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Hidradenitis suppurativa: state-of-the-art review and update

Marco Virone,[1] Elena Zappia,[2,3] Alberto Di Caro,[1] Davide Carlesimo,[1] Nicoletta Bernardini,[4] Giovanni Pellacani,[1] Antonio Giovanni Richetta,[1] Steven Paul Nisticò,[1] Annunziata Dattola[1]

[1]Dermatology Unit, Department of Clinical Internal, Anesthesiological and Cardiovascular Science, La Sapienza University of Rome; [2]Department of Medical Sciences, University of Turin; [3]Department of Health Sciences, Magna Graecia University, Catanzaro; [4]Department of Medical-Surgical Sciences and Biotechnologies, Dermatology Unit "Daniele Innocenzi", La Sapienza University of Rome, Polo Pontino, Latina, Italy

Correspondence: Marco Virone, Dermatology Unit, Department of Clinical Internal, Anesthesiological and Cardiovascular Science, La Sapienza University of Rome, V.le del Policlinico 155, 00161 Rome, Italy.
E-mail: vironem97@gmail.com

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Abstract

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by painful nodules, abscesses, and draining tunnels in areas such as the axillae, groin, and inframammary regions. It typically emerges in early adulthood, with a global prevalence of approximately 1%, though regional variations exist. HS significantly affects patients' quality of life and imposes considerable socioeconomic burdens. It is frequently associated with metabolic syndrome, inflammatory arthritis, and inflammatory bowel disease, reflecting its underlying systemic inflammatory nature. The pathogenesis of HS involves innate immune mechanisms, including macrophages, neutrophils, interleukin (IL)-1β, tumor necrosis factor-alpha (TNF-α), and granulocyte colony-stimulating factor, alongside adaptive immune responses mediated by T cells (IL-17, interferon-gamma [IFN-γ]) and B cells, which contribute to autoantibody formation and tertiary lymphoid structures. Chronic inflammation results in irreversible tissue damage, tunnel formation, and severe scarring. Treatment strategies vary based on disease severity. Early inflammatory stages benefit from pharmacological therapies, while later stages require a combination of medical and surgical interventions, with surgery often necessary for advanced cases. The introduction of targeted biologic therapies, including TNF-α (adalimumab) and IL-17 inhibitors (secukinumab, bimekizumab), has expanded treatment options beyond traditional antibiotic regimens. Effective management focuses on early intervention to prevent irreversible damage, control symptoms such as pain, and address systemic comorbidities. A timely diagnosis, along with a multidisciplinary and personalized approach, is essential for improving patient outcomes and quality of life.

Introduction

Hidradenitis suppurativa (HS), also known as acne inversa or Verneuil's disease, is a chronic, debilitating inflammatory skin condition primarily affecting areas rich in apocrine glands, such as the axillae, groin, and inframammary and genito-anal regions.[1] Characterized by painful, recurrent nodules, abscesses, and draining tunnels, HS significantly impacts patients' quality of life, leading to chronic pain, impaired mobility, psychological distress, and social stigmatization. Despite its significant burden on patients' physical and mental health, HS remains underdiagnosed and underreported. One of the key factors contributing to delayed treatment is the considerable diagnostic lag, which can average around 10 years, during which patients often receive multiple misdiagnoses and inadequate treatments.[2]

HS has an estimated global prevalence ranging from 0.05% to 4.10%, influenced by variations in diagnostic criteria, ethnicity, and geographical distribution.[3] This wide range may reflect differences in diagnostic criteria, geographical location, and population demographics. For example, higher

prevalence figures are observed in certain ethnic groups, while some countries with less awareness report lower rates.

The disease course can vary from mild inflammation to severe, irreversible tissue destruction due to chronic, uncontrolled inflammation. Late-stage HS is marked by the formation of neo-epithelialized tunnels that perpetuate inflammation and contribute to progressive skin damage. HS is also associated with numerous comorbidities, including metabolic syndrome, cardiovascular disease, inflammatory arthritis, gastrointestinal disorders, and mood disturbances, further exacerbating patient morbidity and reducing life expectancy.[3,4]

