PIPELINE PREVIEWS

Pipeline Previews brings to you information on the newest drugs and medical products as they become available to the dermatologic community. This department may include additional information from the manufacturers, plus reports from physicians who wish to share their clinical experience with these new products. In addition, we will inform our readers about the latest drugs receiving Food and Drug Administration (FDA) approval.

Merck and MK-3475 for Advanced Melanoma

Merck has announced that the FDA has accepted for review the Biologics License Application (BLA) for MK-3475, Merck's investigational anti-PD-1 antibody, for the treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab. The FDA granted Priority Review designation with a PDUFA date of October 28, 2014, and the MK-3475 BLA will be reviewed under the FDA's Accelerated Approval program. The FDA previously granted MK-3475 Breakthrough Therapy designation for advanced melanoma, the most dangerous type of skin cancer. If approved by the FDA, MK-3475 has the potential to be the first anti-PD-1 antibody in a new class of immune checkpoint modulators. Merck also announced it plans to file a Marketing Authorization Application for MK-3475 in Europe for advanced melanoma by the end of 2014.

The MK-3475 development program is currently ongoing in 30 tumor types as monotherapy and in combination. Merck anticipates that by the end of 2014, the MK-3475 development program will grow to more than 24 clinical trials across 30 different tumor types, enrolling an estimated 6,000 patients at nearly 300 clinical trial sites worldwide, including four new Phase 3 studies. Ongoing and planned late-stage monotherapy and combination studies include seven Phase 3 registrational trials spanning advanced melanoma (adjuvant, ipilimumab-naïve, and ipilimumab-refractory), advanced non-small cell lung cancer (NSCLC) (previously-treated and previously-untreated), advanced head & neck cancer and advanced bladder cancer; and, ten combination studies, including advanced melanoma, advanced NSCLC, advanced renal cell carcinoma, HER2+ breast cancer and other solid tumors.

Merck has also reported that based on encouraging preclinical data, it plans to initiate a Phase 1 dose-ranging study with its investigational anti-GITR agonistic antibody, MK-4166, in patients with advanced malignances. GITR (glucocorticoid-induced TNFR receptor) is an activating immune checkpoint receptor, which is believed to stimulate immune activity against cancer cells. This will be the second investigational immune checkpoint antibody within Merck's immuno-oncology discovery program to enter clinical development.

Mekinist™ (Trametinib) in Metastatic Melanoma With a BRAF V600 Mutation

GlaxoSmithKline has announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion recommending marketing authorization for Mekinist™ (trametinib) as a single agent in the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib as a single agent has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy. Before taking trametinib, patients must have confirmation of BRAF V600 mutation using a validated test.

The CHMP recommendation for trametinib monotherapy is based on a randomized open label phase III study comparing trametinib to chemotherapy in 322 patients with BRAF mutant melanoma (V600E and V600K) and a non-randomized phase II study in 97 patients with BRAF mutant melanoma split in two cohorts: previously treated or not treated with a BRAF inhibitor.

A CHMP positive opinion is one of the final steps before marketing authorization is granted by the European Commission (EC), but does not always result in marketing authorization. A final decision by the EC is anticipated during the second quarter of 2014.

Phase III Data Shows Secukinumab (AIN457) Improves Psoriasis

Novartis has announced results from the Phase III FEATURE and JUNCTURE studies showing secukinumab (AIN457), a selective interleukin-17A (IL-17A) inhibitor, met both co-primary endpoints at Week 12 based on Psoriasis Area and Severity Index (PASI) 75 and Investigator's Global Assessment modified 2011 (IGA mod 2011) 0/1 response rates compared to placebo. Results from these studies also demonstrated skin clearance at Week 12 based on PASI 90 response rates compared to placebo, usability and acceptability of the secukinumab pre-filled syringe (PFS) and autoinjector pen (AI), and an approximately 50% mean decrease in PASI scores from baseline by Week 3 (300mg) and Week 4 (150mg). These results, along with more than 20 posters were presented for the first time at the 72nd Annual Meeting of the American Academy of Dermatology (AAD) in Denver.

FEATURE results showed the efficacy of secukinumab 300mg and 150mg based on a statistically significant higher proportion of patients who achieved a PASI 75 response at Week 12 compared with placebo patients: 75.9% (300mg) and 69.5% (150mg), versus 0% for placebo (p <.0001). On the co-primary endpoint, the efficacy of secukinumab 300mg and 150mg was shown based on a statistically significant higher proportion of patients who achieved an IGA mod 2011 0/1 response at Week 12 compared with placebo: 69.0% (300mg) and 52.5% (150mg), versus 0% for placebo (P<.0001).

