated patients[25].

The major adverse effects of tofacitinib include increased incidence of infections and increased low density lipoprotein levels; however, the incidence of infection with opportunistic organisms appears to be limited[26]. The former is perhaps expected given the roles of diverse cytokines in host defense. The latter is likely related to inhibition of IL-6 signaling. Anemia and neutropenia were also reported, presumably related to JAK2 inhibition and interference with cytokines, such as erythropoietin and colony stimulating factors. Little reduction in $CD4^+$ T cells has been seen, but significant reduction in NK cells and $CD8^+$ T cells does occur. The side effects of tofacitinib appear to be consequences of blocking cytokine signaling and seemingly not related to off-target effects.

On May 9, 2012, Pfizer announced that the Arthritis Advisory Committee to the FDA voted 8-2 to recommend approval of the investigational agent tofacitinib for the treatment of adult patients with moderately to severely active RA. On August 21, 2012, Pfizer announced that the FDA has extended the action date by three months for the NDA for tofacitinib as an oral treatment for adults with moderately to severely active RA. The FDA determined that additional data analyses recently submitted by Pfizer constitute a major amendment to the application and will require additional time to review. The FDA has not asked that Pfizer complete any new studies. The FDA provided an anticipated Prescription Drug User Fee Act (PDUFA) date of November 21, 2012. Tofacitinib is administered twice a day (5mg or 10mg) for both RA and psoriasis.

Baricitinib (LY3009104)

In December 2009, Incyte Corporation (NASDAQ: INCY) entered into a license, development and commercialization agreement with Eli Lilly & Co. (NYSE: LLY) under which Lilly received exclusive worldwide development and commercialization rights to the JAK1 and JAK2 inhibitor baricitinib (LY3009104, formerly known as INCB28050) and certain back-up compounds for inflammatory and autoimmune diseases.

Under the terms of the agreement, Eli Lilly received worldwide rights to develop and commercialize baricitinib as an oral treatment for all inflammatory conditions. In exchange for these rights, Incyte received an initial payment of $90 million and is eligible for up to $665 million in additional potential development, regulatory, and commercialization milestones, as well as tiered, double-digit royalty payments on future global sales with rates ranging up to 20% if a product is successfully commercialized.

Eli Lilly is currently conducting a randomized, double blind, placebo-controlled, dose-ranging, Phase IIb study of the JAK3-sparing baricitinib (NCT01490632) in patients with moderate-to-severe plaque psoriasis, with primary endpoint results expected in 2013. The primary outcome measure is the efficacy of baricitinib in participants with moderate-to-severe plaque psoriasis determined by PASI at 12-weeks. Eli Lilly plans to develop baricitinib as a once-a-day treatment based on its long half-life.

ASP-015K

Astellas Pharma Inc.'s (OTN: ALPMF) ASP-015K, a JAK3 inhibitor, has completed a Phase IIa, randomized, double-blind, placebo-controlled, sequential group, multiple-dose escalation study to evaluate the efficacy and safety in subjects with moderate-to-severe plaque psoriasis. In the six week Phase IIa proof of concept study of patients with psoriasis, ASP-015K was well tolerated and demonstrated dose dependent improvements in PASI change from baseline. Astellas is currently conducting three Phase IIb studies in patients with rheumatoid arthritis in the U.S., Europe and Japan.

In October 2012, Janssen Biotech, one of the Janssen Pharmaceutical Companies of Johnson & Johnson (NYSE: JNJ), and Astellas Pharma formed a license agreement whereby Janssen gains the exclusive right to develop and commercialize ASP-105K worldwide except for Japan. Under the terms of the agreement, Astellas received an up-front payment of $65 million from

Janssen. Astellas is eligible to receive contingent payments upon the achievement of certain development, regulatory and commercial milestones, which could total up to $880 million. Astellas is further entitled to receive double-digit royalty payments on net sales of ASP-015K in the territory from Janssen. After completion of the Phase IIb studies in the territory, Janssen is responsible for all future costs associated with the development and commercialization of ASP-015K for rheumatoid arthritis and other autoimmune indications in the territory.

Sotrastaurin (AEB071)

Novartis Pharmaceuticals' (NYSE: NVS) sotrastaurin, a highly potent, selective and reversible oral Protein Kinase C (PKC) inhibitor, is in a double blind, randomized, placebo controlled, multi-center, dose finding Phase II study in patients with moderate-to-severe plaque psoriasis (NCT00885196). Sotrastaurin indirectly inhibits T-cell proliferation and prevents the production of inflammatory cytokines by activated t-cells, keratinocytes and macrophages through selective inhibition of the alpha, beta and theta-PKC isoforms. The primary endpoint of the Phase II trial of oral sotrastaurin is to assess PASI-75 at 12-weeks treatment and a function of dose and treatment duration.

In a proof-of-concept study comparing ascending doses of sotrastaurin to placebo, 32 patients with moderate-to-severe plaque psoriasis were treated twice daily for two-weeks. A dose-dependent improvement of psoriasis was observed during the treatment period. The mean reduction of PASI scores over baseline was 69% for the 300mg bid cohort (placebo, 5.3%) with 4 of 6 patients having achieved a PASI-75. In the group receiving 300mg twice daily, a dose dependent inhibition of both lymphocyte proliferation and IL-2 mRNA expression were observed. Sotrastaurin was well tolerated with no serious adverse events in this trial[27].

Sirutin Activators

Sirutin enzyme 1 (SIRT1) is a nuclear sirutin class III deacetylase which inhibits pro-inflammatory cytokine production, likely through the deacetylation of RelA(p65) subunit of NF-kB, inhibition of TNF-α secretion and deacetylation and dephosphorylation of STAT3, which results in decreases production of IL-22[28]. SIRT1 promotes normal keratinocyte differentiation by inhibiting STAT3 and therefore IL-22 production. In psoriatic lesions there is a decreased concentration of SIRT1, likely due to the IFN-γ-mediated inhibition of SIRT1.

SRT2104

GlaxoSmithKline's (NYSE: GSK) SRT2104, a potent highly selective small molecule activator of sirutin SIRT1, has completed a Phase IIa double blind placebo-controlled trial in approximately 40 patients with moderate-to-severe psoriasis (NCT01154101).

In October 2012, Glaxo initiated a Phase I open-label, randomized, controlled, single center study to assess the safety, variability in exposure, and relative bioavailability of new oral formulations of SRT2104 in approximately 40 healthy male volunteers (NCT01702493). This is a two part study and each part consists of screening (within 21 days of the first scheduled dose of SRT2104), treatment period and follow-up visit (approximately 6 days after the last dose). The study's estimated completion is April 2013.

Immunomodulators - Monoclonal Antibodies

Ixekizumab

Eli Lilly & Company's ixekizumab (LY2439821), a humanized monoclonal antibody that binds to and neutralizes the action of the pro-inflammatory cytokine interleukin-17A (IL-17A or IL-17) began three Phase III studies in adults with moderate-to-severe chronic plaque psoriasis.

