

Hidradenitis suppurativa in North America: pathogenesis, severity assessment and biologic treatment

Research summary

Treatment selection in hidradenitis suppurativa (HS) requires two assessments that answer different questions. Hurley stage describes the extent and configuration of irreversible structural disease: stage I lacks tunnels and scarring, stage II has separated areas of recurrent disease with tunnels or scarring, and stage III has extensive interconnected disease. It is particularly useful when deciding whether a lesion or region needs a procedure. The International Hidradenitis Suppurativa Severity Score System (IHS4) instead measures current inflammatory activity: inflammatory nodules + 2 × abscesses + 4 × draining tunnels; scores ≤ 3 , 4–10 and ≥ 11 classify mild, moderate and severe disease, respectively. These classifications are not interchangeable: agreement between IHS4 and Hurley classification was only fair in the IHS4 validation study ($\kappa = 0.32$).

HS is an inflammatory disease of the follicular unit, not simply an infection of apocrine glands. Follicular dysfunction and rupture can expose keratin and microbial material to dermal immune cells; TNF- α , IL-17–associated signalling and neutrophilic inflammation then contribute to persistent lesions. Dysbiosis and anaerobic bacteria may amplify this process without establishing bacteria as its sole cause. This model provides a rationale for TNF and IL-17 blockade, but tissue expression and proposed mechanisms are less decisive than randomised treatment results. In the United States, the approved biologic targets are TNF- α with adalimumab, IL-17A with secukinumab, and IL-17A plus IL-17F with bimekizumab; all occupy the **moderate-to-severe** treatment space, rather than an indication confined to a particular Hurley stage.

The clearest quantified placebo-controlled result here is from PIONEER: at week 12, HiSCR was achieved by 41.8% receiving adalimumab versus 26.0% receiving placebo in PIONEER I ($P=0.003$), and by 58.9% versus 27.6% in PIONEER II ($P<0.001$). The investigators reported similar adalimumab responses regardless of baseline Hurley stage; that observation does not mean established interconnected tunnels resolve with medication. The phase 3 SUNSHINE and SUNRISE trials support secukinumab, particularly every-2-week treatment, and BE HEARD I and II support bimekizumab versus placebo in moderate-to-severe HS. Across these programmes, HiSCR assesses reduction in abscesses and inflammatory nodules without worsening in abscess or draining-tunnel counts; it must not be read as a direct measure of tunnel removal.

The treatment decision therefore rests on active inflammatory burden and structural disease together.

Limited Hurley I disease can often begin with topical or intralesional treatment, a time-limited systemic antibiotic course when appropriate, and treatment of individual persistent lesions. Recurrent, substantial inflammatory disease warrants consideration of an approved biologic without requiring progression to Hurley III. Conversely, a persistent tunnel may need deroofing or excision even when inflammatory counts improve; extensive interconnected disease commonly calls for coordinated medical and surgical care. North American guidance supports combining medical and surgical approaches and regards antibiotics in advanced HS principally as adjunctive because responses are less durable and recurrence is common. Confidence is strongest that approved biologics improve trial-defined inflammatory outcomes in moderate-to-severe populations; it is lower for choosing one biologic over another, predicting response from Hurley stage alone, or expecting a biologic to reverse established structural disease.

Bottom line

- **Use Hurley stage for structural extent and procedural planning, and IHS4 for current activity:** IHS4 is nodules + 2 × abscesses + 4 × draining tunnels; ≤3 is mild, 4–10 moderate and ≥11 severe. **Strength:** validated severity instrument, supported by a reliability study of Hurley staging.
- **TNF-α and IL-17 are clinically validated treatment targets, not the whole pathogenesis:** follicular dysfunction, neutrophils and microbial contributions remain relevant, but mechanistic evidence alone does not establish treatment efficacy. **Strength:** mechanistic reviews plus phase 3 randomised trials.
- **For moderate-to-severe HS, the approved US biologic options are adalimumab, secukinumab and bimekizumab; approval should not be interpreted as a Hurley-stage-specific indication.** Canadian prescribing decisions must follow the applicable Health Canada product monograph rather than an FDA indication. **Strength:** regulatory labeling and phase 3 trial evidence for the treatment class.
- **Adalimumab has replicated week-12 HiSCR benefit:** 41.8% versus 26.0% with placebo in PIONEER I (P=0.003), and 58.9% versus 27.6% in PIONEER II (P<0.001). Similar response across baseline Hurley stages was reported, but does not establish reversal of tunnels. **Strength:** two randomised phase 3 trials.
- **Secukinumab and bimekizumab add placebo-tested IL-17 options for moderate-to-severe disease; the trials do not establish a head-to-head efficacy ranking against adalimumab.** **Strength:** separate phase 3 randomised programmes; comparative selection remains an indirect inference.
- **Do not use a fall in inflammatory lesion count as a reason to leave a persistent tunnel untreated.** Antibiotics may precede biologics in less extensive disease or accompany them in advanced disease; persistent local tunnels and extensive interconnected regions warrant procedural assessment. **Strength:** North American guideline consensus and structural-disease assessment, rather than a trial showing biologics replace surgery.

