

White Paper

BIOLOGICS – THE KEY TO NEXT GENERATION DERMATOLOGY R&D?

Clinical trial considerations and best practices



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INTRODUCTION

Dermatologic conditions, including hair, skin and nail disorders, are estimated to impact one-third of the global population. Drug developers are taking note; the global commercial dermatology market is estimated to reach \$33.7 billion by 2022, rising at a 7.73 percent CAGR from 2015 to 2022.¹ Historically, dermatology treatment options could largely be classified as topical, phototherapy, or conventional drugs delivered systemically. More recently, research has led to exploration of another treatment option: biologics.

The emergence of biologic therapies for dermatologic conditions created a paradigm shift for patients, physicians and sponsors. Typically offered as a second- or third-line therapy, biologics offer treatment options for patients often with the most severe or debilitating presentations of dermatologic conditions. These options are increasing; a May 2016 report from GBI estimates 37 percent of the approximately 800 dermatology products in development are biologic agents.²

This white paper will explore the evolution of biologics within the dermatology landscape, with an emphasis on clinical trial considerations and best practices for sponsors developing biologic agents.

MAKING A CASE FOR BIOLOGICS

Biologics, derived from living organisms, have been in use for decades (e.g., insulin or vaccines derived from eggs). Today's biologics – those developed in the past 15 years – are protein-based drugs created from genetically modified cells. Biologic agents can target more specific areas of the immune system than the “small molecule” systemic drugs that tend to impact the body's overall immunity.

Indications in dermatology that can be treated with biologics include psoriasis, hidradenitis suppurativa, urticaria and alopecia areata. In March 2017, the United

37% of the approximately 800 dermatology products in development are biologic agents.²



States Food and Drug Administration (FDA) approved Regeneron’s dupilumab (Dupixent®) as the first biologic to treat atopic dermatitis.³ Biologics may also be used to treat cancers of the skin, such as melanoma and squamous cell carcinoma. Additionally, anecdotal reports have been published of using biologic drugs (off label) as treatments for pyoderma gangrenosum, scleroderma, systemic lupus erythematosus, dermatomyositis, sarcoidosis, Sweet’s syndrome, Behcet’s disease and the autoimmune bullous diseases such as pemphigus vulgaris.

BIOLOGIC MECHANISM OF ACTION: A GAME CHANGING DISCOVERY FOR PSORIASIS SUFFERERS

Psoriasis was the first dermatologic condition for which a biologic agent was approved. Psoriasis is a common, chronic and inflammatory skin condition caused by T-cell dysregulation within the immune system. Biogen’s alefacept (Amevive®), FDA-approved in 2003 (and subsequently removed from the market), was the first biologic approved in the United States (U.S.) to treat moderate to severe plaque psoriasis. Following this breakthrough, nine additional biologics have been FDA-approved for the treatment of plaque psoriasis.

FDA Approvals for Biologics to Treat Moderate to Severe Plaque Psoriasis⁴

SPONSOR	COMPOUND	DRUG NAME	APPROVAL YEAR	MECHANISTIC CATEGORY
Biogen (Astellia Pharma)	alefacept	Amevive®	2003	Removed from market in 2011
Merck	efalizumab	Raptiva®	2003	Removed from market in 2009
Amgen	etanercept	Enbrel®	2004	TNF-a inhibitor
Janssen Biotech	infliximab	Remicade®	2006	TNF-a inhibitor
AbbVie	adalimumab	Humira®	2008	TNF-a inhibitor
Janssen Biotech	ustekinumab	Stelara®	2009	IL-12/23 inhibitor
Novartis	secukinumab	Cosentyx®	2015	IL-17 inhibitor
Eli Lilly	ixekizumab	Taltz®	2016	IL-17 inhibitor
Janssen Biotech	golimumab	Simponi®	2017	TNF-a inhibitor
Valeant	brodalumab	Siliq™	2017	IL-17 inhibitor

CLASSES OF DERMATOLOGY BIOLOGICS FOR THE TREATMENT OF PSORIASIS⁵

Three FDA-approved classes of biologics exist for the treatment of psoriasis:

1. **TNF-a inhibitors** (tumor necrosis factor-alpha) were the first class of biologics to deliver clinical improvements to moderate to severe psoriasis patients while still having manageable safety profiles. Enbrel was the first TNF-a inhibitor to gain approval (2004), followed by Remicade (2006), Humira (2008), and Simponi (2017).
2. **(IL)-12/23 antagonist** (interleukin) was the second class of biologics to receive FDA approval for psoriasis. Stelara, FDA-approved in 2009, targets cytokines IL 12/23, which are directly involved in psoriasis pathogenesis.
3. **IL-17 inhibitors** followed with Cosentyx (2015) and then Taltz in early 2016. These drugs specifically target IL-17, a cytokine involved directly in skin inflammation, and may offer clinical improvements on endpoints such as PASI 90 and PASI 100 (total skin clearance) over previous therapies.

