

Advancing Our Understanding of Hidradenitis Suppurativa: A Comprehensive Guide for Clinicians Designed to Improve Therapeutic Outcomes for Patients—Part 3

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Despite greater awareness of hidradenitis suppurativa (HS) as a well-defined, chronic inflammatory skin disorder that can flare unpredictably and be highly symptomatic, both patients and clinicians face challenges in facilitating care that is expedient, effective, reasonably safe, and accessible. Fortunately, since the approval of the injectable anti-tumor necrosis factor (TNF)- α agent, adalimumab, in 2015 by the United States Food and Drug Administration (FDA), treating HS inflammation that is not visible clinically but is occurring steadily and progressively below the surface of the skin has proven to be of extreme importance to patients, especially as related to long-term management. The mechanism of action (MOA) of properly selected biologic therapy inhibits both the inflammation associated with active primary HS skin lesions and the subsequent irreversible fibrotic and cicatricial dermal sequelae that form due to destructive changes occurring more deeply within inflamed HS lesions. Over the past decade, the ability to therapeutically and pharmacologically halt the progression of irreversible tissue destruction in HS has emerged, first with anti-TNF- α therapy and then later with anti-interleukin (IL)-17 therapies. In this third article of a 4-part series on HS, information on therapeutic management is expanded to include secukinumab and bimekizumab, both FDA-approved anti-IL-17 monoclonal antibodies for moderate-to-severe HS in adults. Additional topics covered in this article embrace other MOAs and cascades of inflammation that are believed to markedly contribute to HS pathophysiology and provide therapeutic benefit, including systemic Janus kinase inhibitors and glucagon-like peptide-1 receptor agonists. Ultimately, the goal of this 4-part article series is to provide a substantial scientific foundation on the disease state coupled with a practical, reasonably comprehensive, and clinically useful collection of source information that can serve as a valuable “guidance tool” to assist clinicians in managing HS. As stated in the first article of this series, multiple authors have separately contributed individual sections inclusive of supporting references. All authors were primarily responsible for their individual sections but also participated in the review and finalization of the complete series of articles. The order of the authors reflects the order of appearance of their primary sections in the 4-part article series.

KEYWORDS: Hidradenitis suppurativa, secukinumab, bimekizumab, systemic Janus kinase inhibitors, glucagon-like peptide-1 receptor agonists

SECUKINUMAB FOR HIDRADENITIS SUPPURATIVA

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Secukinumab is a recombinant human monoclonal antibody targeting interleukin (IL)-17A, a key pro-inflammatory cytokine implicated in the pathophysiology of hidradenitis suppurativa (HS).¹ The IL-17 family consists of 6 members, IL-17A through IL-17F, with IL-17A being the most biologically active subtype.² Secukinumab selectively binds to free IL-17A, neutralizing its activity by preventing interaction with the IL-17 receptor, and has undergone thorough evaluation of its efficacy and safety profile.^{3–14}

Randomized clinical trial outcomes in HS. The SUNSHINE (NCT03713619) and SUNRISE (NCT03713632) phase 3 clinical trials evaluated secukinumab in adults with HS.⁴ These 2 identical, multicenter, randomized, placebo-controlled studies evaluated the clinical efficacy and safety of secukinumab compared to placebo at Week 16 as assessed by achievement of Hidradenitis Suppurativa Clinical Response (HiSCR; defined as a decrease in abscess and inflammatory nodule count by 50% with no increase in draining fistulas). Two dosing regimens, 300 mg every 2 weeks (Q2W) and 300 mg every 4 weeks (Q4W), were evaluated over a 52-week

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TABLE 1. Secukinumab clinical trials for hidradenitis suppurativa (HS)

STUDY NAME	STUDY TYPE	RELEVANT OUTCOMES	RELEVANT COMMENTS
Kimball et al ⁴	Phase 3, multicenter randomized, placebo-controlled	SUNSHINE Week 16 HiSCR: 45% (Q2W), 42% (Q4W), and 34% (placebo) SUNRISE Week 16 HiSCR: 42% (Q2W), 46% (Q4W), and 31% (placebo)	Both dosing regimens demonstrated benefit. Clinical response was significantly greater in the Q2W group compared to placebo. Participants experienced sustained response through 52 weeks.
Kimball et al ⁵	Long-term extension trial (up to Week 104)	Time to LOR: Q2W vs placebo: 283 days vs 239 days Q4W vs placebo: 365 days vs 171 days Risk reduction for LOR: Q2W vs placebo risk reduction: 13% ($P=0.25$) Q4W vs placebo risk reduction: 30% ($P=0.04$)	Primary endpoint (time to LOR) was not statistically significant. Numerically longer maintenance of response was seen for both Q2W and Q4W secukinumab groups compared to placebo.