Results from JUNCTURE also showed the efficacy of secukinumab 300mg and 150mg based on a statistically significant higher proportion of patients who achieved a PASI 75 response at Week 12 compared with placebo: 86.7% (300mg) and 71.7% (150mg), versus 3.3% for placebo (*P*<.0001). On the co-primary endpoint, the efficacy of secukinumab 300mg and 150mg was shown based on a statistically significant higher proportion of patients who achieved an IGA mod 2011 0/1 response at Week 12 compared with placebo: 73.3% (300mg) and 53.3% (150mg), versus 0% placebo (*P*<.0001).

Additionally, more secukinumab patients in both studies experienced an improvement in PASI of greater than or equal to 90% (PASI 90) from baseline as compared to placebo, which is a higher standard of skin clearance compared to PASI 75. In FEATURE 60.3% (300mg) and 45.8% (150mg) of secukinumab patients achieved a PASI 90 response at Week 12 compared to 0% of placebo patients (*P*<.0001). In JUNCTURE, 55% (300mg) and 40% (150mg) of secukinumab patients achieved a PASI 90 response at Week 12 compared to 0% of placebo patients (*P*<.0001).

In FEATURE (n=177), the most common adverse events (AEs) in any treatment group including placebo were diarrhea, nasopharyngitis and headache. There were a total of four serious adverse events in the study – three (5.1%) in the 300mg secukinumab arm and one (1.7%) in the placebo arm. Two patients (one in secukinumab 300mg arm, one in placebo arm) discontinued due to AEs. In JUNCTURE (n=182), the most common AEs in any treatment group including placebo were nasopharyngitis, headache, pruritus and hypertension. There were a total of five serious adverse events in the study – one (1.7%) in the 300mg secukinumab arm, three (4.9%) in the 150mg secukinumab arm and one (1.6%) in the placebo arm. One patient in the placebo arm discontinued due to adverse event.

A secondary endpoint of both FEATURE and JUNCTURE measured patient satisfaction and usability with self-injection of secukinumab via PFS and AI, respectively. Satisfaction was assessed in both studies using a self-administered Self-Injection Assessment Questionnaire (SIAQ) which measures overall subject experience with subcutaneous self-injection before the first self-injection and after dosing on the domains of feelings about injections, self-confidence, satisfaction with self-injection, injection-site reactions, ease of use, and self-image. Overall, patient-reported acceptability of both the PFS and AI were high at baseline across both studies and remained high during the study. These studies were presented in separate posters at AAD.

Studies presented at AAD are part of a clinical program reporting results in moderate-to-severe plaque psoriasis with more than 3,000 patients in over 35 countries.

FEATURE is a randomized double-blind, placebo-controlled, multicenter, Phase III study involving 177 subjects with moderate-to-severe plaque psoriasis. In this study, prefilled syringes (PFS) were introduced into the secukinumab clinical program. The co-primary endpoints were assessed at Week 12 and compared secukinumab efficacy versus placebo according to PASI 75 and Investigator's Global Assessment modified 2011 (IGA mod 2011) 0/1 response. Secondary endpoints included PASI 90 response up to Week 12 and patient satisfaction with self-injection of secukinumab via PFS determined by a self-administered Self-Injection Assessment Questionnaire (SIAQ). The trial is ongoing.

JUNCTURE is a double-blind, placebo-controlled, multicenter, Phase III study involving 182 subjects with moderate-to-severe plaque psoriasis. In this study, the autoinjector/pen (AI) was introduced into the secukinumab clinical program. The co-primary endpoints were PASI 75 and Investigator's Global Assessment modified 2011 (IGA mod 2011) 0/1 response for secukinumab vs placebo at Week 12. Secondary endpoints included PASI 90 response up to Week 12 and patient satisfaction with self-injection of secukinumab via the AI device determined by a self-administered Self-Injection Assessment Questionnaire (SIAQ). The trial is ongoing.

FDA Approves Xolair® (omalizumab) for Urticaria

Genentech has announced that the FDA approved Xolair ® (omalizumab) for the treatment of chronic idiopathic urticaria (CIU), a form of chronic hives. The new use is for people 12 years of age and older who remain symptomatic despite treatment with H1-antihistamine therapy5. Until now, H1-antihistamines have been the only approved therapy for CIU, with about 50 percent of patients having an inadequate response.

CIU is diagnosed when hives occur without an identifiable cause, spontaneously present, and reoccur for more than six weeks. CIU can have burdensome symptoms including swelling, severe itch, pain, and discomfort that may last for many months and even years. Approximately 1.5 million people in the U.S. develop CIU at some stage in their life. Women are twice as likely as men to experience CIU and most develop symptoms between the ages of 20 and 40.