While still in clinical trials, Merck's tildrakizumab is a new development, an IL-23p19 inhibitor thought to block the cytokine IL-23 and thereby blocking inflammation. Other biologics undergoing studies for the treatment of psoriasis include MedImmune's siplizumab, Centocor Ortho Biotech's Orthoclone, Novartis' basiliximab, and Biogen's daclizumab.

BENEFITS AND RISKS OF BIOLOGICS VS. OTHER DERMATOLOGY THERAPIES

When evaluating the risks and benefits of biologics over topical or other systemic treatments in dermatology, it is prudent to examine efficacy and safety, patient compliance, cost and quality of life.

SAFETY PROFILE OF DERMATOLOGIC BIOLOGICS

Biologics have the advantage over topical therapies when it comes to addressing the underlying disease, rather than just the symptoms, as topical therapies do not address the inflammatory mechanism of the disease nor associated comorbidities. Additionally, as compared to "traditional" immunosuppressive drugs – which have a broader impact on the immune system – biologics target

a specific immune process so the number of adverse events associated with their use is usually lower.

"Biologics tend to have greater efficacy and better safety than other systemic medications, perhaps because, in part, they are more targeted to specific factors," said Steven R. Feldman, M.D., Ph.D., Center for Dermatology Research and the Departments of Dermatology, Pathology and Public Health Sciences at Wake Forest University School of Medicine in Winston-Salem, NC. "Biologics are not associated with the renal toxicity, hepatotoxicity and other side effects associated with non-biologic systemic treatments,"⁶ he continued.

Biologics are not without side effects, however. Commonly reported are allergic reaction and antibody formation, injection or infusion site reactions, flu-like symptoms and infections. Less commonly, but of

greater concern are malignancy, demyelinating disease, thrombocytopenia, autoimmune hemolytic anemia, congestive cardiac failure, antinuclear antibodies and lupus-like syndrome, and hepatitis.⁷

Two FDA-approved treatments for plaque psoriasis should be noted for safety issues. Merck's Raptiva®, prior to being withdrawn from the U.S. market in 2009, had a box warning to highlight the risk of bacterial sepsis, viral meningitis, invasive fungal disease, progressive multifocal leukoencephalopathy (PML) and other infections.⁸ Valeant's Siliq™, approved in 2017, has a box warning due to suicidal behavior, and is only available through a restricted program.⁹

PATIENT COMPLIANCE

Biologics are typically a third-line treatment option for patients who don't respond or have insufficient response to topicals or phototherapy. Choosing a treatment for psoriasis may be challenging due to insurance requirements and the unpredictable and chronic nature of the disease. Compliance is a key factor for consideration when looking at the administration of the regimen, e.g., a self-administered injection vs. in-clinic intravenous infusions. Frequency, dosing, need for monitoring, and safety concerns also influence compliance and are frequent topics of discussion between patients and their physicians. Patients should also be made aware non-compliance with treatment regimens may lead to anti-drug antibody formation and may prevent them from receiving the full potential benefits of the therapy.

Perhaps most important in patient compliance for dermatology treatments is goal setting. Patient advocacy group The National Psoriasis Foundation addressed this in its "Treat 2 Target" program¹⁰ which provides a set of treatment goals for patients to use with their providers. The goals, published in the *Journal of the American Academy of Dermatology* in November 2016, include

Frequency, dosing, need for monitoring, and safety concerns also influence compliance and are frequent topics of discussion between patients and their physicians.

having three and six month doctor visits to monitor progress after initial or a new treatment has begun with a goal of one percent or less of psoriasis covering the body.¹¹ The Foundation also provides a [treatment comparison chart](#) to help patients and physicians make informed decisions regarding options.