HiSCR: Hidradenitis Suppurativa Clinical Response; LOR: loss of response; Q2W: every 2 weeks; Q4W: every 4 weeks

period. While both demonstrated benefit, Q2W dosing yielded a slightly better overall response. At Week 16 in SUNSHINE, HiSCR was achieved by 45%, 42%, and 34% of participants in the Q2W, 4-week dose (Q4W), and placebo groups, respectively. In SUNRISE, HiSCR 42%, 46%, and 31% was achieved at Week 16 in the Q2W, Q4W, and placebo groups, respectively. Clinical response was significantly greater in the 2-week group compared to placebo (SUNSHINE: 45% Q2W vs 34% placebo, $P=0.0070$; SUNRISE: 42% Q2W vs 31% placebo, $P=0.015$); however, the Q4W group in SUNSHINE did not reach statistical significance. Participants experienced sustained response through 52 weeks as well as improvement in skin pain, health-related quality of life (HRQoL), and overall health status.⁴ These data provided a basis for an expanded indication in adolescents. Pediatric approval was obtained in March 2026 for patients aged >12 years weighing ≥ 30 kg (66 pounds) using safety data and pharmacokinetic modeling extrapolated from SUNSHINE and SUNRISE and already approved pediatric indications.¹⁴ This more recent pediatric approval, which now encompasses adolescent patients with HS, is a major therapeutic step forward for affected patients, their loved ones and caretakers, and for the clinicians and staff caring for them. Secukinumab clinical trials are depicted in **Table 1**.

Long-term data through Week 204 show sustained efficacy. Although the primary endpoint, time to loss of response, was not statistically met, numerically longer maintenance of response was seen for both the Q2W and Q4W secukinumab groups

compared to placebo.⁵ Further post-hoc analyses demonstrated efficacy regardless of prior biologic exposure with sustained clinical response, and continuous efficacy through Week 204, and support that early treatment initiation more often achieves clinical response compared to the presence of pre-existing long-standing HS.^{6,12,13}

Safety data with secukinumab in HS.

Secukinumab has demonstrated consistent safety and tolerability throughout long-term studies.^{4,5} However, IL-17 inhibitors are generally not recommended in patients with inflammatory bowel disease (IBD), as prior studies demonstrated a worsening of IBD with IL-17 inhibition.⁷ IBD is associated with HS, with a prevalence of up to 2% for Crohn's disease and 1.3% for ulcerative colitis.⁸ No cases of IBD were noted in the SUNSHINE study, while 1% of patients in the SUNRISE study developed IBD. Candidiasis was reported in a small percentage of patients, with comparable rates to placebo. Injection-site reactions were uncommon.⁴ A systematic review and meta-analysis evaluating injection-site reactions, including erythema, pain, and pruritus, showed that secukinumab had the lowest prevalence of injection-site reactions compared to other biologics.⁹

Secukinumab is available in a 300-mg/2-mL single-dose pen or prefilled syringe. The United States (US) Food and Drug Administration (FDA)-recommended dose of secukinumab for HS is a 300-mg subcutaneous injection once weekly for 4 weeks followed by a dose once Q4W. Up-titration to Q2W is recommended in the case of inadequate response to Q4W. A post-hoc analysis of nonresponders to Q4W

demonstrated improvement with up-titration to Q2W.^{10,11}

BIMEKIZUMAB FOR HS

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Bimekizumab is a humanized immunoglobulin G1 monoclonal antibody that antagonizes both IL-17A and IL-17F, is capable of inhibiting both homodimers and heterodimers of both IL-17 subfractions, and is supported for use in HS by multiple research studies (**Table 2**).^{15–21} This dual IL-17A/IL-17F inhibitor is FDA approved for the treatment of adults affected by a variety of inflammatory diseases, including moderate-to-severe HS, moderate-to-severe plaque psoriasis (PsO) in patients who are candidates for systemic therapy or phototherapy, active psoriatic arthritis (PsA), active nonradiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation, and active ankylosing spondylitis.^{16,22} This section will focus on the efficacy and safety of bimekizumab for HS, including characteristics of dual IL-17A/IL-17F inhibition.

Is dual inhibition of IL-17A/IL-17F clinically relevant? There is strong support that dual inhibition of IL-17F and IL-17A provides augmented mechanistic and therapeutic benefit for inflammatory skin and joint disorders associated with increased IL-17 activation, including plaque PsO, psoriatic arthropathies, and HS, due to a more complete suppression of IL-17 pro-inflammatory signaling.^{8,16,23–29} Available evidence supporting the advantages of dual IL-17A/IL-17F inhibition over IL-17A inhibition alone, including for HS, includes the following:

- IL-17A and IL-17F both act synergistically with TNF- α and IL-1, cytokines that are pathophysiologically active in HS, to enhance and perpetuate cascades of inflammation induced by these cytokines;
- IL-17A and IL-17F exhibit similar homology and, together with other cytokines, synergistically drive neutrophil influx into inflammatory lesions, a key feature of HS;
- IL-17A and IL-17F are biologically similar isoforms and are both upregulated in HS;
- IL-17A and IL-17F are regulated differently by duration of effect and how they are stimulated (IL-17F is preferentially