Xolair is the first biologic medicine and first medicine approved by the FDA for CIU since non-sedating H1-antihistamines. Xolair is approved for people 12 years and older with CIU who remain symptomatic despite treatment with H1-antihistamine therapy. Xolair is not used to treat other forms of urticaria (hives) and is not for use in children less than 12 years of age. It is jointly developed by Genentech and Novartis Pharma AG and is co-promoted in the U.S. with Novartis Pharmaceuticals Corporation.

The efficacy and safety profile of Xolair for the treatment of CIU was evaluated in two clinical studies called ASTERIA I and ASTERIA II. In these studies, patients 12 to 75 years old received doses of Xolair at 150 mg, 300 mg or placebo. Xolair or placebo

was given every four weeks for 24 weeks (ASTERIA I) and 12 weeks (ASTERIA II). In addition, patients continued to receive H1-antihistamine medicines they had been taking for CIU before starting treatment with Xolair.

The efficacy of Xolair in patients 12 years and older who remained symptomatic despite taking H1-antihistamines was assessed using a scale known as the average (mean) weekly Itch Severity Score (ISS) at Week 12. The weekly ISS has potential scores ranging from 0 to 215. In ASTERIA I, Xolair 150 mg improved ISS from the starting measurement by 47 percent (-6.7) and Xolair 300 mg improved ISS from the starting measurement by 66 percent (-9.4) at Week 12, compared to a 25 percent (-3.6) score improvement for patients who received placebo. Also, a larger proportion of patients (36 percent) treated with Xolair 300 mg reported no itch and no hives at Week 12, compared to patients treated with Xolair 150 mg (15 percent), and patients in the placebo group (9 percent). Similar results were observed for the ASTERIA II study.

Xolair for subcutaneous use is an injectable prescription medicine used to treat adults and children 12 years of age and older with moderate to severe persistent allergic asthma who have had a skin or blood test that is positive for allergic asthma and whose asthma symptoms are not controlled by asthma medicines called inhaled corticosteroids and chronic idiopathic urticaria (CIU; chronic hives without a known cause) who continue to have hives that are not controlled by H1 -antihistamine treatment.

Xolair is not used to treat other allergic conditions, other forms of urticaria (hives), acute bronchospasm (serious and sudden breathing problems) or status asthmaticus (acute, severe, prolonged asthma attack that can be life threatening). Xolair is not for use in children less than 12 years of age.

Dalvance(TM) for Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

Durata Therapeutics, Inc. has announced that the FDA's Anti-Infective Drugs Advisory Committee voted 12 to 0 that Durata has provided substantial evidence of the safety and effectiveness of its investigational drug, DalvanceTM (dalbavancin) for injection, for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA). While not bound by the guidance provided by the Committee, the FDA will consider the Committee's deliberations as part of its review of the New Drug Application (NDA) for Dalvance, which was accepted for priority review by the FDA in November 2013 with an action date of May 26, 2014.

A total of 21 clinical trials have been conducted with dalbavancin in the entire clinical program, with the five Phase 3 trials evaluating nearly 3,000 patients. Two Phase 3 trials, DISCOVER 1 and DISCOVER 2 were conducted under a Special Protocol Assessment (SPA) with the FDA and included more than 1,300 patients with ABSSSI.

Dalvance is a second generation, semi-synthetic lipoglycopeptide, which consists of lipophilic side-chains attached to glycopeptides. If approved, Dalvance would be the first drug for ABSSSI requiring only two once-weekly 30-minute intravenous doses (1000 mg on Day 1 and 500 mg on Day 8). Dalvance demonstrates bactericidal activity in vitro against a broad range of bacteria, such as Staphylococcus aureus (including methicillin-resistant strains) and Streptococcus pyogenes, as well as certain other streptococcal species.

Neotensil™ Daily Under-Eye Reshaping Procedure

Neotensil™ Daily Under-Eye Reshaping Procedure is an innovative, revolutionary solution that reshapes and transforms the appearance of eye bags and lax skin underneath the eyes, within one to three hours. Invented by Living Proof scientists and world-class dermatologists, Neotensil creates an invisible, wearable polymer film that performs like invisible shapewear for aging skin. It represents a new category of non-invasive, at-home anti-aging procedures powered by Living Proof's breakthrough skin technology, Strateris® Strateris forms a breathable, invisible and wearable film that adheres to the skin and intrinsically wants to shrink and become flat, reshaping and compressing the appearance of bulges and underlying, lax skin. Future product iterations relying on the Strateris technology could potentially offer a diverse array of fresh approaches to cosmetic challenges, such as combating the effects of aging on the forehead, neck or décolletage, as well as medical solutions for dermatological conditions.