PATIENT QUALITY OF LIFE AND MEDICATION COSTS

Quality of life considerations for psoriasis patients extend beyond the actual treatment paradigm and may include anxiety, social dysfunction, sleep disturbance and somatic symptoms. A 2014 study examined quality of life and mental health in psoriasis patients comparing biologic treatments to other modalities. The study concluded that patients treated with biologics saw a 52.2 percent decrease in General Health Questionnaire (GHQ-30) scores, as compared to a 24 percent and 17 percent decrease among systemic and topical treatments respectively.¹² This data suggests biologics may lead to better outcomes for some psoriasis patients.

The cost of biologics is rising, and is typically more expensive than oral systemic therapies. However, a study published in the *British Journal of Dermatology* found biologics to treat moderate to severe plaque psoriasis to "reduce costs associated with major changes in the pattern of healthcare delivery, reduce the number of

inpatient admissions by more than half and reduce the mean number of inpatient days by more than 75 percent.”¹³ This suggests the higher cost of biologics may be offset by reductions in hospital stays – typically for infectious disease – and improved patient outcomes.

MOVING TO CLINICAL TRIALS: CONSIDERATIONS FOR BIOLOGIC AGENTS

PATIENT INCLUSION AND EXCLUSION CRITERIA

As compared to conventional systemic dermatologic treatments, perhaps the most significant difference in developing biologics is the patient inclusion/exclusion criteria. Biologics are typically only indicated for patients with the more severe disease presentation – usually a BSA of 10-25 percent or more – and those that have already exhausted front-line treatments like topicals or phototherapy. With this in mind, biologics sponsors must be thoughtful and specific about inclusion/exclusion criteria for clinical trial protocols.

SITE SELECTION AND ENROLLMENT

Differences in clinical trial sites are most pronounced when comparing site selection in the U.S. vs. European countries. In the U.S., many dermatology sites are private practices with high patient volumes. In Europe, hospital or university-based practices are more common. In both cases, the site’s ability to administer the biologic should be evaluated. For example, with IV infusions, some private practices may not have the facilities or staff to administer, or prefer to not participate due to the higher risk of reactions (vs. systemic therapies).

SAFETY MANAGEMENT

Traditional dermatologic treatments generally have favorable safety profiles, with few adverse events reported during clinical trials. Biologics diverge in that safety must be a strong consideration, especially in

COMMONLY USED EXCLUSION CRITERIA

Previous biologics in the patient’s history

- If the patient failed off a biologic agent, he/she may be considered recalcitrant and may not respond to new biologic treatment

Immunosuppressed patients

- Personal history of malignancy
- Immunosuppressive/immunomodulating drugs
- HIV positive
- Tuberculosis (TB)
- Viral hepatitis; hepatitis B and C
- Opportunistic and recurring infections
- Demyelinating disease
- Family history of lymphoma/leukemia

Pregnancy

Live vaccines

Phase II or Phase III trials – where pharmacokinetic (PK) draws and close oversight are required.

Other safety considerations for dermatologic biologics include avoiding use in patients with serious and active infections. As previously referenced, TB and viral hepatitis are typically exclusionary for clinical trials. Patients with a history of malignancy and those who are pregnant are also typically excluded.

Beyond these overarching exclusions, type-specific safety risks based on mechanism include:¹⁴

- TNF-a antagonists** > Hepatitis B, malignancy, demyelinating diseases, congestive heart failure, live vaccines
- (IL)-12/23 antagonists** > Malignancy, live vaccines
- IL-17A antagonists** > Inflammatory bowel disease, live vaccines

TNF-a can potentially increase the risk of infections and malignancy, particularly in patients with rheumatoid arthritis and inflammatory bowel disease.¹⁵ Reactivation of latent TB is also a known risk factor. Concerns over use with patients with demyelinating disorders like multiple sclerosis and cardiovascular disease are also associated with this class of biologics.

Biologic therapies may also require more involvement from the medical monitor on the study, as well as the use of a data safety and monitoring board (DSMB), which is not typical for a dermatology trial.

ENDPOINTS

Endpoints for biologics do not typically differ from those of other modalities within dermatology. Skin clearance is the primary indicator of treatment effectiveness, and is measured using the physician-reported Psoriasis Area and Severity Index (PASI) and Static Physicians Global Assessment (sPGA). Other assessments include patient questionnaires: Psoriasis Symptom Inventory (PSI), the Dermatology Life Quality Index (DLQI), treatment satisfaction, and global health status.