- produced by some signal transducer and activator of transcription (STAT) 5 cytokines and IL-1 β and is more highly upregulated in HS lesions than IL-17A);
- higher levels of IL-17 have been consistently noted in HS lesions and in perilesional tissue compared to control skin;
 - both IL-17A and IL-17F have been observed in early HS lesions, with IL-17F-producing cells shown to localize to IL-1-expressing cells in chronic HS lesions;
 - dysfunctional T-regulatory cells in HS express greater amounts of IL-17F;
 - elevated IL-17 serum levels that correlate with disease severity have been observed in patients with HS; and
 - clinical data support greater efficacy with dual IL-17A/IL-17F inhibition for PsO and PsA.^{8,16,23–29}

Overview of clinical efficacy data. As stated above, **Table 2** includes a selection of completed clinical trials of bimekizumab, with relevant study endpoints and outcomes highlighted.^{15–21} The 2 identical phase 3, 48-week, randomized controlled trials (RCTs; N=1,014) established rapid and deep clinically significant responses with bimekizumab for moderate-to-severe HS with recommended dosing established, including marked reductions in abscesses, nodules, and draining tunnels, and early successful responses maintained or increased over the 48-week study duration; an improvement in Dermatology Life Quality Index (DLQI) scores and a rapid reduction in worst skin pain as early as 2 weeks were also noted.¹⁶ These 2 RCTs (BE HEARD I [NCT04242446] and BE HEARD II [NCT04242498]) were the first phase 3 studies in HS to report HiSCR75 and HiSCR90 to Week 48; a progressive increase in HiSCR50 and HiSCR75 outcomes was noted in the initial treatment period (through Week 16) with bimekizumab 320 mg Q2W and the maintenance treatment period (Week 16 through Week 48) with either bimekizumab 320 mg Q2W or Q4W, *thus supporting the option of switching to Q4W when a favorable initial response is observed as defined in the FDA-approved indication*.¹⁶ A 2-year evaluation, inclusive of pooled results from the 2 phase 3 RCTs and their open-label extensions, assessed outcomes in 446 patients who

TABLE 2. Bimekizumab clinical trials for hidradenitis suppurativa

STUDY NAME	STUDY TYPE	RELEVANT OUTCOMES	RELEVANT COMMENTS
Glatt et al ¹⁵	Phase 2 RCT, N=90	HiSCR50 vs placebo at Week 12; HiSCR75, HiSCR90, pain, and DLQI Week 12 • 46% taking BMZ achieved HiSCR75 and 32% achieved HiSCR90	BMZ significant improvement over placebo
Kimball et al ¹⁶	Phase 3 RCTs, N=505 and N=509	HiSCR50 vs placebo at Week 16; HiSCR75, DLQI, and worst skin pain at Week 16 • BMZ Q2W: 48% of patients in BE HEARD I and 52% in BE HEARD II achieved HiSCR50 at Week 16	BMZ Q2W to Q4W showed HiSCR50/75 improvements sustained over 48 weeks
Sayed et al ¹⁷	Pooled Phase 3 RCT, N=556	TEAEs per 100 patient-years, skin pain, and HRQoL over 2 years • Well tolerated, no new safety signals	Durable improvement in skin pain and HRQoL
Mansilla-Polo et al ¹⁸	Real-world data, N=40	IHS4, HS-PGA, pain VAS, and DLQI at Week 16 • Improved IHS4; decreases in HS-PGA, pain VAS, and DLQI	Real-world data supportive of RCT data
Pender et al ¹⁹	Real-world data, N=15	HiSCR or HS-PGA, DLQI at Week 16 • Two-thirds of patients responded, most on concomitant treatments, improved DLQI	Higher responses than RCT
Chovatiya et al ²⁰	Extension trial, N=556	HiSCR based on disease duration • HiSCR50/75/90/100 maintained at Year 1 and Year 2	Duration of disease impacted HiSCR90/100
Mansilla-Polo et al ²¹	Retrospective, N=84	IHS4, HS-PGA, pain VAS, and DLQI at Week 16 and Week 24 • More than 50% of patients achieved IHS4 at Week 16 and Week 24, improved pain VAS and DLQI	Significant improvements in patients with higher disease severity and previous biologic exposure

BMZ: bimekizumab; DLQI: Dermatology Life Quality Index; HiSCR50: Hidradenitis Suppurativa Clinical Response of at least 50%; HRQoL: health-related quality of life; HS-PGA: Hidradenitis Suppurativa-Physician Global Assessment; IHS4: International Hidradenitis Suppurativa Severity Score System; Q2W: every 2 weeks; Q4W: every 4 weeks; RCT: randomized controlled trial; TEAE: treatment-emergent adverse event; VAS: visual analog scale

received continuous bimekizumab for 2 years.¹⁷ Overall, sustained efficacy and safety were observed over the 2 years of evaluation with most patients achieving HiSCR50/75/90/100 at Year 2 (85.4%, 77.1%, 57.6%, and 44.2%, respectively).¹⁷