The first Phase III study will include about 1,300 patients with a 12-week randomized double-blind placebo-controlled induction period followed by a randomized maintenance dosing period and long-term evaluation stage (NCT01646177). Additional Phase III studies investigating ixekizumab in patients with moderate-to-severe chronic plaque psoriasis include: multi-center, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of LY2439821 to Etanercept and placebo in patients with moderate-to-severe plaque psoriasis (NCT01646177) and a multi-center, open-label, long-term study to evaluate the efficacy and safety of LY2439821 in Japanese patients with moderate-to-severe psoriasis (NCT01624233).

The results of the randomized, double- blind placebo controlled, parallel group dose ranging Phase II trial of ixekizumab met its primary endpoint in patients with moderate-to-severe plaque psoriasis. In the 142-subject study, significantly more patients achieved a PASI-75 response in the 150mg (82%), 75mg (83%) and 25mg (77%) ixekizumab groups compared with placebo (8%) at week 12. The 10mg dose (29%) did not separate from placebo at week 12.

> **"Approximately 40 percent of patients in the two highest dose groups (with ixekizumab) had complete clearance of psoriasis plaques on the skin..."**

According to the company, secondary endpoints of the Phase II study included an evaluation of the percentage of patients achieving at least 90% and 100% improvement in PASI, (PASI-90 or PASI-100) at week 12. In patients treated with ixekizumab, the percentages of patients achieving a PASI-90 response were 71% (150mg), 59% (75mg) and 50% (25mg), which were significantly higher than with placebo (none). PASI-100 responses were significantly better at the 150mg dose (39%) and 75mg dose (38%) when compared with placebo (zero).

In the Phase II trial, the PASI-75 response was significantly better than placebo as early as week two at the highest dose, and significant differences from placebo in PASI scores were seen as early as week 1 at the two highest doses and by week 4 for the remaining two doses. Differences from placebo were sustained to week 20 in both PASI-75 responses and PASI scores.

Skin disease severity also was evaluated by static Physician Global Assessments (sPGA), with patients having a score of 3-5 (moderate to severe disease) at baseline. The percentage of patients achieving an sPGA of 0 (clear disease) or 1 (minimal disease) at week 12 were 71% (150 mg), 72% (75 mg), 70% (25 mg) and 25% (10 mg) compared with 8% (placebo), with the highest three doses being significantly higher than placebo. The percentage of patients achieving an sPGA score of 0 at week 12 were 46% (150mg), 38% (75 mg), 20% (25 mg), 7% (10mg) and zero (placebo), again with the highest three ixekizumab doses being significantly higher than placebo[29].

Secukinumab (AIN457)

In 2011, Novartis initiated its Phase III program of secukinumab (AIN457), a fully human antibody neutralizing IL-17A, for the treatment of moderate-to-severe plaque psoriasis and psoriatic arthritis. Data from the Phase III program of secukinumab in psoriasis are expected to be announced in 2013.

In October 2011, at the annual European Academy of Dermatology and Venereology (EADV) Congress, Novartis announced positive results from three double blind, parallel group, placebo-controlled Phase II trials showing that secukinumab produced a quick and significant improvement of symptoms in patients with moderate-to-severe plaque psoriasis.

The three Phase II studies presented at EADV were designed to evaluate the safety and efficacy of secukinumab in different doses and administration regimens. The primary endpoint of the studies was PASI-75 responses at week 12, with PASI-90 responses at week 12 among the secondary endpoints. The primary endpoint was met for one or more of the doses (25, 75 and 150mg, subcutaneously; 3 mg/kg, 10mg/kg and 3x10mg/kg, intravenously) and regimens (Early, Monthly and Single) studied in each trial. In all three studies, 60% of patients experienced adverse events with secukinumab in the first twelve weeks compared to 61% with placebo. Serious adverse events were reported in 3% of secukinumab patients vs. 1% with placebo[30].

In one study, 81% of patients receiving 150mg of secukinumab subcutaneously once a month experienced at least a 75% improvement of psoriasis signs and symptoms as measured by PASI versus 9% for placebo at week 12 ($p<0.001$). In another study, results also showed that 83% of patients who were given an intravenous starting dose of secukinumab experienced at least a 75% improvement of symptoms versus 10% for placebo. A third study showed that receiving secukinumab in the first month was beneficial to 55% of patients versus 2% for placebo at week 12 ($p<0.001$)[31].

In September 2012, at the annual EADV, new data from the sub-analyses undertaken on the double-blind, parallel, placebo- controlled Phase II study show secukinumab was nearly three times more effective than placebo at reducing moderate-to-severe plaque psoriasis on the hands and/or feet when given every week for the first month of treatment (54% of patients vs. 19.2 % respectively, $p=0.005$), as measured by Investigator's Global Assessment (IGA). Patients also benefited if they received secukinumab once every four weeks, with 39.0% experiencing either "clear" or "minimal" psoriasis after 12 weeks of treatment[32]. The Phase II study which involved 404 patients was designed to evaluate the safety and efficacy of secukinumab in different regimens (weekly for the first month; once every four weeks; or single dose) of 150mg given subcutaneously.

The sub-analyses included assessment of secukinumab treatment efficacy in 131 patients with hand and/or foot psoriasis. Another analysis found that these secukinumab treatment schedules also notably reduced the signs and symptoms of finger nail psoriasis compared to placebo[33].

Other new data presented at the 2012 EADV in the total moderate-to-severe plaque psoriasis study population show that secukinumab improved skin-related quality of life in 25-times more patients after 12-weeks of treatment when given every week for the first month,

compared to placebo (40.8% vs. 1.6%, p<0.001), as measured by the Dermatology Life Quality Index (DLQI). In this same treatment group, significantly more patients experienced improvements in pain and discomfort compared to placebo (36.2% vs. -1.5%) from baseline; and in anxiety and depression versus placebo (16.3% vs. 6.2%), as measured by EuroQol (EQ-5D)[34].

Brodalumab (formerly AMG 827)

Amgen Inc.'s (NASDAQ: AMGN) brodalumab is a human monoclonal antibody that selectively binds to and blocks signaling via the IL-17 receptor, thereby stopping the binding of several IL-17 family members associated with psoriasis. In March 2012, Amgen announced that brodalumab would move into Phase III for moderate-to-severe psoriasis.

Results from a Phase II trial evaluating the safety and efficacy of brodalumab in 198 patients with moderate-to-severe plaque psoriasis have been published. The 12-week, randomized, double-blind, placebo-controlled, dose-ranging study achieved its primary endpoint with the mean percentage improvement in PASI score higher in all brodalumab groups compared to placebo (p<0.00). The majority of subjects treated with brodalumab 210mg every other week achieved total clearance of their skin disease (PASI-100 of 62 percent).

In this study, treatment with brodalumab every other week resulted in mean improvements in PASI scores of 85.9% (140mg), 86.3% (210mg) and 45.0% (70mg) versus 16% with placebo (all p<0.001). A monthly dose of brodalumab at 280mg was associated with a mean PASI improvement of 76%. Approximately 30% of patients in the placebo group had worsening psoriasis.

