With ongoing uncertainty surrounding the continued rollout of the Patient Protection and Affordable Care Act, the national healthcare outlook in 2014 is very much in flux. Yet, despite widespread concern from both physicians and patients regarding insurance coverage and reimbursements, the pharmaceutical industry is poised for steady growth in the upcoming year and beyond. In particular, the dermatology therapeutic landscape shows continued promise in several areas. As investigation continues into several novel agents across various wings of the specialty, from cosmetics to oncology, dermatologists have reason to hope that their treatment armamentariums will soon be expanding.

**Clinical Dermatology**

Although many agents are under investigation for a variety of dermatologic conditions, the two disease states that appear to have generated the most pipeline interest are psoriasis and melanoma.

**Psoriasis.** Several agents have made headlines this past year on the psoriasis front. One of these is the oral molecule apremilast. At the 2013 AAD Meeting in Miami, Celgene presented findings from a Phase III study showing the efficacy of apremilast. The ESTEEM 1 study evaluated efficacy and safety in a range of patients, approximately one-third of whom were systemic and/or phototherapy treatment-naïve. Additionally, nearly 30 percent of the overall study population had prior biologic therapy, which included biologic-failures. The study showed that a significantly higher percentage of apremilast-treated patients demonstrated PASI-75 at week 16 than did placebo patients (33.1 percent vs. 5.3 percent). Moreover, apremilast demonstrated maintenance of effect over time.

Another oral agent whose profile has grown over the last year is tofacitinib (Pfizer), an oral Janus Kinase (JAK) inhibitor. Approved in 2012 for rheumatoid arthritis, tofacitinib has been under investigation in Phase III trials for patients with moderate to severe psoriasis for much of this past year. In October, tofacitinib manufacturer Pfizer announced results from two Phase III trials: OPT Compare (A3921080) and OPT Retreatment (A3921111), the first two of five studies in the Phase III Oral Psoriasis Treatment (OPT) Program, one of the largest global clinical trial programs in moderate to severe chronic plaque psoriasis to date. In the first trial, tofacitinib met the primary endpoint of non-inferiority to high-dose etanercept at a 10mg BID dose, while the second trial showed that a greater proportion of patients continuing tofacitinib treatment maintained response during the treatment withdrawal phase compared to patients who switched to placebo.

No new safety signals for tofacitinib were observed in these studies, and the efficacy and safety profile of tofacitinib in psoriasis remains consistent with that seen in the Phase II clinical trial. However, whether the FDA will evaluate these studies and allow tofacitinib to be approved without significant restriction for the psoriasis population...
as it did for approval in rheumatoid arthritis remains to be seen, according to Alan Menter, MD. In the December 2012 edition of Practical Dermatology (available online at www.practicaldermatology.com), Dr. Menter noted that tofacitinib has been associated with minor changes in lipid profiles and hematologic parameters. “How the FDA will evaluate this in light of the growing interest in comorbidities data in the psoriasis population remains to be seen,” Dr. Menter observed. “In addition, the short-term and long-term impact of the new impressive IL-17 inhibitors on these comorbidities, both positively and negatively, is still to be determined.”

Pfizer anticipates top-line results for the OPT Pivotal 1 and OPT Pivotal 2 trials to be available in the second quarter of 2014, and these four studies, in addition to a long-term extension study, will form the potential psoriasis submission package to regulatory authorities.

Another investigational agent that has shown promise is secukinumab (AIN457, Novartis), an interleukin-17A (IL-17A) inhibitor that has yielded impressive efficacy results in Phase III trials. Results from the head-to-head Phase III FIXTURE study show that secukinumab was significantly superior to the anti-TNF medication etanercept in moderate to severe plaque psoriasis. Results were presented this fall at the 22nd Congress of the European Association of Dermatology and Venereology (EADV) in Istanbul, Turkey; FDA submission is anticipated.

The pivotal FIXTURE study met all primary and pre-specified key secondary endpoints (p<0.0001 for placebo comparisons and p=0.0250 for Enbrel comparisons), according to Novartis. FIXTURE compared two doses of secukinumab—300mg and 150mg—with etanercept 50mg and placebo. The co-primary endpoints, assessed at Week 12, were measured according to the Psoriasis Area and Severity Index 75 (PASI 75) and the Investigator’s Global Assessment (IGA mod 2011).

Both doses of secukinumab were more effective than etanercept throughout the 52-week study, beginning as early as Week 2 and confirmed by Week 12. More secukinumab patients achieved PASI 90 or PASI 100, compared to etanercept: 72 percent of secukinumab 300mg patients achieved at least a PASI 90 by week 16, 24 percent achieved PASI 100 by Week 12. “The drug is very fast,” observes Mark Lebwohl, MD, an investigator in the trials who presented the data at EADV. The response is “durable,” Dr. Lebwohl adds. “An enormous proportion of patients responded at week 12.”