Differentiation of outcomes from real-life clinical use vs data from RCTs. Although limited by methodology, patient numbers, and other confounding variables, reports evaluating real-life clinical use and retrospective analyses have been supportive overall and generally consistent with RCT outcomes regarding the efficacy and safety of bimekizumab for HS.^{18,19,21,30,31} Importantly, results from RCTs are different and more stringent by their design and protocol requirements than are real-world studies and analyses; one approach is not necessarily “better than” or more clinically relevant than the other, especially based on what specific information the reader is looking

to glean from the results. A multicenter, retrospective, observational study of adults with moderate-to-severe HS (N=78) treated with bimekizumab for up to 48 weeks reported some *considerations related to real-world evidence that are highly clinically relevant*. These considerations, which are commonly encountered in many patients with HS under real-world conditions, include the following: (1) patients seen in clinical practice often present with a greater severity of HS that renders them ineligible for enrollment in most RCTs; (2) many patients in clinical practice are affected by 1 or more comorbidities that are otherwise excluded from many RCTs; and (3) several patients in clinical practice undergo combined medical and procedural approaches to comprehensively treat their HS, which excludes them from RCT eligibility, with medical therapy (such as bimekizumab) used to treat inflammatory HS lesions and procedural/

surgical approaches used to treat the irreversible fibrotic/cicatrical deeper HS lesions (especially patients staged as Hurley stage III).³¹ It is important to have an open mind and to critically evaluate outcomes from both RCTs and real-world evidence.

The combination of medical and procedural approaches can contribute markedly to the effectiveness of HS management, especially in patients who are already affected by extensive structural damage.³¹ This underscores the importance of recognizing that comprehensive management of HS is not only dependent on medical therapy selection, as was reviewed along with other therapeutic principles discussed in Part 2 of this article series.³² *Nevertheless, when trying to control the magnitude of HS-associated inflammation and proactively attempt to prevent progression to irreversible fibrotic/cicatrical lesions, optimizing the selection of the most effective medical therapy that is also deemed a safe choice for the given patient is important.* In the multicenter, retrospective observational study of adults with HS referenced above, 60% of patients were noted to have Hurley stage III disease at baseline, with a mean of 5 affected anatomic areas, and many had undergone previous treatment with adalimumab and/or secukinumab; bimekizumab was used for up to 48 weeks in 78 patients, with 56 patients (71.8%) completing 48 weeks of bimekizumab therapy. Notably, use of bimekizumab resulted in a marked progressive decrease in the severity of HS (based on International Hidradenitis Suppurativa Severity Score System [IHS4] disease severity rating) throughout the 48-week study, as evidenced by a shift from 88.5% rated as severe at baseline (IHS4 score >11) to 47.5% and 25% rated as severe at Weeks 16 and 48, respectively; approximately 1 in 4 patients achieved complete clinical remission (IHS4=0 score) at Week 48.³¹ Statistically significant progressive decreases ($P<0.001$) from baseline to Week 48 in the mean number of draining tunnels (from 3.3 to 1.0) and monthly flares (from 2.0 to 0.5) were also observed in this study.³¹ Although the study group is relatively small, these observations are clinically relevant, as it is unlikely that the realistic nature of this patient population with regard to disease severity, comorbidities, and combination approaches encountered in clinical practice will ever be captured in a large-scale RCT.

Overview of patient-reported outcomes (PROs).

The 2 pivotal phase 3 RCTs with bimekizumab vs placebo showed marked improvements in PROs that paralleled the clinical improvements similarly observed over the course of the studies.¹⁶ For example, favorable outcomes with the DLQI and skin pain indices vs placebo, including rapid and clinically meaningful reductions in worst skin pain, and favorable responses with other scoring systems (ie, IHS4 and Hidradenitis Suppurativa Quality of Life [HISQoL]) were all observed.^{16,33,34} A comprehensive analysis of PROs based on pooled 48-week results from the 2 pivotal phase 3 RCTs showed that bimekizumab achieved clinically meaningful improvements across multiple well-established PROs related to HRQoL incorporated as PRO study parameters for HS.³⁵ Bimekizumab exhibited marked clinical improvements within 4 weeks across multiple PROs that were maintained over 12 months. By Week 16, greater numerical reductions correlating with improvements in specific PROs were noted with bimekizumab vs placebo, with further improvements noted from Week 16 through Week 48 with bimekizumab use.³⁵