The study also evaluated secondary endpoints including PASI-75, PASI-90 and PASI-100, which indicate 75%, 90% and 100% reductions in patient PASI scores from baseline, respectively. In patients dosed with 140mg of brodalumab, 77% achieved a 75% reduction in their PASI score, 72% achieved a 90% reduction and 38% experienced total clearance (PASI-100) (all p<0.001). In patients dosed with 210mg of brodalumab, 82% achieved a 75% reduction, 75% achieved a 90% reduction and 62% experienced total clearance (PASI-100) (all p<0.001)[35].

The most commonly reported adverse events in the combined brodalumab groups were common cold (8%), upper respiratory tract infection (8%) and injection site redness (6%). Two cases of grade three neutropenia were reported in the 210mg brodalumab group.

Brodalumab showed a high level of response in patients with moderate-to-severe plaque psoriasis with a rapid onset of action within days.

Brodalumab inhibits multiple members of the interleukin-17 cytokine family through antagonism of the interleukin-17RA receptor. Secukinumab and ixekizumab specifically neutralize interleukin-17A[36].

In April 2012, Amgen and AstraZeneca Plc (NYSE: AZN), signed an agreement to jointly develop and commercialize five monoclonal antibodies from Amgen's clinical inflammation portfolio: AMG 139, AMG 157, AMG 181, AMG 557 and brodalumab. The agreement does not include certain territories previously partnered by Amgen for brodalumab with Kyowa Hakko Kirin and AMG 557 with Takeda.

Under the terms of the agreement, AstraZeneca will make a one-time $50 million upfront payment to Amgen and the companies will share both costs and profits. Based on current plans, approximately 65 percent of costs for the 2012-2014 period will be funded by AstraZeneca. Thereafter, the companies will split costs equally. Amgen will book sales globally and will retain a low single-digit royalty for brodalumab and a mid single-digit royalty for the rest of the portfolio, after which the companies will share profits equally.

AstraZeneca will lead the development and commercial strategy of AMG 139, AMG 157 and AMG 181, while Amgen will lead the development and commercial strategy of brodalumab and AMG 557. Each development and commercialization lead will be under the oversight of joint governing bodies. For brodalumab, Amgen will promote the product in dermatology indications in the U.S. and Canada, and in rheumatology indications in the U.S., Canada and Europe. AstraZeneca will promote brodalumab in respiratory and, initially, in dermatology indications across all territories outside the U.S., Canada and those markets where Amgen has existing partnerships.

According to data presented at the 2012 Digestive Disease Week Annual Meeting in May 2012, researchers terminated a randomized, double blind, placebo-controlled Phase II study of brodalumab in patients with moderate-to-severe Crohn's disease after a review of safety data from 117 of 226 planned patients indicated a worsening of Crohn's disease symptoms. Exacerbated symptoms, including adverse events and study withdrawal because of illness progression occurred in 31% of the 210mg group, which is the highest dose used

> **"IL-17 and IL-23 are known to be absolutely central to psoriasis pathogenesis because drugs targeting either cytokine are highly effective treatments for this disease."**

in the Phase II study in psoriasis patients[37]. To our knowledge at the time of this publication, Amgen has not announced whether this will affect the plans to initiate Phase III trials of brodalumab in psoriasis.

MK-3222 (formerly SCH 900222)

Merck & Co. Inc.'s (NYSE: MRK) MK-3222 is a p19 subunit anti-interleukin-23 (IL-23) monoclonal antibody candidate being investigated for the treatment of psoriasis. MK-3222 is anticipated to enter Phase III clinical trials in 2012. A Phase II randomized, double-blinded, placebo-controlled, parallel-design, dose-range finding study of subcutaneous MK-3222 in subjects with moderate-to-severe chronic plaque psoriasis is ongoing (NCT01225731).

Given the proven role of IL-23 in several models of autoimmune inflammation and psoriasis, substantial interest exists in targeting this cytokine with neutralization immunotherapy. If the IL-23/Th17/IL-17 immune pathway operates in humans as in mice, then specific blockade of the IL-23 immune pathway may be an effective and safer therapy for immune-mediated inflammatory diseases and place this drug as a standard setting paradigm for psoriasis therapy.

Tregalizumab (BT-061)

In June 2011, Abbott Laboratories (NYSE: ABT) and Biotest AG (OTC: BIESF) entered into a global agreement to develop and commercialize tregalizumab, a novel anti-CD4 antibody for the treatment of RA and psoriasis. Tregalizumab is a humanized monoclonal antibody that works by activating the body's T-regulatory cells, a subset of T-cells, strengthening a natural function of the body that prevents excessive immune reactions. Unlike other anti-CD4 antibodies that have been in development, BT-061 does not cause depletion of CD4 positive T-cells that would give rise to weakened immune responses.

Under the terms of the agreement, Abbott and Biotest will co-promote tregalizumab in the five major European markets (Germany, France, United Kingdom, Italy and Spain) and Abbott will have exclusive global rights to commercialize tregalizumab outside those countries. Biotest received an upfront fee of $85 million. Pending achievement of certain development, regulatory, commercial and sales-based milestones, Biotest would be eligible to receive additional milestone payments from Abbott, potentially totaling $395 million, and royalties. Biotest will be responsible for manufacturing the initial clinical supply of tregalizumab and the companies will share responsibility for commercial production.

Biotest announced that in collaboration with Abbott a Phase IIa clinical trial with repeated doses has been completed in which tregalizumab was tested for the treatment of chronic plaque psoriasis. This Phase IIa trial was a placebo-controlled, double-blind, multi-center, multinational, multiple dose, dose-escalation study to evaluate the safety and efficacy of tregalizumab in different doses and mode of administrations. Patients were treated subcutaneously (s.c.) or intravenously (i.v.) weekly for eight consecutive weeks in six different escalating dose groups.

Fifty-five patients with chronic plaque psoriasis were enrolled. Patients received tregalizumab as monotherapy at doses between 12.5-25mg as s.c. injections or 0.5 and 2mg as i.v. infusions. Tregalizumab was administered once weekly for 8 weeks. In each treatment group, six patients received active treatment and two patients received placebo. Fifteen of the forty-one patients (37%) receiving tregalizumab exceeded a PASI-50 response including two patients with more than a 75% improvement. Responses were seen in four patients receiving placebo, but none reached a PASI-75 response. The strongest improvements in PASI were observed in the 2.5mg i.v. and 25mg s.c. dose groups[38].

After the treatment period, patients were observed for further 12 weeks (90 days) without tregalizumab treatment. Some of the patients experienced a long-lasting improvement in PASI and PGA scores, with an improvement in PASI-score persisting for up to 90 days after single dose administration.

The tolerability of tregalizumab, has also been confirmed in the concluded Phase IIa trial. Further development in of tregalizumab for the treatment of psoriasis will be based on results of larger clinical trials in rheumatoid arthritis that are still ongoing (NCT01481493).