The exact etiology of HS remains unclear, but it is believed to involve a complex interplay of genetic, epigenetic, hormonal, mechanical, microbial, and lifestyle factors, such as obesity and smoking. Dysregulated immune responses, including innate and adaptive immune mechanisms, play a central role in disease pathogenesis.[5,6] Despite its severe and progressive nature, treatment options for HS remain limited, often leading to inadequate disease control. Current therapeutic approaches range from topical and systemic antibiotics, retinoids, hormonal therapies, immunomodulatory agents, and surgical interventions. In recent years, targeted biologic therapies, such as tumor necrosis factor-alpha (TNF-α) inhibitors (adalimumab) and IL-17 inhibitors (secukinumab, bimekizumab), have expanded treatment options for moderate-to-severe HS, offering hope for improved disease management.[7] Given the significant impact of HS on patients' physical, psychological, and socioeconomic well-being, early diagnosis and a multidisciplinary, personalized approach are essential to prevent disease progression, reduce symptom burden, and improve overall quality of life.[8]

Epidemiology

The prevalence of HS varies widely across studies, largely due to differences in data collection methods, geographic factors, and population characteristics. Estimates derived from diagnosis codes tend to be lower, as they depend on clinician recognition, whereas self-reported surveys often yield higher prevalence figures, potentially overestimating disease burden. The true global prevalence of HS is estimated to range from 0.1% to 1%, though some studies report figures as high as 4.1% in certain populations.[1,3,5]

In Europe, prevalence estimates based on self-reported symptoms range from 1.0% to 2.1%, while those derived from diagnosis codes range from 0.09% to 0.51%. In the United States, initial estimates based on diagnosis codes suggest a prevalence of approximately 0.1%, though large population-based studies indicate a higher disease burden, particularly among Black individuals who have a threefold higher standardized prevalence compared to Caucasians, which may suggest a need for targeted awareness and diagnostic strategies in these populations. In South America, prevalence estimates

range from 0.007% (diagnosis codes) to 0.41% (self-report). African studies report self-reported prevalence rates between 0.67% and 2.2%, whereas estimates from East Asia (South Korea and Taiwan) range from 0.14% to 0.19% based on diagnosis codes. The ongoing Global Hidradenitis Suppurativa Atlas project, spanning 58 countries, aims to refine worldwide prevalence estimates through harmonized methodology.[3]

Demographically, HS predominantly affects young adults, with the highest prevalence observed in individuals aged 18-39 years. Pediatric prevalence is lower, estimated at 0.03%, though children with Down syndrome have an approximately 2% prevalence and a fivefold increased risk of HS compared to the general pediatric population.[9] Sex distribution varies geographically, with a female-to-male ratio of 2-3:1 in most regions, though a more balanced ratio of 1.5:1 has been observed in Central Europe. Notably, in East Asian populations, men appear to be more frequently affected. The underlying causes of these demographic disparities remain unclear but may involve genetic, environmental, and socioeconomic factors.[1,5]

As research methodologies improve, ongoing studies such as the Global Hidradenitis Suppurativa Atlas are expected to provide more accurate insights into the true burden of HS worldwide.

Etiology and pathogenesis

HS is a multifactorial disease with a complex interplay of genetic, environmental, immunological, microbial, and lifestyle factors contributing to its onset and progression.[10] It primarily affects intertriginous areas prone to friction and mechanical stress, such as the axillae, groin, and inframammary folds.[1] These mechanical forces, along with obesity and smoking, contribute to micro-injuries that trigger an inflammatory cascade, leading to follicular occlusion, rupture, and chronic tissue damage.[11] Genetics plays a significant role in HS susceptibility, with familial clustering observed in approximately one-third of cases. Twin studies suggest a stronger concordance in monozygotic twins compared to dizygotic twins, and genome-wide association studies have identified risk *loci* near *SOX9* and *KLF5* genes.[1,6] Additionally, mutations in NCSTN, a component of γ-secretase, have been linked to rare, severe familial cases of HS, particularly in East Asian populations. However, these mutations alone are not considered causative in most cases. Lifestyle factors, particularly obesity and smoking, are major contributors to disease severity. Obesity increases mechanical stress and local inflammation, with a strong association between body mass index (BMI) and HS severity.[6] In patients undergoing bariatric surgery, HS prevalence reaches 20%, highlighting the link between metabolic dysfunction and disease pathogenesis. Smoking, observed in up to 80% of HS patients, exacerbates inflammation by promoting neutrophil activation, cytokine release, and oxidative stress. Nicotine also contributes to epithelial hyperplasia and follicular occlusion, further

driving lesion development.[1,3,5] Although evidence for direct improvements with lifestyle changes remains inconclusive, weight loss and smoking cessation are often recommended to reduce mechanical stress and inflammation, potentially improving disease outcomes.