As pain is consistently noted as a common major burden in patients with HS, it is critical that clinicians and their staff not overlook the importance of asking the patient if they are experiencing pain and, if so, assessing its severity and impact on their life. An analysis of pooled 48-week results from the 2 phase 3 RCTs evaluated pain outcomes; the results from both the exploratory and post-hoc analyses up to 48 weeks using validated HS-specific pain measures demonstrated that bimekizumab induced rapid, continuous, and clinically meaningful decreases in skin pain.³⁶ Another analysis of patients treated in the 2 pivotal phase 3 RCTs showed that rapid reduction in HS lesions by bimekizumab within 16 weeks translated to markedly improved PROs related to HRQoL, which were maintained over a prolonged duration of this study.³⁷ *These data on skin pain and rapid lesion reduction support the importance of not delaying escalation of therapy selection to an agent that can markedly diminish symptomatology such as pain, rapidly decrease inflamed HS lesions in patients with moderate-to-severe HS, and halt disease progression to prevent formation of irreversible HS lesions.*

In the 2-year evaluation that includes the 2 phase 3 RCTs and their open-label extensions,

bimekizumab consistently achieved efficacy inclusive of lesional, skin pain-associated, and HRQoL outcomes, which were maintained through 2 years of follow up.¹⁷ It is important to note that draining tunnels, which are a hallmark of progressing HS disease, were markedly reduced in number at Year 1, with only minimal increase when observed through Year 2 in patients without draining tunnels at baseline. Notably, the control of draining tunnels correlating with halting disease progression and the marked reduction in skin pain maintained over 2 years with bimekizumab use translated to a high proportion of patients noting impressive Hidradenitis Suppurativa Symptom Questionnaire skin pain responses and DLQI scores of 0/1.¹⁷

Overview of clinical safety data. The safety of bimekizumab is supported by an extensive body of patient exposure worldwide, with approval by 23 regulatory agencies in 52 countries, including for moderate-to-severe PsO, active PsA, and moderate-to-severe HS; 14 phase 3/3b clinical studies have been completed in HS, PsO, PsA, ankylosing spondylitis, and nr-axSpA.³⁸ Safety analyses in PsO over 4 years and in HS over 2 years have demonstrated favorable and consistent safety results, with adverse events (AEs) consistent with the known safety profile of bimekizumab, a trend toward decreased frequency of AEs over time, and no new safety signals.^{17,39}

Prior to starting therapy, it is suggested that patients undergo all age-appropriate vaccinations according to current immunization guidelines.²²

Importantly, FDA-approved labeling notes no contraindications with bimekizumab.²² Nevertheless, specific warnings and recommendations are relevant and based on AEs reported in RCTs with bimekizumab for HS, with certain observations and suggestions also made here. Avoid use of bimekizumab in patients with an active clinically important infection until that infection is resolved. A common example would be herpes zoster. If a patient is affected by herpes zoster, withhold bimekizumab, treat the herpes zoster infection, and then consider restarting bimekizumab after the infection has resolved.

Oral candidiasis can occur in patients treated with anti-IL-17 agents, with reported rates higher with bimekizumab due to the dual inhibition of IL-17A/IL-17F; FDA-approved

prescribing information states oral candidiasis occurred in 7.8% of patients treated with bimekizumab Q2W vs 0% with placebo.^{16,22} Most cases were mild or moderate in severity, were responsive to conventional oral or topical antifungal therapy (ie, oral fluconazole, topical nystatin), and did not lead to discontinuation of bimekizumab therapy.¹⁶ Repeated occurrences of oral candidiasis are less common and can be similarly treated. Tinea infections were reported but at a lower rate than candidiasis.²²

Evaluation of patients for tuberculosis (TB) prior to initiating bimekizumab therapy is recommended in the FDA-approved prescribing information.²² Avoid bimekizumab use in the presence of active TB; initiate treatment for latent TB prior to starting bimekizumab.²²

IBD has been associated with the use of agents that inhibit IL-17.⁴⁰ It is recommended to avoid bimekizumab specifically in patients with active IBD in the FDA-approved prescribing information.²² Adjudicated definite or probable new-onset IBD was noted in 7 patients treated with bimekizumab in the phase 3 RCTs, with 4 discontinuing therapy.¹⁶ Interestingly, of the 8 patients who had a previous history of IBD in these same RCTs, none experienced flares of IBD.¹⁶ Clinical judgment and shared decision-making among the dermatology clinician, the patient, and the patient's primary physician(s) are prudent in cases where there is a strong personal or family history of IBD.