AbGn-168H

AbGenomics International, Inc. expects to initiate Phase II trial of AbGn-168H, a humanized monoclonal antibody against CD-162, for the treatment of psoriasis in the third quarter of 2012. A Phase I safety, tolerability, pharmacokinetics and pharmacodynamics study of single rising, open-label doses of AbGn-168H administered by intravenous infusion to patients with chronic plaque psoriasis was completed with no results published (NCT00848055). A Phase I safety, tolerability and

pharmacokinetics study of single rising doses of AbGn-168H administered by intravenous infusion (125µg/kg, 500µg/kg, 1 mg/kg, 2 mg/kg) or subcutaneous injection (125µg/kg, 1 mg/kg) to healthy male volunteers (randomized, double-blind, placebo-controlled within dose groups) was also completed (NCT01378364). In the single rising dose Phase I study, a clear biological/ pharmacological effect consistent with the proposed mechanism of action of AbGn-168H was demonstrated.

In August 2012, AbGenomics announced that it obtained agreement from FDA for its proposed plans for a Phase II clinical trial of AbGn-168H. The Phase II clinical trial of AbGn-168H will be a multi-center, placebo-controlled, double-blind trial. The primary objective of the study is to demonstrate that AbGn-168H provides safe, durable and remissive therapeutic effect in psoriatic patients.

Other Biologicals

CF101

Can-Fite BioPharma (TA: CFBI) is conducting a randomized, double-blind placebo-controlled, dose-finding Phase II/III study of the efficacy and safety of daily CF101 in patients with moderate-to-severe plaque psoriasis. CF101 is an an oral small molecule drug formulated in a tablet. The mechanism of action for CF101 is A3 Adenosine Receptor (A3AR) mediated and includes modulation of key signaling proteins, such as PI3K, PKA, PKB/Akt, IKK and NF-κB, resulting in inhibition of inflammatory cytokine production.

In October 2012, Can-Fite announced the continuation of patient enrollment in its psoriasis Phase II/III clinical study with CF101. This decision follows an interim analysis of safety and efficacy data from the first 103 patients who completed 24 weeks of treatment in the trial. The positive clinical effects of the CF101 at the 2mg BID dose relative to placebo were observed in a variety of standard psoriasis assessment parameters, with the responses accumulating steadily over the 24-week treatment period. These clinical effect data corroborate the published Phase II study and confirm the dose selection. The favorable safety profile of CF101 further supports its development for the systemic treatment of moderate-to-severe psoriasis. To allow the trial to meet its full objectives, the company intends to complete patient enrollment for this psoriasis Phase II/III clinical study comparing CF101 at 2mg BID to placebo, as standalone therapy. The study will include approximately 300 patients overall and is currently conducted in 17 U.S., European and Israeli medical centers.

The primary clinical endpoint of the Phase II/III trial (NCT01265667) is the proportion of patients achieving Physicians Global Assessment (PGA) outcome of 0 or 1 at 12 weeks. Two main secondary outcomes will be the proportion of patients achieving PASI-75 at 12 weeks and change from baseline in percentage of body surface area of psoriasis involved at 12 weeks.

A Phase II multi-center, randomized, double-blind dose ranging (1-4mg) placebo-controlled trial in moderate-to-severe plaque-type psoriasis was completed. Results of this Phase II trial showed CF101 was well tolerated and demonstrated evidence of efficacy in patients with moderate–to-severe plaque psoriasis. In the 2 mg CF101-treated group, a progressive improvement in the mean change from baseline in the PASI score versus placebo throughout the study period was observed, with a statistically significant difference on weeks 8 and 12 (P = 0.047; P=0.031, respectively). In this group, 35.3% of the patients achieved PASI-50 response, and 23.5% of the patients achieved a PGA score of 0 or 1[39].

Toll-like Receptor (TLR) Antagonists

IMO-3100

In October 2012, Idera Pharmaceuticals, Inc. (NASDAQ: IDRA) announced that a randomized, double blind, and placebo-controlled Phase II study of IMO-3100 in patients with moderate-to-severe plaque psoriasis has completed enrollment. IMO-3100 is an immunomodulator that inhibits the activity of TLR7 and TLR9 and modulates the production of multiple pro-inflammatory mediators, including TNF-α, INF-α, IL1-β, IP-10, IL-17, and IL-23. Idera plans to report top-line data from the Phase II study by the end of 2012.

The role of TLR7 and TLR9 in psoriasis is well established and TLR8 may also contribute to this disease. Blocking the activation of these receptors through a TLR antagonist represents a novel approach to the treatment of psoriasis. IMO-3100 is designed to block induction of multiple cytokines mediated through TLR7 and TLR9. IMO-3100 has demonstrated potent activity in reducing pathologic and immunologic manifestations in preclinical mouse models of psoriasis.

In Phase I studies in healthy subjects, IMO-3100 has been well tolerated at the doses administered, and has shown target engagement of TLR7 and TLR9. The

> **"The role of TLR7 and TLR9 in psoriasis is well established and TLR8 may also contribute to this disease."**

results provide evidence that IMO-3100 suppressed TLR7- and TLR9-mediated immune responses in the trial.

The multiple-dose Phase I clinical trial randomized 24 healthy subjects to receive saline, IMO-3100 at 0.32mg/kg twice/week, or IMO-3100 at 0.64mg/kg/week, for four weeks. The primary objective of this study was the evaluation of safety and tolerability of IMO-3100. Secondary objectives were to assess IMO-3100 pharmacokinetics and pharmacodynamic mechanism of action.

The Phase I study results were presented at the Keystone Symposia meeting "Immunoregulatory Networks" being held April 1-6, 2011 in the presentation (Abstract #333) entitled "IMO-3100, a novel toll-like receptor antagonist for autoimmune and inflammatory diseases: safety and pharmacodynamics in a multiple-dose Phase I clinical trial."

IMO-3100 was well tolerated in both treatment regimens. There were no serious adverse events and no treatment discontinuations. Mild injection site reactions were the most common adverse events. The pharmacokinetics of IMO-3100 were found to be dose-proportional and showed no evidence of accumulation after repeated dosing. Pharmacodynamics mechanism of action demonstrated in the Phase I study was the suppression of multiple cytokines including IFN- α, IL-6, MIP-1β, and IL-1Ra, mediated through TLR7 and TLR9 was observed in both IMO-3100 groups, when post-dose responses were compared to pre-dose responses in each subject. Suppression of multiple cytokines was maintained in IMO-3100 treated subjects throughout the four-week treatment period, based on responses measured from the third day after the first dose through four or more days after the last dose. No consistent suppression of any cytokines was observed in placebo-treated subjects.

The Phase II trial is designed to evaluate the safety and markers of efficacy of IMO-3100 as a monotherapy. In the study, 45 patients with moderate-to-severe plaque psoriasis will receive IMO-3100 at 0.16 or 0.32mg/kg or placebo (saline) by subcutaneous injection once weekly for four weeks. Assessments of safety will be performed starting from the treatment period until day 56. Psoriasis intensity will be monitored throughout the study. Skin biopsies of an active psoriasis plaque will be obtained prior to treatment and one week after the last treatment, and will be analyzed by immunohistologic staining for changes in epidermal thickness, immune cell infiltrates and cytokine expression. This trial is being conducted at multiple sites in the U.S., and skin biopsies will be analyzed at a central laboratory.