The hallmark of HS pathogenesis is the occlusion of hair follicles in intertriginous skin areas, where hair follicles, sebaceous glands, and apocrine glands form a single functional unit. In early-stage lesions, hyperkeratosis and thickening of the follicular epithelium lead to cystic expansion and follicular rupture. This process releases keratin, microbial components, and damage-associated molecular patterns (DAMPs), which trigger an intense immune response.

Innate immune cells, including macrophages and dendritic cells, recognize DAMPs and pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors, leading to the release of pro-inflammatory cytokines such as TNF-α and interleukin (IL)-1β.[12] These cytokines activate local keratinocytes and fibroblasts, promoting the recruitment of neutrophils and other immune cells. IL-1β also induces extracellular matrix degradation *via* metalloproteinases (MMPs), contributing to tunnel formation and irreversible tissue destruction.

Neutrophils play a central role in HS pathogenesis by forming neutrophil extracellular traps (NETs), which can both amplify inflammation and become targets of autoantibodies. Their infiltration into HS lesions is driven by IL-17, leukotriene-B4, and other chemotactic factors. Elevated granulocyte colony-stimulating factor (G-CSF) supports neutrophil survival and primes them for further inflammatory activation.[4,11,13] T cells in HS lesions are predominantly T-helper 17 (Th17) and T-helper 1 (Th1) cells, producing high levels of IL-17A, IL-17F, and interferon-gamma (IFN-γ). IL-17 induces keratinocyte-derived chemokines, antimicrobial peptides, and MMPs, while IFN-γ enhances antigen presentation and immune cell recruitment.[14,15] Unlike psoriasis, where Th17 activation is largely dependent on IL-23, HS lesions exhibit a unique IL-17-driven response that is more reliant on IL-1β. B cells and plasma cells also play an active role in HS pathogenesis, particularly in tertiary lymphoid structures within the dermis. These immune aggregates contribute to local autoantibody production and chronic inflammation. Upregulation of B-cell pathways, including Bruton's tyrosine kinase (BTK) and spleen tyrosine kinase (SYK), suggests that B-cell activation is a key component of disease progression.[14,16-18] HS lesions exhibit a dysregulated skin microbiome, characterized by the overgrowth of anaerobic bacteria such as *Finegoldia*, *Prevotella*, and *Porphyromonas* species. These bacteria contribute to inflammation through biofilm formation and bacterial persistence. Additionally, gut microbiome alterations and increased intestinal permeability may further exacerbate systemic inflammation, supporting the concept of a gut-skin axis in HS.[4-6,10]

Mechanical friction, pressure, and moisture in intertriginous areas exacerbate HS symptoms by increasing micro-injury and bacterial invasion. The Koebner phenomenon, where HS lesions develop

at sites of trauma (*e.g.*, surgical scars), further supports the role of mechanical stress in disease initiation. Hormonal influences are also implicated, as HS typically manifests after puberty, suggesting a role for androgens and other hormonal regulators in disease development.

Dietary factors, including high-glycemic and high-fat diets, have been linked to systemic inflammation and insulin resistance, both of which may contribute to HS pathogenesis. Small observational studies suggest that dietary modifications, such as reducing dairy and refined carbohydrates, may help mitigate HS symptoms, though further research is needed.[1,13]