Elevation of liver enzymes is sometimes encountered in clinical trials with biologic agents, including bimekizumab. The FDA-approved prescribing information for bimekizumab recommends baseline liver function tests (transaminases, alkaline phosphatase, bilirubin) prior to starting therapy and periodically thereafter based on "routine patient management"; it is recommended that bimekizumab be avoided in patients with acute liver disease or cirrhosis.²² Data reported over 2 years from 5 phase 3/3b trials with bimekizumab showed a low transaminase enzyme elevation rate (3× the upper limit of normal) of 3.5/100 patient-years (PY) that actually decreased to 2.3/100 PYs from Year 1 to Year 2; rates seen with bimekizumab were similar to rates reported with active study comparators, including placebo, adalimumab, secukinumab, and ustekinumab, during controlled study periods.⁴¹

Similar to what has been observed with some other chronic inflammatory skin disorders, increased risk of suicidal ideation and behavior (SI/B) has been reported among patients with HS.^{42,43} Importantly, there has been no definitive causal association between SI/B and bimekizumab as stated in the FDA-approved prescribing information.²² The suggestion that bimekizumab, and many other therapies used to treat PsO and HS in dermatology, may increase the risk of SI/B is at least partially refuted by the inherent association of SI/B with many chronic inflammatory skin disorders, including psoriasis and HS, and more strongly refuted by data in patients with PsO treated with bimekizumab and other biologic agents.^{43–45} An analysis of mental health changes/neuropsychiatric events monitored across 9 bimekizumab phase 2/3 clinical trials for PsO was inclusive of 7,166 PYs of bimekizumab exposure.⁴⁴ The adjudicated SI/B rate was 0.09 to 0.54/100 PY for the general PsO population, 0.09 to 0.19/100 PY for anti-IL-23, 0.09 to 0.14/100 PY for anti-IL-17A, and 0.13 for anti-IL-17A/IL-17F (bimekizumab); additionally, low depression and SI/B levels were reported with bimekizumab based on established screening/monitoring questionnaires used during the clinical studies.⁴⁴ Based on these data collected in multiple studies of patients treated for moderate-to-severe PsO, the SI/B risk with bimekizumab was low and consistent with or less than ranges reported in the general PsO population and consistent with anti-IL-17A and anti-IL-23 biologic agents.⁴⁴ Nevertheless, and consistent with the FDA-approved prescribing information, it is important that all patients seen with HS be evaluated to determine if there is a history or current presence of severe depression or SI/B before initiating therapy for HS; if worsening depression, significant mood changes, or SI/B emerge, prompt medical attention is warranted.²²

Recommended dosing of bimekizumab in HS. In adults with moderate-to-severe HS, administer bimekizumab 320 mg by subcutaneous injection Q2W over a period of 16 weeks (total of 9 injections) then Q4W thereafter.²⁶ Bimekizumab is available as a 320-mg/2-mL (160 mg/mL) single-dose prefilled syringe or single-dose prefilled autoinjector.²²

SYSTEMIC JANUS KINASE (JAK) INHIBITORS FOR HS

Andrew Ferrier, MD

Given the contribution of multiple JAK/STAT-signaling cytokines to HS pathobiology, JAK inhibition represents a rational therapeutic strategy.^{46,47} Isolated case reports of JAK inhibition support pathway plausibility in severe, refractory disease.⁴⁸

Povorcitinib. The most extensively studied agent is povorcitinib, an oral JAK1-selective inhibitor. In a randomized, dose-ranging phase 2 study, povorcitinib produced clinically meaningful improvements vs placebo, helping to establish JAK1 as a tractable target in HS.⁴⁹ These findings progressed to 2 large, global phase 3 programs (STOP-HS1 [NCT05620823] and STOP-HS2 [NCT05620836]). Data presented at the 2026 American Academy of Dermatology Annual Meeting showed that both povorcitinib doses (45 mg and 75 mg once daily) met the primary endpoint (HiSCR50 at Week 12) vs placebo, with responses continuing to rise through Week 54. Week 12 HiSCR50 was 40.2% and 40.6%, respectively, vs 29.7% in STOP-HS1 and 42.3% and 42.3% vs 28.6% in STOP-HS2; by Week 54, responses were 60.2% and 61.9% and 57.3% and 64.3% with continuous povorcitinib (observed cases).⁵⁰ Higher-stringency outcomes also accrued, including HiSCR75 at Week 12, with increasing numbers achieving HiSCR90/100 by Weeks 24 and 54.⁵⁰ Beyond lesion counts, draining tunnels declined from Week 3 (~35–42% by Week 12, ~39–51% by Week 24, and ~36–62% at Week 54), flares were reduced vs placebo, and a high percentage of patients achieved clinically meaningful improvements in several measures of QoL (eg, pain, DLQI). Safety remained consistent with prior experience (acne, nasopharyngitis, upper respiratory tract infection, headache; low laboratory abnormality rates).⁵⁰

Upadacitinib. Running in parallel, upadacitinib (JAK1-preferential) has generated supportive real-world and randomized data. In a single-center retrospective cohort (N=20), HiSCR50 was achieved in 75% of patients by Week 4 and 100% by Week 12, with accompanying improvements in pain and quality of life with acceptable short-term safety.⁵¹ In a subsequent phase 2 randomized, placebo-controlled study, a once-daily 30 mg dose improved signs and symptoms, with HiSCR50 at Week 12 exceeding a prespecified

historical placebo benchmark; benefits were durable through Week 40 and consistent across Hurley stage and prior anti-TNF exposure, with meaningful pain reductions and a favorable safety profile.⁴⁷ A phase 3 program is underway in adult and adolescent patients refractory to anti-TNF therapy (STEP-UP HS; NCT05889182).⁵²