Secukinumab efficacy was sustained over the full one-year duration of the study. There were no major safety signals identified in FIXTURE or the broader secukinumab Phase III clinical trial program in moderate to severe plaque psoriasis. In FIXTURE, the incidence of adverse events (AEs) was similar between both secukinumab treatment arms (300mg and 150mg), and was comparable to etanercept. The most common AEs in any treatment group (including placebo) throughout the 52-week treatment period were nasopharyngitis and headache (occurring in between 12-36 patients per 100 patient years in all groups). Serious AEs (SAEs) were experienced by six percent of secukinumab 300mg patients, five percent of secukinumab 150mg patients, and six percent of etanercept patients.

IL-17A is a central cytokine involved in the development of psoriasis. Research shows that IL-17A, in particular, plays a key role in driving the body’s autoimmune response in disorders such as moderate to severe plaque psoriasis. Targeting IL-17 addresses the pathogenesis of psoriasis further along the pathway than current therapies, Dr. Lebwohl says.

Dr. Lebwohl notes that individuals who are naturally IL-17 deficient tend to develop Candida infections at higher rates than the general population, but there was no trend toward infections among secukinumab-treated subjects in the trials.

While he is reluctant to predict the FDA’s actions, Dr. Lebwohl is optimistic about the drug. “The data are sufficient for this drug to be on the market,” he says, “and I think it is a drug that will do well.”

Melanoma. Earlier this year, the FDA designated “breakthrough therapy” status to Merck’s lambrolizumab for the treatment of advanced melanoma. Lambrolizumab is an investigational antibody therapy targeting programmed death receptor. It disrupts the action of the immune checkpoint protein PD-1 and inhibits the ability of some cancers to evade the immune system. In a Phase IB clinical trial, patients with advanced melanoma treated with lambrolizumab had an objective response rate of 41 percent and a complete response rate of nine percent. The breakthrough designation will expedite the development and review of a lambrolizumab.

Another melanoma agent that has generated headlines over the past year is the intrallesional agent (IL) PV-10, which is under investigation for treatments of patients with AJVCC Stage IIIIB-IV melanoma. At the European Cancer Congress held past September in The Netherlands, data showed that patients treated with PV-10 showed a best overall objective response rate (BORR) of 51 percent (26 percent complete response) with the amount of tumor burden accessible to PV-10 injection prognostic for outcome. In addition, in 66 percent of patients treated with PV-10, a primary tumor together with up to two untreated bystander lesions constituted all disease present, and these
patients achieved a BORR of 62 percent. Researchers concluded that for patients who are refractive to other local treatments, such as surgery and radiation, intralesional PV-10 provides a viable strategy to maintain locoregional control of the disease with minimal intervention, and can potentially delay, reverse, or prevent progression to life-threatening visceral disease.

In addition to these developments, another agent currently in Phase III trials may increase survival in patients with late-stage melanoma. At the 2013 Society for Melanoma Research Congress in Philadelphia, new data for Amgen’s investigational agent talimogene laherparepvec showed that it increased overall survival in patients with unresected stage IIIB, IIIC, or IV melanoma compared to granulocyte-macrophage colony-stimulating factor (GM-CSF). Median overall survival was 23.3 months in the talimogene laherparepvec arm vs. 19 months in the GM-CSF arm. Moreover, differences in survival rates were pronounced in the subset of patients with stage IIIB, IIIC, or IV M1a disease or who received talimogene laherparepvec as first-line treatment, each comprising approximately 50 percent of the study population. The most frequently observed adverse events were fatigue, chills, and pyrexia. Serious adverse events, which included disease progression, cellulitis, and pyrexia, occurred in 26 percent of talimogene laherparepvec patients and 13 percent of GM-CSF patients.

Finally, FDA’s recently gave priority review designation to GlaxoSmithKline’s supplemental NDAs for combined use of Tafinlar (dabrafenib) and Mekinist (trametinib) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 E or K mutation. The applications are based on recent Phase I/II data comparing the combination therapy to dabrafenib monotherapy. Both agents were approved individually earlier this year. The FDA has assigned a Prescription Drug User Fee Act (PDUFA) target date of January 8, 2014 for the Mekinist (trametinib) supplement and January 9, 2014 for the Tafinlar (dabrafenib) supplement.

**COSMETIC DERMATOLOGY**

In the world of aesthetic medicine, the approval of Juvéderm Voluma XC has been hailed as a potentially new plateau for injectable procedures. But several other promising developments may play an important role in the evolution of the cosmetic injectable treatment spectrum in this coming year and beyond. Among these is the treatment of submental fat, which has proven an elusive area to correct
with the available injectable treatments.