As discussed earlier in this article, physical injury to the skin typically exacerbates psoriasis and also represents a trigger of pDC activation in psoriatic skin, indicating a potential link between skin damage, release of self-DNA and local pDC activation. LL37, an endogenous antimicrobial peptide overexpressed in psoriatic skin, is the key mediator of pDC activation in psoriasis. LL37 breaks innate tolerance to self-DNA by forming a complex that is delivered to and retained within early endocytic compartments of pDCs to trigger TLR9 and induce IFN production. A fundamental mechanism by which pDCs sense and respond to self-DNA coupled with an antimicrobial peptide, was discovered and suggests that through this pathway pDCs drive autoimmunity in psoriasis[40].

Activation of TLR7, TLR8 and TLR9 in pDC and mDC through the interaction of these receptors with the antimicrobial peptide LL37 complexed with self-RNA or DNA contributes to psoriasis development. Therefore, inhibition of TLRs 7, 8 and 9 through the use of a TLR antagonist could provide therapeutic effect in this autoimmune disease[41].

A key difference between the cytokine-targeted (antibody) approaches and the TLR-targeted approach is that the latter inhibits the induction but not the constitutive levels of multiple cytokines[42]. Another important difference is that TLRs 7, 8 and 9 inhibit inflammasome activation and suppress the induction of IL-1β. The preclinical data in mouse models of IL-23 induced psoriasis was presented in October 2012 at the 8th Annual Meeting of the Oligonucleotide Society. The inflammasome is an intracellular, multiprotein complex that regulates the release of Il-1β and other pro-inflamatory members of the IL-1 cytokine family in response to exogenous and endogenous danger signals. IL-1β is a critical proinflammatory mediator implicated in many auto-immune diseases and has been a focus of the biotechnology and pharmaceutical companies.

In 2001, the first successful drug in this class, Amgen's Kineret (anakinra), a recombinant for of the IL-1 receptor antagonist (IL-IRA) was approved for the treatment of rheumatoid arthritis. Xoma Corporation's (NASDAQ: XOMA) gevokizumab (XOMA-052), a humanized monoclonal antibody which binds strongly to IL-1β, is in Phase III clinical trials for Behçet's disease and non-infectious uveitis. Regeneron Pharmaceuticals, Inc.'s (NASDAQ: REGN) Arcalyst® (rilonacept), a

recombinant protein with high affinity for IL-1β has completed Phase III trials for the treatment of gout and is marketed for cyrinopyrinapathy, Novartis' Ilaris® (canakinumab), a humanized monoclonal IL-1β antibody also approved for cyrinopyrinapathy, is in a pivotal Phase III trials systemic juvenile idiopathic arthritis (SJIA) and a Phase II study in patients with TNF associated periodic syndrome (TRAPS).

Idera is also developing a second TLR antagonist, IMO-8400, which targets TLR8 in addition to TLR7 and TLR9. The company expects to initiate Phase I study for IMO-8400 during the fourth quarter of 2012.

Oxidized Phospholipids

VB-201

VBL Therapeutics is developing VB-201, a first-in-class orally available, specific innate immunity disease modifying synthetic phospholipid of the Lecinoxiod family. Central to the overall mechanism of action for VB-201 are the targeted antagonism of TLR2 and TLR4 co-receptor CD-14, and the inhibition of chemokine-mediated migration of monocytes to inflamed tissue.

Results from a Phase II double-blind, randomized, dose-ranging, placebo-controlled study of VB-201 were presented at the American Academy of Dermatology 70th Annual Meeting in March 2012 during an oral presentation titled "Safety and Efficacy of VB-201, a Novel Immune-modulator, on Inflammation of Atherosclerotic Disease in Patients with Moderate to Severe Plaque Psoriasis: A Phase II Randomized Placebo Controlled Trial."

The Phase II study of VB-201 enrolled approximately 185 patients with moderate-to-severe psoriasis. Patients received either 20mg or 80mg of VB-201 or placebo once-daily for 12 weeks. In the Phase II study, VB-201 demonstrated an excellent safety and tolerability profile. There were no treatment-related serious adverse events observed, and the overall rates of adverse events were similar across the VB-201 drug and placebo dosing arms. Statistically significant improvements in the psoriasis efficacy endpoints, Physician Global Assessment and Patient Global Assessment (p=0.019), were achieved. A statistically significant dose response in PASI was demonstrated across quintiles of VB-201 through blood levels (p=0.04). Overall, improvement in psoriasis measures did not reach a plateau, with a continued widening of the separation between the treatment and placebo groups at the 12-week termination point of the trial. An additional trial of VB-201 is underway with higher dosage and longer duration.

Additionally, based on encouraging preclinical results, a sub-study was conducted during the Phase II trial to evaluate the effect of VB-201 on atherosclerosis in psoriasis patients. In the pre-defined cardiovascular sub-study, PET-CT scans were used to evaluate the effect of VB-201 on the suppression of active inflammation in atherosclerotic lesions. VB-201 showed a statistically significant, dose-responsive mean reduction of 12.7 percent of the inflammation associated with vascular endothelial lesions (80mg dose group, p=0.04) over the 12-week dosing period. Patients already maintained on statin therapy received additional responses in the range of 10 to 68 percent reduction in vascular inflammation. A dose response was seen across quintiles of VB-201 through blood levels (p=0.037).

Sphingosine-1-phosphate (S1P1) receptor agonists

Ponesimod

Actelion Ltd's (OTC: ALIOF) ponesimod, a selective sphingosine-1-phosphate (S1P1) receptor agonist, is currently in development as an immunomodulator, with the potential for once-a-day oral dosing for multiple autoimmune disorders. S1P1 inhibits keratinocyte proliferation and induces keratinocyte differentiation and migration. S1P1 is believed to regulate peripheral T cell levels by stimulating their release from lymphoid organs rather than promoting T- cell proliferation.

Actelion has commenced a multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of two doses of ponesimod in patients with moderate-to-severe chronic plaque psoriasis. The study is estimated to enroll 320 patients and study drug will be administered for up to 28 weeks. Enrollment commenced in the fourth quarter of 2010 and study results are expected in the fourth quarter of 2012. Ponesimod has been evaluated in a Phase II study involving 60 psoriasis patients.

A decision regarding potential partnership or direction of future development of ponesimod is expected by the end of the year.

Cathespin S Inhibitors

RWJ-445380

Johnson & Johnson has completed a Phase IIa randomized, double blind, placebo-controlled, parallel group, multi-center, study to investigate the safety,

> **"A decision regarding potential partnership or direction of future development of ponesimod is expected by the end of the year."**

tolerability, pharmacokinetics and pharmacodynamics of RWJ-445380 administered to patients with plaque psoriasis. RWJ-445380 is a Cathepsin S inhibitor. The study was conducted in approximately 60 patients assigned to one of 5 treatment are receiving the placebo, 50mg, 100mg, 200mg, or 300mg dose.