Other JAK inhibitors. Beyond these JAK1-focused agents, a phase 2a umbrella RCT demonstrated higher Week 16 HiSCR with brepocitinib (dual tyrosine kinase 2 [TYK2]/JAK1) vs placebo (51.9% vs 33.3%); ropsacitinib (selective TYK2) did not separate from placebo.⁵³ Taken with the povorcitinib and upadacitinib programs, these data reinforce JAK1 as the most validated target within the pathway to date for HS.

Potential uses of JAK inhibitors for HS.

Although JAK inhibitors are not yet approved for HS, contemporary HS guidelines acknowledge their off-label use.⁵⁴ Cohorts with HS are enriched for obesity, smoking, dyslipidemia, and cardiometabolic disease, all relevant to class warnings and patient selection.^{47,50,51} Accordingly, thoughtful risk stratification and routine safety surveillance are recommended. In practice, JAK inhibitors may be positioned as primary systemic therapy where rapid pain control and tunnel reduction are priorities; next-line options after anti-TNF or IL-17 exposure; or bridge/adjuncts in complex, refractory cases requiring multimodal regimens.

Across study designs, systemic JAK inhibition has delivered consistent improvements in lesions, tunnels, flares, and pain in real-world and randomized upadacitinib data and twin phase 3 povorcitinib trials. As programs mature, comparative effectiveness vs cytokine-specific biologics and longer-term safety will ultimately determine placement in the treatment algorithm, but current evidence supports JAK1 inhibition as a compelling, mechanism-based strategy for moderate-to-severe HS.^{47,50–53}

ROLE OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS IN THE TREATMENT OF HS

Michael Payette, MD, MBA

Glucagon-like peptide-1 (GLP-1) is an endogenous hormone produced primarily by the enteroendocrine cells of the intestinal wall in response to food intake. By binding the GLP-1 receptor, GLP-1 plays a critical role in the regulation of blood sugar, by increasing insulin

and decreasing glucagon secretion⁵⁵; appetite, through action on the hypothalamus and gut to increase satiety⁵⁶; gastrointestinal motility, via slowing of gastric emptying⁵⁵; the gut-brain-pancreas axis, by impacting both digestion and food metabolism⁵⁷; and blood pressure, by causing vasodilation and inhibiting the sympathetic nervous system.⁵⁸ GLP-1 receptor agonists (RAs), such as tirzepatide, semaglutide, and liraglutide, are synthetic peptides that mimic endogenous GLP-1, and use of these therapies has exploded in popularity due to their applications in type 2 diabetes and weight loss. Recently, GLP-1 RAs have expanded into the treatment of dermatologic inflammatory diseases, in particular psoriasis and HS.

Benefits of weight loss in HS management.

In HS, the direct benefit of weight loss is apparent, as obesity is both a predisposing and exacerbating risk factor for HS, increases skin friction, contributes to HS flares, inhibits wound healing, and leads to the co-occurrence of metabolic syndrome and type 2 diabetes in affected individuals.⁵⁹ Patients with HS who have a body mass index (BMI) >30 have been shown to have elevated levels of irisin protein, peroxisome proliferator-activated receptor γ , and the insulin-like growth factor-1 receptor, which are markers of metabolic disorders and obesity.^{60,61} These same individuals also show increased expression of the IL-17 receptor, a notable pro-inflammatory cytokine involved in HS pathogenesis and an established target for treatment.⁶⁰ Several studies have demonstrated that weight loss via bariatric surgery reduces both the prevalence and severity of HS lesions.^{62,63} However, the benefit of these medications appears to go beyond just weight loss.

GLP-1 RAs and anti-inflammatory effects. The most exciting therapeutic benefit of these medicines is their potential to be anti-inflammatory. A systematic review of GLP-1 RAs in patients with HS by Krajewski et al⁶⁴ demonstrated significant reductions in inflammatory nodules, abscess formation, and overall disease severity. Al-Badri and Azar⁶⁵ showed that GLP-1 RAs inhibit TNF- α , another notable pro-inflammatory cytokine involved in HS pathogenesis and an established target for treatment, and Hogan et al⁶⁶ found that GLP-1 RAs can reduce invariant natural killer T-cell levels, which is significant as activation of these cells results in increased expression

of pro-inflammatory cytokines such as interferon- γ , TNF- α , and IL-17. In a study by Mei et al,⁶⁷ liraglutide therapy was associated with reduced TNF- α levels, reduced activation of the nuclear factor- κ B pathway, reduced secretion of monocyte chemoattractant protein 1, as well as suppression of IL-17, IL-22, and IL-23.