Kythera’s proprietary injectable formulation, ATX-101, has been formulated specifically to address this area and has shown considerable promise. It is a purified synthetic version of deoxycholic acid, a naturally occurring molecule in the body that aids in the breakdown of dietary fat. In two recent Phase III trials, ATX-101 met all primary and secondary endpoints. The data, announced this past fall and presented at the American Society for Dermatologic Surgery (ASDS) Annual Meeting in October, show that patients treated with 2mg/cm^2 of ATX-101 versus placebo experienced a visible reduction in submental fat. The identical multicenter, double-blind, randomized, placebo-controlled trials enrolled more than 1,000 subjects with moderate to severe submental fat. Based on validated rating scales used to evaluate primary efficacy endpoints at 12 weeks, active treatment with ATX-101 produced at least a one-grade improvement in both clinician and patient ratings in 70.3 percent (REFINE-1) and 66.9 percent (REFINE-2) of subjects, versus 18.7 percent and 22.4 percent of controls, respectively. In addition, Patient-Reported Submental Fat Impact Scale (PR-SMFIS, a secondary endpoint) scores showed that treated subjects were statistically significantly more likely to perceive themselves to be happier, less bothered, less self-conscious, less embarrassed, younger, or less overweight after treatment with ATX-101.

In addition to the positive data for ATX-101, Kythera announced earlier this year that it has commenced an underwritten public offering of shares of its common stock to raise aggregate proceeds of $100 million. All of the shares of the common stock to be sold in the offering will be offered by KYTHERA. The company intends to use the net proceeds of the offering to fund the ongoing development and preparation for potential commercialization of ATX-101.

Subcutaneous Abdominal Fat. Another injectable agent under investigation for the treatment of fat is Lithera’s LIPO-202 (Salmeterol Xinafoate), which is preparing to enter late-stage clinical trials. If successfully developed, LIPO-202 would be the first injectable treatment for the targeted, non-ablative reduction of subcutaneous abdominal fat. To assist with the development of LIPO-202, Lithera recently appointed Lincoln Krochmal, MD as Chief Medical Officer. Previously, Dr. Krochmal was President and Chief Executive Officer of Excaliard Pharmaceuticals, an aesthetics company acquired by Pfizer, Inc.

Fillers. Clinicians can expect continued growth in the area of dermal fillers. Specifically, fillers marketed under the Teoxane brand, currently available in more than 90 markets outside the US, may soon see domestic approval and commercialization. That’s because the Alphaeon Corporation, a wholly-owned subsidiary of Strathspey Crown Holdings, LLC, has acquired an exclusive license for the full line of Teoxane products. As part of the relationship, Alphaeon will market the full line of Teoxane hyaluronic acid-based dermal fillers and cosmeceutical products to credentialed physician specialists (CPSS). Teoxane products contain 100 percent non-animal origin, resorbable hyaluronic acid.

Topical Botulinum Toxin. Outside the injectable arena, clinical investigators are continuing to explore the potential of topical botulinum toxin. RT-001 is a topical gel under evaluation for the temporary elimination of facial wrinkles in the crow’s feet area. In 2010, data from a Phase II trial suggested a bright future for the agent. Revance, developer of RT-001, is now prepared to enter its Phase III program, suggesting that topical toxins may, indeed, be on the way in several years.

The possibility of topical botulinum toxins has yielded much conjecture over the last several years, but it remains to be seen whether the eventual approval and commercialization of such a product would be a positive or negative development for the broader field of aesthetics. According to Mark Rubin, MD, whether the investigational botulinum toxin gel translates into an effective product that patients will want to use is a matter of debate, as several logistical issues may pose problems. “Patients will likely need to wait 30 to 40 minutes in an office with the gel on their face, as opposed to waiting one minute for an injection,” Dr. Rubin wrote in the January 2013 edition of Practical Dermatology”. “Nevertheless, topical toxins could represent a major step in cosmetic dermatology for the practical reason that they might open the possibility for patients with a fear of needles and injections to receive toxins,” Dr. Rubin observed. Also, a topical-based toxin may allow physicians to finesse the drug a bit more. “By applying small amounts or leaving the gel on the skin for shorter time frames than are being used in clinical trials, it may be possible to finesse the drug better for other applications,” said Dr. Rubin. “For example, small doses of toxin applied superficially to the skin may reduce the size of pores and stunt oil production. This could open a whole new world for the potential use of toxins in the glands.”

**BRIGHTER DAYS**

The investigational agents discussed in this article represent only the highlights of the larger spectrum of dermatology pipeline. While not every investigational agent earns approval, the volume and variety of agents being developed in several areas of the specialty point to brighter days ahead for patients.