Evidence at a glance

Source	Design	Population (n)	Comparison	Key result	Ref
PIONEER I and II	Two phase 3 randomised trials	Moderate-to-severe HS (n not stated here)	Adalimumab vs placebo	Week-12 HiSCR: 41.8% vs 26.0% in PIONEER I (P=0.003); 58.9% vs 27.6% in PIONEER II (P<0.001); response reported as similar across baseline Hurley stages	
SUNSHINE and SUNRISE	Two phase 3 randomised trials	Moderate-to-severe HS (n not stated here)	Secukinumab vs placebo	Every-2-week secukinumab improved clinical signs and symptoms; response was reported as sustained up to week 52	
BE HEARD I and II	Two phase 3 randomised trials	Moderate-to-severe HS (n not stated here)	Bimekizumab vs placebo	Improved HiSCR50 versus placebo; responses were reported as maintained through the 48-week trials	
US FDA, 2024: bimekizumab	Regulatory label	Moderate-to-severe HS	Approved indication; not a comparative study	FDA labeling includes HS; it does not assign eligibility by Hurley stage	
US and Canadian Hidradenitis Suppurativa Foundations, 2019: Part II	Clinical management guideline	People with HS	Medical treatments by clinical context	Adalimumab recommended for moderate-to-severe HS; systemic antibiotics may be monotherapy in mild disease but are principally adjunctive in advanced disease. Recommendation grade not stated here	
IHS4 development and validation	Multicentre validation study	People with HS (n not stated here)	IHS4 vs other severity assessments	IHS4 ≤3: mild; 4–10: moderate; ≥11: severe; agreement with Hurley classification κ = 0.32	
Hurley staging reliability	Inter- and intrarater reliability study	People with HS (n not stated here)	Agreement between and within raters	Moderate inter-rater and substantial intrarater reliability; stage III was particularly useful for identifying structural disease relevant to surgery	
HS pathogenesis reviews	Scholarly mechanistic reviews	Human HS tissue and mechanistic literature	Pathogenic models, not treatment comparisons	Follicular dysfunction, inflammatory cytokines, neutrophils and microbial factors support a multifactorial model; mechanistic association alone cannot establish biologic efficacy	

Findings

1. Which pathogenic pathways—follicular occlusion, TNF, IL-17, neutrophils, and microbiome—justify approved biologic targets?

Follicular injury initiates a self-amplifying inflammatory process

Hidradenitis suppurativa (HS) is best understood as an inflammatory disease centred on the follicular

unit, rather than a primary disorder of apocrine glands or a conventional skin infection. Follicular plugging and dilatation can precede rupture; keratin, cellular damage signals and microbial material then enter the surrounding dermis and provoke innate and adaptive immune responses. Repeated injury helps sustain inflammatory nodules, abscesses and tunnels. This model explains why a biologic directed against an inflammatory cytokine can reduce active lesions without necessarily removing the follicular and structural abnormalities from which lesions arise.

The sequence is not settled as a universal, one-way mechanism. Histological and molecular interpretations place substantial inflammatory activity at the follicular infundibulum and interfollicular epidermis, and question whether occlusion must always be the *first* event rather than one component of an autoinflammatory keratinization process. Genetic susceptibility, smoking, obesity, mechanical stress and the local microbial environment have all been proposed as contributors to follicular injury or inflammatory amplification, but their presence does not identify a single initiating pathway for every lesion. Thus, follicular occlusion provides the anatomical framework for HS; it does not, by itself, establish which cytokine will be the best therapeutic target in an individual.

TNF and IL-17 provide the strongest target rationale

TNF- α , IL-1 β and IL-17 are elevated in HS lesional inflammatory tissue, and TNF- α overexpression has also been described in perilesional skin and correlated with clinical disease severity. TNF can act across immune and tissue-cell compartments, while inflammatory signalling at the follicular epithelium recruits and activates further immune cells. These observations provide a biological rationale for TNF inhibition, but an expression–severity correlation is not proof that TNF is the initiating cause of HS or a validated predictor of response to TNF blockade. The rationale is strengthened by randomized clinical evidence: in the PIONEER trials, week-12 clinical response occurred in 41.8% with adalimumab versus 26.0% with placebo in PIONEER I ($P=0.003$), and 58.9% versus 27.6% in PIONEER II ($P<0.001$). Those treatment effects demonstrate that TNF-dependent inflammation is therapeutically consequential in the studied population; they do not establish that all HS inflammation is TNF-dependent.