At the time of publishing, the most recent FDA approval of a biologic for plaque psoriasis, Siliq™, used PASI as the primary endpoint. Lawrence J. Green, M.D., Associate Clinical Professor of Dermatology at George Washington University School of Medicine, stated, “Siliq is the only product that has demonstrated 100 percent improvement in the psoriasis area and severity index (PASI 100) during clinical trials as a primary endpoint.”¹⁶

LOOKING TO THE FUTURE

Given the momentum in development and continued need for safe and effective dermatological biologic treatments, we expect to see impressive advancement and growth in the sector. Biologics are proving to positively impact patients in both skin clearance and quality of life. While further research is needed, the safety and efficacy of biologic treatments are welcomed by patients and physicians.

REFERENCES

1. Market Research Reports press release. "Global Dermatology Market: Increasing Proliferation Of Lucrative Late-Stage Products To Drive Growth." Aug. 23, 2016. <https://globenewswire.com/news-release/2016/08/23/866142/0/en/Global-Dermatology-Market-Increasing-Proliferation-Of-Lucrative-Late-Stage-Products-To-Drive-Growth-MarketResearchReports-biz.html>
2. "Global Dermatology Market to 2022 - Innovative Pipeline and Increasing Uptake of Biologics to Diversify Treatment Options and Drive Strong Growth." GBI Research. May 2016. <https://www.reportlinker.com/p03876502/Global-Dermatology-Market-to-Innovative-Pipeline-and-Increasing-Uptake-of-Biologics-to-Diversify-Treatment-Options-and-Drive-Strong-Growth.html>
3. Mechcatie, E. "Dupilumab: FDA approves first biologic for atopic dermatitis." *Dermatology News*. Mar. 28, 2017. <http://www.mdedge.com/edermatologynews/article/134493/atopic-dermatitis/dupilumab-fda-approves-first-biologic-atopic>
4. CenterWatch. "FDA Approved Drugs for Dermatology." Accessed May 10, 2017. <https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/3/dermatology>
5. Mitra, S. "Biologics continue to flare up the psoriasis market, indicating opportunities in the larger dermatology space." DRG blog. Published July 20, 2016. <https://decisionresourcesgroup.com/drg-blog/biologics-continue-flare-psoriasis-market-indicating-opportunities-larger-dermatology-space/>
6. Koutnik-Fotopoulos, E. "An Overview of Biologics." *The Dermatologist*. July 2013. Vol. 21, Issue 7. <http://www.the-dermatologist.com/content/overview-biologics>
7. Hassan, I., et al. "Biologics in Dermatology: A Brief Review." *British Journal of Medical Practitioners*. Dec. 2013. Vol. 6, Number 4. <http://www.bjmp.org/files/2013-6-4/bjmp-2013-6-4-a629.pdf>
8. FDA press release. "Safety Concerns and Labeling Changes for Psoriasis Drug Raptiva." April 8, 2009. <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm143347.htm>
9. FDA press release. "FDA approves new psoriasis drug." Feb. 15, 2017. <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm541981.htm>
10. National Psoriasis Foundation. "Hitting the bullseye with psoriasis treatments." Accessed May 10, 2017 at: <https://www.psoriasis.org/treat-to-target>
11. National Psoriasis Foundation. "Your path to clear skin starts now." Accessed May 10, 2017 at: <https://www.psoriasis.org/treat-to-target/patients>
12. Takahashi, H., et al. "Biologics are more potent than other treatment modalities for improvement of quality of life in psoriasis patients." *The Journal of Dermatology*. Jul. 16, 2015. Accessed May 10, 2017 at: <http://onlinelibrary.wiley.com/doi/10.1111/1346-8138.12544/full>

13. Fonia, A., et al. "A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis." Jul. 19, 2010. *British Journal of Dermatology*. Accessed May 10, 2017. <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2133.2010.09944.x/full>
14. Krader, C. "Pearls to optimize safety, success with biologics." *Dermatology Times*. Dec. 5, 2016. <http://www.dermatologytimes.com/dermatology/pearls-optimize-safety-success-biologics>
15. Mansouri, Y., Goldenberg, G. "Biologic Safety in Psoriasis." *The Journal of Clinical and Aesthetic Dermatology*. Feb. 2015. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4345931/>
16. Valeant Pharmaceuticals press release. "Valeant Receives FDA Approval of SILIQ™ (Brodalumab) for Moderate-to-Severe Plaque Psoriasis." Feb. 16, 2017. <https://ir.bauschhealth.com/news-releases/2017/02-16-2017-120330247>



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