Fumaric Acid Esters (FAE)

FP187

Forward Pharma A/S's FP187, a fumaric acid ester, is in a Phase II clinical trial for the treatment of moderate-to-severe plaque psoriasis in 18 sites in Germany. The randomized, double-blind, placebo controlled Phase II efficacy and safety trial of FP187 (NCT01230138) tests two different dose levels (250mg and 375mg) and two different daily dosing schedules (twice daily and three times daily) over twenty weeks of treatment in three active arms. An additional open (flexible dosing) treatment has been amended to the trial. The study has enrolled 252 moderate-to-severe plaque psoriasis patients. The primary outcome measure is the proportion of patients achieving PASI-75 compared to placebo after 20 weeks of treatment. Secondary endpoints include Physicians Global Asset (PGA) and quality of life.

Retinoic Therapies

Talarozole (formerly R115866, planned trade name Rambazole)

GlaxoSmithKline has completed a randomized, evaluator-blind, placebo-controlled, parallel-group dose-ranging study of the safety and efficacy of oral talarozole in the treatment of plaque psoriasis in 176 patients (NCT00716144). The primary outcome measure was PASI-75 success at visit 6 (12 weeks on treatment). Talarozole is a new generation all-trans retinoic acid metabolism blocking agent (RAMBA), highly specific against retinoic acid 4-hydroxylase.

A Phase I open label, single- arm trial of systemic talarozole in patients with moderate-to-severe plaque type psoriasis was conducted. Patients were treated with 1mg/day for 8 weeks, followed by a 2-week treatment-free follow-up period. Nineteen (intent-to–treat patients) were treated and 14 patients completed the entire study. Two patients discontinued due to lack of efficacy and three due to adverse events. At the end of the 8-week treatment, 26% of the patients showed at least a 50% reduction in PASI compared to baseline. At the end of the 2-week follow-up period 47% of the patients demonstrated a 50% or greater reduction in PASI. Kinectic data showed no evidence of accumulation of either talarozole or retinoic acid in the plasma.

Proprietary Mechanism of Action

Apo805K1

ApoPharma, part of the Apotex group, is currently recruiting patients in a double blind, placebo–controlled multicenter, multiple sequential dose escalating Phase II study of Apo805K1 (NCT01483924) in patients with moderate-to-severe plaque psoriasis. Apo805K1, a prodrug of Apo805, is the potassium salt of H-D-Glu(D-Trp-OH)--OH. The compound is a synthetic hemoregulatory dipeptide developed for the treatment of autoimmune diseases including psoriasis.

The purpose of the Phase II study is to evaluate the primary outcome measures of safety and tolerability in 60 patients with moderate-to-severe plaques psoriasis. The secondary outcome measures are pharmacokinetics, pharmacodynamics and efficacy of twelve weeks of treatment with 10mg, 30mg, 60mg and 100mg of Apo805K1. The efficacy of Apo805K1 will be assessed by analyzing the proportion of subjects achieving PASI-75 and PASI-50 across the different treatment arms and at different time points throughput the trial. PGA and LS-PGA scores will be assessed. According to ClinicalTrials.gov, the final data collection date for the safety and tolerability is expected in November 2012.

Conclusion

Psoriasis is a common chronic inflammatory disease in which the exact cause is unknown and alternative treatment options are needed. It is an autoimmune disease affecting 125 million people worldwide that is not highlighted as frequently as other chronic diseases. The effects of chronic plaque psoriasis on patient's reduced health related quality of life are similar to those seen with arthritis, hypertension, heart disease, diabetes and depression.

New insights into the immunopathogenesis of psoriasis have opened the door for future therapies. Research into the cause of psoriasis may lead to new, less toxic and more efficacious therapeutic alternatives for patients. More than a dozen products with different mechanisms of action than currently available treatments are currently in Phase II or Phase III clinical trials with key data expected in the next 6-12 months.

For example, Celgene's apremilast is expected to be the next systemic oral small molecule and first PDE4 inhibitor treatment for psoriasis that will be submitted to

the FDA for approval in the second half of 2013. Based on available clinical data, apremilast given orally at 20 or 30mg twice daily, appears to be efficacious, safe, and tolerable for patients with moderate-to-severe plaque psoriasis.

Other late-stage product candidates are advancing, with Phase III clinical trial results for Pfizer's tofacitinib, a JAK inhibitor, and Novartis' AIN457, an IL-17 inhibitor, also expected in 2013. These two compounds will be the first to announce Phase III trial data for the treatment of psoriasis in their respective classes and, if positive, will offer new therapeutic options for patients.

In 2013, Eli Lilly and Incyte should report Phase IIb data for baricitinib, an orally administered selective JAK1 and JAK2 inhibitor that unlike Pfizer's tofacitinib is JAK3-sparing. The data from ongoing trials in psoriasis may demonstrate differences in the safety and efficacy of the different JAK inhibitors.

In the near-term, results from several randomized mid-stage trials are expected before the end of 2012. For example, data from Idera Pharmaceuticals' Phase II trial with IMO-3100, which has completed enrollment, and data from Actelion's Phase II trial with ponesimod are both expected to be announced before the end of 2012.

Going forward, new insight into the cause of psoriasis, more effective treatments, and identification of novel drug targets could provide new hope for the treatment of one of the most prevalent autoimmune diseases.

Table 1. Companies with Phase II or Phase III psoriasis programs mentioned in this report

Company	Product	Class	Stage
Abbott Laboratories/Biotest AG	Tregalizumab (BT-061)	Immunomodulators - Monoclonal Antibodies	Phase II
AbGenomics International, Inc.	AbGn-168H	Immunomodulators - Monoclonal Antibodies	Phase I*
Actelion Ltd.	Ponesimod	Sphingosine-1-phosphate (S1P1) receptor agonists	Phase II
Amgen /Astra Zeneca/Kyowa Hakka Kirin	Brodalumab	Immunomodulators - Monoclonal Antibodies	Phase II
ApoPharma	Apo805K1	Proprietary mechanism of action	Phase II
Astellas Pharma/Janssen Biotech	ASP-015K	Kinase Inhibitor - JAK	Phase II
Can-Fite BioPharma	CF101	Immunomodulators - Small Molecules	Phase II/III
Celgene Corporation	Apremilast	Phosphodieserase 4 (PDE4) inhibition	Phase III
Eli Lilly & Company	Ixekizumab	Immunomodulators - Monoclonal Antibodies	Phase III
Eli Lilly & Company/Incyte Coproration	Baricitinib	Kinase Inhibitor - JAK	Phase II
Forward Pharma A/S	FP187	Fumaric Acid Esters (FAE)	Phase II
GlaxoSmithKline	Talarozole (R115866)	Retinoic therapies	Phase II
GlaxoSmithKline	SRT2104	Sirutin Activators	Phase II
Idera Pharmaceuticals	IMO-3100	Toll-like Receptor (TLR) antagonist	Phase II
Johnson &Johnson	RWJ-445380	Cathespin S Inhibitors	Phase II
Merck & Co.	MK-3222	Immunomodulators - Monoclonal Antibodies	Phase II
Novartis Pharmaceuticals	Sotrastaurin (AEB071)	Kinase Inhibitor - PKC	Phase II
Novartis Pharmaceuticals	Secukinumab (AIN457)	Immunomodulators - Monoclonal Antibodies	Phase III
Pfizer Inc.	Tofacitinib	Kinase Inhibitor - JAK	Phase III
VBL Therapeutics	VB-201	Oxidized phospholipids	Phase II

* Phase 2 planned for 2012

Legal Disclaimer

This report has been prepared by MD Becker Partners LLC from information sources believed to be reliable. MD Becker Partners expressly disclaims any and all liability which may be based on such information, errors therein or omissions therefrom, or in any other written or oral communication related thereto.