GLP-1 RAs, anti-inflammatory effects, and clinical improvements. These anti-inflammatory benefits correlate to clinical and symptomatic improvements in patients with HS. A retrospective study of 30 patients with obesity and HS treated with weekly semaglutide (~0.8 mg for ~8.2 months) resulted in lower weight (117.7 to 111.6 kg), decreased flare frequency (every 8.5 weeks to every 12 weeks), improved DLQI score (13 to 9), and modest reductions in inflammatory markers such as hemoglobin A1c and C-reactive protein.⁶⁸ Similarly, a prospective case series of 14 patients with both HS and obesity who were treated with liraglutide 3 mg for 3 months demonstrated reductions in BMI (39.3 to 35.6); waist circumference (121.3 to 110.6 cm); systemic inflammatory markers such as CRP (4.5 to 3.0 mg/L), homocysteine (16.2 to 13.3 μ mol/L), and plasma cortisol (15.9 to 12.6 μ g/dL); and improved DLQI (12.3 to 9.7).⁶⁹ In a study by Gouvion et al⁷⁰ that looked at 66 patients with HS who were treated with a GLP-1 RA for at least 3 months (median follow-up time of 18.5 months), 62% experienced a ≥ 1 -point reduction in their Hidradenitis Suppurativa Physician Global Assessment score, 60% reported a decrease in pain, and 67% reported a reduction in the frequency of their flares. Additionally, these positive changes were observed in a subgroup of patients in which their other therapies remained unchanged, suggesting a direct effect of the GLP-1 RA.

Words of caution and the need for additional studies. While these findings are encouraging, it is important to recognize that most data to date come from small observational or retrospective studies with multiple possible confounders. RCTs are absent, and many patients in these small trials were treated with other therapies known to improve HS, including but not limited to systemic anti-inflammatories, antihormonal therapies, and biologic medications. It is also important to recognize that the complex pathogenesis of HS includes genetic predispositions, immune system dysregulation, and the impact of

environmental and behavioral factors. Lastly, not all patients experience benefit from GLP-1 RAs, with some patients experiencing increased inflammation and more flares.⁶⁴ Future studies that are prospective and controlled are required to add granularity to our understanding of how these potentially promising therapies might be optimally used in managing patients with HS.

WHAT IS COMING UP NEXT?

In the fourth and final article of this series on HS, topics to be reviewed are office-based procedures in HS management, patient support programs for HS, putting it all together in managing HS, and a discussion on what is likely to be coming in the future to further improve HS management and the quality of life for patients affected by this difficult and life-altering condition.

DISCLOSURES

Dr. Del Rosso is a consultant/advisor, research investigator, and/or speaker for AbbVie, Almirall, Alumis, Amgen, Apogee, Arcutis, Bausch Health/OrthoDermatologics, Beiersdorf, Biofrontera, Bluefin, Blueprint Medicines, Botanix, Bristol Myers Squibb, Cara, Celgene, Ferndale, Galderma, Incyte, Janssen, Johnson & Johnson, La Roche-Posay, LEO Pharma, Lilly, L'Oréal, MC2 Therapeutics, MoonLake, Novan, Oruka, Pelthos Therapeutics, Pfizer, Regeneron, Sanofi, Sun Pharma, Takeda, Trevi, UCB, and Verrica. **Dr. Dasilva** reports being an investigator for Galderma and Novartis; consultant/promotional speaker for AbbVie, Arcutis, Castle Biosciences, Dermavant/Organon, Galderma, Incyte, Johnson & Johnson, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi/Regeneron, UCB, Takeda, Vanta Diagnostic, and Verrica; and a board member and associate editor for the *Journal of Clinical and Aesthetic Dermatology* and ReachRx. **Dr. Bunick** has served as an investigator and/or consultant for AbbVie, AbSci, Almirall, Alumis, Amgen, Apogee, Arcutis, AvantGuard, Avene, Botanix, Castle Biosciences, Connect BioPharma, Daiichi Sankyo, Dermavant, Disc Medicine, EPI Health/Novan, Galderma, Highlight Therapeutics, Incyte, LEO Pharma, Lilly, Novartis, Ortho Dermatologics, Palvella, Pfizer, Primus, Priovant, Regeneron, Sanofi, South Beach Symposium, Sun Pharma, Takeda, Timber, Teladoc, Triveni, UCB, Veradermics, and ZenZema. **Dr. Murina** is a speaker for AbbVie, Amgen, Botanix, Galderma, Johnson & Johnson, Ortho Dermatologics, Pfizer, and UCB and has served as a consultant for Johnson & Johnson, LEO Pharma, Lilly, Novartis, Ortho Dermatologics, Sun Pharma, Takeda, UCB, and Veradermics. **Dr. Lee** has served as an advisory board member and/or investigator for Incyte and Novartis. **Dr. Hsiao** has served as an advisor, investigator, and/or

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