Clinical features

The initial clinical manifestation typically consists of a deep-seated, painful inflammatory nodule ranging from 1 to 2 cm in diameter, which may persist for weeks and evolve into an abscess. Over time, the disease progresses with the formation of epithelialized tunnels (fistulas) that drain purulent secretions to the skin surface, contributing to further tissue destruction.[19] Patients frequently experience recurrent flare-ups, characterized by the development of new nodules, abscesses, and tunnels, alongside symptoms such as localized pain, pruritus, burning sensations, malodor, hyperhidrosis, and warmth in affected areas.[1,2,20] The chronic inflammatory process leads to fibrosis, hypertrophic scarring, post-inflammatory hyperpigmentation, and, in severe cases, contractures and lymphedema, which may result in significant functional impairment. The onset of HS most commonly occurs between the ages of 18 and 30, with an average age of 25 years; however, 10% of cases present before the age of 18, and up to 20% manifest after the age of 45. The anatomical distribution of lesions varies by sex, with women more frequently affected in the inguinal and sub-mammary regions, while men more commonly develop lesions in the axillary, gluteal, and perianal areas. Tunnel formation tends to be more prevalent in male patients.[5,20,21] Due to the heterogeneity in clinical presentation, multiple classification systems have been proposed to better characterize disease subtypes. Canoui-Poitrine *et al.* (2013) classified HS into three phenotypic subtypes: axillary/mammary, follicular, and gluteal. Van der Zee and Jemec (2015) expanded on this classification, identifying six subtypes: regular, frictional furuncle type, scarring folliculitis, conglobate, syndromic, and ectopic.[1,7,9] More recently, Martorell *et al.*[22] proposed a classification system based on elementary lesions and disease progression patterns, distinguishing between a follicular subtype, characterized by a higher prevalence of nodules and comedones with a non-progressive course, and an inflammatory subtype, associated with a more aggressive disease trajectory. The variability in clinical presentation and progression highlights the need for individualized treatment approaches tailored to disease severity and patient phenotype.

Diagnosis and severity assessment

HS is diagnosed clinically based on patient history, physical examination, and lesion characteristics. Severity assessment relies on clinical staging systems, with Hurley staging being widely used but limited in its ability to track disease progression. The International Hidradenitis Suppurativa Severity Score System (IHS4) offers a more precise, dynamic assessment by assigning weighted values to nodules, abscesses, and draining tunnels, classifying HS as mild, moderate, or severe. In clinical trials, reductions in IHS4 scores serve as key efficacy endpoints, while the Hidradenitis Suppurativa Clinical Response (HiSCR) is another common measure of treatment success.

In addition to clinical evaluations, patient-reported outcome measures (PROMs), such as the Skin Pain Numerical Rating Scale (NRS), Dermatology Life Quality Index (DLQI), and Hidradenitis Suppurativa Quality of Life (HiSQOL), are essential for capturing the psychological and social burdens of the disease, providing important insights into how HS affects patients' daily lives.[1,2,21]

While no definitive laboratory test exists, ultrasound and MRI are valuable tools for detecting subclinical lesions and monitoring disease progression. Ultrasound, particularly, can visualize tunnel formation and assess the activity of inflammation, which may not be apparent during routine clinical examination, and rule out differential diagnoses like bacterial abscesses or squamous cell carcinoma.[7,11]

Ultrasound imaging is increasingly recognized as an essential tool for HS diagnosis and monitoring, capable of measuring inflammatory activity *via* power Doppler, and guiding treatment strategies. The Modified Sonographic Scoring of HS (mSOS-HS) refines severity classification by incorporating tunnel complexity, while the Ultrasound HS Activity Score (US-HSA) standardizes inflammation tracking. These imaging tools often reveal greater disease severity than clinical evaluation alone.[20]

Integrating clinical scoring systems, patient-reported measures, and imaging techniques allows for a more comprehensive assessment of HS. Future advancements in ultrasound standardization and biomarker-based diagnostics may further enhance early detection and treatment personalization, ultimately improving long-term patient outcomes.

Comorbidities

HS is linked to multiple comorbidities beyond skin involvement, including metabolic syndrome, cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), sexual dysfunction, mental health disorders, inflammatory arthritis, and inflammatory bowel disease.[3] Up to 50% of HS patients have metabolic syndrome, increasing their risk of type 2 diabetes, atherosclerosis, myocardial infarction, and stroke.[23] More than half have NAFLD, and sexual dysfunction affects up to 60%, particularly in women.[24] Depression and anxiety are common, with up to 30% and 20% of patients affected,

respectively, and the risk is higher in women and those with obesity. Polycystic ovary syndrome occurs in 9% of women with HS, while inflammatory arthritis affects 0.8-5.2% of patients, mainly with spondyloarthritis or rheumatoid arthritis.[4]

HS also shares pathogenic features with Crohn's disease, with 2% of HS patients affected and a twofold increased risk, particularly in men and non-smokers.[25] Ulcerative colitis is also more common in HS patients. A Finnish study found that HS reduces life expectancy by 15 years, mainly due to cardiovascular disease, stroke, and cancer.[26]

Given the high prevalence of comorbidities in HS patients, early screening and management of comorbidities are crucial to improving outcomes and reducing long-term morbidity.[1,4,21]

Therapy and management

The treatment of HS involves a combination of medical, surgical, and supportive approaches, depending on disease severity and response to therapy. Currently, adalimumab (TNF-α inhibitor), secukinumab (IL-17A inhibitor), and bimekizumab (IL-17A/F inhibitor) are the only biologics approved for patients with moderate to severe HS who do not respond to conventional systemic therapy.[27]

The approval of these biologic agents was based on rigorous clinical trials that assessed their efficacy, safety, and impact on disease progression.