This report is for informational purposes only and should not be construed as investment advice or as any recommendation of a transaction. MD Becker Partners is not soliciting any action based upon it. Specifically, this material is not, and is not to be construed as, an offer to buy or sell any security or other financial instrument referred to herein. To the extent any of the information in this report may be deemed to be investment advice, such information is impersonal and not tailored to the investment needs of any specific person. Furthermore, this report is not intended for distribution to, or use or access by, any person in any jurisdiction where such distribution, use or access would be contrary to applicable law or regulation or which would subject MD Becker Partners to any additional registration or licensing requirements.

MD Becker Partners is not a broker/dealer registered with FINRA (formerly known as NASD) or any other regulatory agency and in the performance of the management and strategy consulting services described in this website, MD Becker Partners shall not be considered to be acting in any broker/dealer or underwriting capacity and therefore MD Becker Partners will not receive any compensation as such.

With respect to any companies discussed in this report, MD Becker Partners or its affiliates may provide, may have provided, or may seek to provide management and strategy consulting services to such issuers that could affect the objectivity of such information. MD Becker Partners or such affiliates do not and will not hold positions or otherwise trade or effect transactions in the securities of the companies discussed herein and do not accept payment of any fees in company stock or any form of security.

References

[1] J Am Acad Dermatol. 2003 Aug;49(2 Suppl):S51-6. Genetics of psoriasis: the potential impact on new therapies. Bowcock AM, Barker JN.

[2] National Psoriasis Foundation. "About Psoriasis: Psoriasis Causes and Known Triggers." Web. http://www.psoriasis.org/about-psoriasis/causes

[3] Clin Dermatol. 2000 Nov-Dec; 18(6):701-9. Psoriasis and other papulosquamous diseases in infants and children. Capella GL, Finzi AF.

[4] Br J Dermatol. 2006 Feb;154(2):325-31. Age, gender, quality of life and psychological distress in patients hospitalized with psoriasis. Sampogna F, Chren MM, Melchi CF, Pasquini P, Tabolli S, Abeni D; Italian Multipurpose Psoriasis Research on Vital Experiences (Improve) Study Group.

[5] J Am Acad Dermatol. 1999 Sep;41(3 Pt 1):401-7. Psoriasis causes as much disability as other major medical diseases. Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM.

[6] J Invest Dermatol. 1995 Jul;105(1 Suppl):25S-29S. Direct and indirect control of T-cell activation by keratinocytes. Nickoloff BJ, Turka LA, Mitra RS, Nestle FO.

[7] Immunity. 2000 Nov;13(5):715-25. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, Vega F, Yu N, Wang J, Singh K, Zonin F, Vaisberg E, Churakova T, Liu M, Gorman D, Wagner J, Zurawski S, Liu Y, Abrams JS, Moore KW, Rennick D, de Waal-Malefyt R, Hannum C, Bazan JF, Kastelein RA.

[8] J Invest Dermatol. 2009 Jan;129(1):79-88. Epub 2008 Jul 17. Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, Abello MV, Novitskaya I, Pierson KC, Gonzalez J, Krueger JG, Lowes MA.

[9] J Immunol. 2008 Oct 1;181(7):4733-41. Induction of IL-17+ T cell trafficking and development by IFN-gamma: mechanism and pathological relevance in psoriasis. Kryczek I, Bruce AT, Gudjonsson JE, Johnston A, Aphale A, Vatan L, Szeliga W, Wang Y, Liu Y, Welling TH, Elder JT, Zou W.

[10] J Invest Dermatol. 2011 Mar;131(3): 677-87. Epub 2010 Nov 18. Integrative responses to IL-17 and TNF-α in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. Chiricozzi A, Guttman-Yassky E, Suárez-Fariñas M, Nograles KE, Tian S, Cardinale I, Chimenti S, Krueger JG.

[11] J Immunol. 2010 Feb 15;184(4):1793-8. Epub 2010 Jan 8. IL-24 transgenic mice: in vivo evidence of overlapping functions for IL-20, IL-22, and IL-24 in the epidermis. He M, Liang P.

[12] Psoriasis: Targets and Therapy 2012:2 29–43 © 2012 Levy et al, publisher and licensee Dove Medical Press Ltd.

[13] J Invest Dermatol. 2006 Oct;126(10): 2194-201. Epub 2006 Jun 1. The risk of lymphoma in patients with psoriasis. Gelfand JM, Shin DB, Neimann AL, Wang X, Margolis DJ, Troxel AB.

[14] Br J Dermatol. 2011 Apr;164(4):862-72. doi: 10.1111/j.1365-2133.2011.10257.x. Cardiovascular safety of ustekinumab in patients with moderate to severe psoriasis: results of integrated analyses of data from phase II and III clinical studies. Reich K, Langley RG, Lebwohl M, Szapary P, Guzzo C, Yeilding N, Li S, Hsu MC, Griffiths CE.

[15] JAMA. 2011 Aug 24;306(8):864-71. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. Ryan C, Leonardi CL, Krueger JG, Kimball AB, Strober BE, Gordon KB, Langley RG, de Lemos JA, Daoud Y, Blankenship D, Kazi S, Kaplan DH, Friedewald VE, Menter A.

[16] Br J Dermatol. 2011 May;164(5):1091-6. doi: 10.1111/j.1365-2133.2011.10213.x. Epub 2011 Apr 11. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. Gniadecki R, Kragballe K, Dam TN, Skov L.

[17] J Am Acad Dermatol. 2008 May;58(5):826-50. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, Lebwohl M, Koo JY, Elmets CA, Korman NJ, Beutner KR, Bhushan R.

[18] Ann Rheum Dis. 2004 Jun;63(6):751-2; author reply 752. Infliximab efficiency and failure. Rozin AP.

[19] Arch Dermatol. 2002 May;138(5):686-8. New developments in the treatment of psoriasis. Lebwohl M.

[20] Br J Dermatol. 2011 May;164(5):1091-6. doi: 10.1111/j.1365-2133.2011.10213.x. Epub 2011 Apr 11. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. Gniadecki R, Kragballe K, Dam TN, Skov L.

[21] Lancet. 2012 Aug 25;380(9843):738-46. Epub 2012 Jun 29. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. Papp K, Cather JC, Rosoph L, Sofen H, Langley RG, Matheson RT, Hu C, Day RM.

[22] Specialty Pharma Times, Surveying the Pipeline of Biologics to Treat Inflammatory Conditions. Stacey Ness, PharmD, Published Online: Monday, December 5, 2011. Web. http://www.pharmacytimes.com/print.php?url=/publications/issue/2011/August2011/Surveying-the-Pipeline-of-Biologics-to-Treat-Inflammatory-Conditions-

[23] F1000 Med Rep. 2012;4:5. Epub 2012 Mar 1. Kinase inhibitors in the treatment of immune-mediated disease. Kontzias A, Laurence A, Gadina M, O'Shea JJ.

[24] J Immunol. 2011 Apr 1;186(7):4234-43. Epub 2011 Mar 7. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). Ghoreschi K, Jesson MI, Li X, Lee JL, Ghosh S, Alsup JW, Warner JD, Tanaka M, Steward-Tharp SM, Gadina M, Thomas CJ, Minnerly JC, Storer CE, LaBranche TP, Radi ZA, Dowty ME, Head RD, Meyer DM, Kishore N, O'Shea JJ.

[25] Br J Dermatol. 2012 Sep;167(3):668-77. doi: 10.1111/j.1365-2133.2012.11168.x. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a Phase 2b randomized placebo-controlled dose-ranging study. Papp KA, Menter A, Strober B, Langley RG, Buonanno M, Wolk R, Gupta P, Krishnaswami S, Tan H, Harness JA.

[26] Transplantation. 2009 Jan 15;87(1):79-86. The effect of the JAK inhibitor CP-690,550 on peripheral immune parameters in stable kidney allograft patients. van Gurp EA, Schoordijk-Verschoor W, Klepper M, Korevaar SS, Chan G, Weimar W, Baan CC.

[27] J Clin Invest. 2008 Sep;118(9):3151-9. The PKC inhibitor AEB071 may be a therapeutic option for psoriasis. Skvara H, Dawid M, Kleyn E, Wolff B, Meingassner JG, Knight H, Dumortier T, Kopp T, Fallahi N, Stary G, Burkhart C, Grenet O, Wagner J, Hijazi Y, Morris RE, McGeown C, Rordorf C, Griffiths CE, Stingl G, Jung T.

[28] FASEB J. 2011 Mar;25(3):916-27. Epub 2010 Nov 23. STAT3-dependent effects of IL-22 in human keratinocytes are counter-regulated by sirtuin 1 through a direct inhibition of STAT3 acetylation. Sestito R, Madonna S, Scarponi C, Cianfarani F, Failla CM, Cavani A, Girolomoni G, Albanesi C.

[29] Br J Dermatol. 2012 Oct;167(4):710-3. doi: 10.1111/bjd.12025. Brodalumab and ixekizumab, anti-interleukin-17-receptor antibodies for psoriasis: a critical appraisal: ORIGINAL ARTICLE: Papp KA, Leonardi C, Menter A et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. N Engl J Med 2012; 366: 1181-9.ORIGINAL ARTICLE: Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med 2012; 366: 1190-9. Spuls PI, Hooft L.

[30] Br J Dermatol. 2012 Oct 27. doi: 10.1111/bjd.12110. [Epub ahead of print] Efficacy and safety of secukinumab in the treatment of moderate to severe plaque psoriasis: a randomised, double-blind, placebo-controlled phase II dose-ranging study. Papp KA, Langley RG, Sigurgeirsson B, Abe M, Baker DR, Konno P, Haemmerle S, Thurston HJ, Papavassilis C, Richards HB.

[31] Nature Reviews Immunology 12, 322 (May 2012) | doi:10.1038/nri3220. Immunotherapy: Therapeutic targeting of IL-17 for psoriasis. Olive Leavy

[32] Paul C, Mroweitz U, Nakayama J et al. Secukinumab, a fully human, anti-interleukin (IL)-17A monoclonal antibody improves signs and symptoms of hand and foot psoriasis: results from a phase II regimen-finding trial. Presented at: 21st Congress of the European Academy of Dermatology and Venereology; 27-30 September, 2012; Prague, Czech Republic. Poster PRA12-0816.

[33] Gottlieb AB, Reich K, Philipp S et al. Secukinumab improves signs and symptoms of nail psoriasis: results from a phase II regimen-finding trial. Presented at: 21st Congress of the European Academy of Dermatology and Venereology; 27-30 September, 2012; Prague, Czech Republic. Poster PRA12-0668.

[34] Wilsmann-Theis D, Terui T, Draelos Z et al. Improvement with secukinumab on patient reported skin related quality of life (QoL) and health status among moderate-to-severe plaque psoriasis patients: results from a phase II regimen-finding trial. Presented at: 21st Congress of the European Academy of Dermatology and Venereology; 27-30 September, 2012; Prague, Czech Republic. Poster: PRA12-0822

[35] N Engl J Med. 2012 Mar 29;366(13):1181-9. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. Papp KA, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G, Aras G, Li J, Russell CB, Thompson EH, Baumgartner S.

[36] Anti-interleukin-17 monoclonal antibody ixekizumab in psoriasis. Wu JJ. N Engl J Med. 2012 Jul 19;367(3):274-5; author reply 275.

[37] Targan SR. #Mo2083: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of AMG 827 in Subjects With Moderate to Severe Crohn's Disease. Presented at: the 2012 Digestive Disease Week Annual Meeting; May 19-22, San Diego.

[38] ESDR- 2010 Poster No. 379 Selective activation of naturally occurring regulatory T cells (Tregs) by the monoclonal antibody BT-061 as a novel therapeutic opportunity in psoriasis: Early clinical results after single doses. Ahmed Abufarag (1), Silke Aigner (1), Niklas Czeloth (1), Benjamin Dälken (1), Helga Koch (1), Gabriele Niemann (1), Christoph Uherek (1), Frank Osterroth (1), Andrea Wartenberg-Demand (1), Walter E. Haefeli (2), Rudolf E. Schopf (3), Alexander Enk (4)

[39] J Eur Acad Dermatol Venereol. 2012 Mar;26(3):361-7. doi: 10.1111/j.1468-3083.2011.04078.x. Epub 2011 Apr 20. Treatment of plaque-type psoriasis with oral CF101: data from an exploratory randomized phase 2 clinical trial. David M, Akerman L, Ziv M, Kadurina M, Gospodinov D, Pavlotsky F, Yankova R, Kouzeva V, Ramon M, Silverman MH, Fishman P.

[40] Nature. 2007 Oct 4;449(7162):564-9. Epub 2007 Sep 16. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B, Cao W, Wang YH, Su B, Nestle FO, Zal T, Mellman I, Schröder JM, Liu YJ, Gilliet M.

[41] J Exp Med. 2009 Aug 31;206(9):1983-94. Epub 2009 Aug 24. Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. Ganguly D, Chamilos G, Lande R, Gregorio J, Meller S, Facchinetti V, Homey B, Barrat FJ, Zal T, Gilliet M.

[42] IMO-8400, a Novel Antagonist Candidate for Autoimmune Diseases, Suppresses TLR7-, TLR8- and TLR9-Mediated Immune Responses in Non-Human Primates Lakshmi Bhagat, Dong Yu, Tim Sullivan, Nicola La Monica, Ekambar R. Kandimalla and Sudhir Agrawal: Copy of presentation made at FOCIS 2012