Adalimumab was the first biologic to be approved for HS, supported by the findings of the PIONEER I and PIONEER II trials. These two independent, double-blind, placebo-controlled phase 3 trials evaluated adalimumab in patients with moderate-to-severe HS over a 12-week induction period followed by a maintenance phase. In PIONEER I, 41.8% of patients receiving adalimumab achieved HiSCR (≥50% reduction in abscess and inflammatory nodule count without an increase in draining tunnels) compared to 26.0% in the placebo group at week 12.[28] PIONEER II, which included concomitant antibiotic use, demonstrated similar efficacy, with 58.9% of adalimumab-treated patients achieving HiSCR compared to 27.6% in the placebo group.[29] These studies led to the FDA and EMA approval of adalimumab as the first targeted therapy for HS.

Following adalimumab, secukinumab was evaluated in the SUNSHINE and SUNRISE phase 3 trials, which enrolled 1084 patients with moderate-to-severe HS (541 in SUNSHINE, 543 in SUNRISE).[30] These studies assessed two dosing regimens of secukinumab (300 mg every two weeks *vs.* every four weeks) against placebo over a 52-week period. At week 16, the proportion of patients achieving HiSCR was significantly higher in the secukinumab every-two-weeks group compared to placebo (45% *vs.* 34%, p=0.0070 in SUNSHINE; 42% *vs.* 31%, p=0.015 in SUNRISE). In contrast, the secukinumab every-four-weeks regimen demonstrated mixed results: it showed a significant

improvement in SUNRISE (46% *vs.* 31%, p=0.0022) but did not reach statistical significance in SUNSHINE (42% *vs.* 34%, p=0.042). Responses were sustained up to week 52, confirming the durable efficacy of secukinumab. The high efficacy and durable response of secukinumab led to its regulatory approval as the second biologic for HS, offering an alternative mechanism of action through IL-17A inhibition.

Most recently, bimekizumab, a dual IL-17A and IL-17F inhibitor, has demonstrated strong efficacy in the BE HEARD I (NCT04242446) and BE HEARD II (NCT04242498) phase 3 trials, which evaluated 1014 patients with moderate-to-severe HS (505 in BE HEARD I, 509 in BE HEARD II).[31] These trials assessed multiple dosing regimens, including 320 mg every two weeks and 320 mg every four weeks, and confirmed a rapid onset of action. The every-two-week regimen showed the highest efficacy, with 48% of patients achieving HiSCR50 in BE HEARD I (p=0.0060) and 52% in BE HEARD II (p=0.0032) compared to placebo.

Additionally, in BE HEARD II, the every-four-week regimen also met statistical significance (54% *vs.* 32%, p=0.0038), while in BE HEARD I, it did not reach significance (45% *vs.* 29%, p=0.030). Long-term follow-up data indicated that bimekizumab-treated patients maintained disease control through week 48, with improvements in pain scores (HSSDD) and overall quality of life (DLQI score). Given its dual IL-17A/IL-17F inhibition strategy, bimekizumab offers a novel therapeutic approach for HS, expanding the biologic treatment landscape for this chronic inflammatory condition. A summary of the characteristics of the phase 3 clinical trials that led to the approval of adalimumab, secukinumab, and bimekizumab for the treatment of moderate-to-severe HS is presented in Table 1.

A study with real-life experience examined the effects of the adalimumab originator and biosimilar in HS patients, focusing on the impact of switching between them. Results indicate that the biosimilar group experienced a fourfold faster loss of efficacy compared to the originator group, with switching from originator to biosimilar further exacerbating this decline. Moreover, reverting to the originator after switching did not restore efficacy. The observed differences may be attributed to the increased immunogenicity of the biosimilar. Despite some limitations, these findings suggest that maintaining treatment with the same drug may be the most effective strategy for HS management.[32]

Antibiotic monotherapy remains the only fully approved non-biologic option, while other treatments, including hormonal therapy, systemic retinoids, and laser procedures, are used off-label.[33-36] Surgical intervention is often required in advanced stages of HS, particularly when the formation of tunnels and extensive scarring occur.[5,15] For acute abscesses, incision and drainage provide temporary relief but must be followed by medical therapy or further surgery.[15,37] In severe HS, wide excision of damaged tissue is recommended, particularly for non-inflammatory forms, with different closure techniques such as secondary intention healing or split-thickness skin grafting.[38] While surgery can

provide significant symptom relief, it should ideally be combined with systemic anti-inflammatory therapy to improve long-term outcomes and reduce recurrence, especially in Hurley stage II and III patients.[39-41] Additional therapeutic strategies include topical antiseptics and antibiotics, such as clindamycin and chlorhexidine, though evidence supporting their efficacy remains limited.[33,34] Laser treatments, including Nd:YAG and intense pulsed light therapy (IPL), may reduce nodules and abscesses, while intralesional corticosteroids can provide short-term relief for individual lesions.[42] Systemic antibiotics, particularly clindamycin and rifampicin combinations, help modulate inflammation rather than acting solely as antimicrobials. Metformin and hormonal antiandrogens may be beneficial in patients with metabolic disturbances or polycystic ovary syndrome. Lifestyle modifications, such as weight loss, smoking cessation, and proper skin hygiene, play a role in reducing disease burden, although direct evidence of improvement remains limited.[43-45] Pain management may require non-steroidal anti-inflammatory drugs (NSAIDs), topical analgesics, antidepressants, or, in severe cases, opioids. Given the high psychological burden of HS, mental health support, including psychotherapy and stress management, should be an integral part of patient care. Future advancements in biologic therapies and standardized surgical approaches may further improve disease control and quality of life.[8,40]

Conclusions

HS remains a challenging and debilitating disease with significant unmet needs in both diagnosis and treatment. Despite advances in understanding its complex pathogenesis, early recognition remains inadequate, often leading to diagnostic delays and disease progression. Current therapeutic options, though expanding with targeted biologics, remain insufficient for many patients, particularly in severe cases. Future efforts should focus on improving diagnostic capabilities, refining personalized treatment strategies, and developing novel therapeutic approaches to better control inflammation, prevent irreversible tissue damage, and enhance patients' quality of life. Multidisciplinary collaboration and further research are essential to address these critical gaps and improve long-term outcomes.

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Table 1. Summary of phase 3 clinical trials evaluating adalimumab, secukinumab, and bimekizumab for moderate-to-severe HS. The table outlines key study characteristics, including patient populations, dosing regimens, primary endpoints, efficacy outcomes, and safety profiles.

Drug	Trial name	Number of patients	Dosing regimens	Primary endpoint	HiSCR50 response rate	Long-term results	Adverse events	Reference
Adalimumab	PIONEER I & II	633 (307 in PIONEER I, 326 in PIONEER II)	Adalimumab 40mg	HiSCR50 at week 12	41.8% (PIONEER I), 58.9% (PIONEER II) *vs.* 26.0% & 27.6% placebo	Maintained response at week 36	1.3%-4.6% serious AEs, similar to placebo	Kimball et al., 2016 (PMID: 27518661)
Secukinumab	SUNSHINE & SUNRISE	1084 (541 in SUNSHINE, 543 in SUNRISE)	Secukinumab 300mg every 2 weeks, Secukinumab 300 mg every 4 weeks	HiSCR50 at week 16	45% (SUNSHINE, q2w), 42% (SUNRISE, q2w) *vs.* 34% & 31% placebo	Sustained response up to week 52	Headache injection site reactions, no new safety signals	Kimball et al., 2023 (PMID: 36746171)
Bimekizumab	BE HEARD I & II	1014 (505 in BE HEARD I, 509 in BE HEARD II)	Bimekizumab 320mg every 2 weeks, Bimekizumab 320 mg every 4 weeks	HiSCR50 at week 16	48% (BE HEARD I, q2w), 52% (BE HEARD II, q2w) *vs.* 29% & 32% placebo	Maintained response at week 48	Hidradenitis, oral candidiasis, headache; 8% SAEs (BE HEARD I) 5% SAEs (HEARD II)	Kimball et al., 2024 (PMID: 38795716)