The IL-17 axis offers a related but distinct point of intervention. IL-17-family cytokines participate in inflammatory signalling between immune cells and keratinocytes, with downstream chemokine production and neutrophil recruitment; TNF and IL-17 signalling can reinforce the same inflammatory tissue response. IL-17A blockade with secukinumab was evaluated against placebo in the randomized SUNSHINE and SUNRISE trials, and combined IL-17A/IL-17F blockade with bimekizumab was evaluated against placebo in BE HEARD I and BE HEARD II. These trials provide clinical evidence for intervening at the IL-17 pathway, beyond the evidence from tissue expression alone. They do not demonstrate that dual IL-17A/IL-17F inhibition is mechanistically necessary for every patient, nor does the separate placebo-controlled evidence establish a direct efficacy ranking between TNF and IL-17 inhibition. The North

American medical-management guideline identified TNF and type-17 inflammatory pathways as therapeutic interests, but its published biologic discussion predates the later IL-17 phase 3 programmes; mechanistic interpretation must therefore be read alongside the newer trial evidence rather than treated as a prediction made by that guideline.

Neutrophils and the microbiome: amplifiers, not established biologic selectors

Neutrophils are prominent effectors of the HS inflammatory response. Follicular rupture releases contents that attract neutrophils and lymphocytes; IL-17-associated keratinocyte activation offers a plausible route to continued neutrophil recruitment and abscess formation. This connects the visible suppurative phenotype to cytokine blockade, but it does not make neutrophils a disease-specific initiating lesion or show that a neutrophil-rich examination predicts preferential response to an IL-17 inhibitor over a TNF inhibitor. More broadly, inflammatory mediators interact in a self-amplifying network rather than a single cytokine cascade.

Microbial findings require the same distinction between contribution and causation. Follicular disruption can expose dermal tissue to bacteria, and persistent anaerobic organisms or altered local microbial communities may help maintain inflammation. Conversely, bacterial colonization may follow occlusion and tissue damage; HS should not be reduced to an infection whose microbial eradication would necessarily switch off the underlying disease. The available pathogenic models therefore support considering microbiome-associated signals as potential amplifiers of innate immunity, not as evidence that a particular organism selects TNF versus IL-17 blockade. No established microbial signature, tissue cytokine level or neutrophil measure is a validated clinical test for choosing between these approved biologic targets. The defensible mechanistic conclusion is narrower: follicular injury creates a setting for chronic inflammation, and randomized treatment effects show that TNF and IL-17 signalling are actionable parts of that process in some patients.

2. How should Hurley stage and IHS4 be used to define mild, moderate, and severe disease for treatment selection?

Hurley stage and the International Hidradenitis Suppurativa Severity Score System (IHS4) answer different questions. **Hurley stage describes the extent of established structural disease**, particularly scarring and tunnels; **IHS4 measures current inflammatory activity**, including draining tunnels. Record both rather than treating their mild, moderate and severe categories as interchangeable. Agreement between the systems was only fair in the IHS4 validation study ($\kappa = 0.32$), despite good correlation ($\rho > 0.6$), demonstrating that they classify some patients differently.

Classify structure and activity separately

Hurley stage I denotes abscesses or inflammatory lesions without established sinus tracts or scarring; stage II denotes recurrent lesions with separated tracts and scarring; and stage III denotes diffuse involvement with multiple interconnected tracts and scarring across an affected region. These are anatomical descriptions, not scores that should be expected to fall promptly when inflammation improves. In a reliability study, Hurley staging had moderate inter-rater and substantial intrarater reliability and performed best for recognition of stage III disease, but the authors noted that it had not been validated as a comprehensive severity instrument. Document the regions examined and their stage, as well as the overall stage used for treatment planning: a single extensively tunnelled region and several regions with discrete lesions pose different procedural problems even if summarized under the same overall stage.

Calculate IHS4 as **number of inflammatory nodules + 2 × number of abscesses + 4 × number of draining tunnels**. An IHS4 score of ≤ 3 is **mild**, **4–10 moderate**, and ≥ 11 **severe**. The weighting makes a draining tunnel more consequential than an inflammatory nodule in the activity score, but it does not count a scar or a non-draining tunnel as an active draining tunnel. At each assessment, record the component counts as well as the total. That preserves the distinction between improvement in nodules and abscesses and persistence of drainage, which an isolated total can obscure. IHS4 was developed and validated as a *dynamic* severity measure for clinical and trial settings; its original validation found good correlation with Hurley stage, expert opinion, Physician's Global Assessment and modified Sartorius score ($p > 0.6$), but a more moderate correlation with Dermatology Life Quality Index ($p = 0.36$).

For treatment selection, describe **Hurley I with low IHS4** as limited disease without established tunnels, and **Hurley III** as extensive structural disease requiring assessment beyond suppression of active lesions. Hurley II is heterogeneous: its separated tunnels and scars establish structural progression, while IHS4 distinguishes relatively quiet disease from a substantial concurrent inflammatory burden. Conversely, a patient with a low current IHS4 may still have consequential established tunnels or scarring. A low activity score should therefore not erase the anatomical indication for procedural assessment; nor should Hurley stage alone obscure active, painful or widespread inflammation. Hurley and IHS4 should be interpreted alongside affected sites, symptoms, drainage, functional impact and prior treatment course rather than used as automatic treatment thresholds.

Preserve the distinction between clinical severity and trial eligibility

"Moderate-to-severe HS" in a biologic trial is an **enrolment definition**, not necessarily an IHS4 score of 4 or greater or a simple synonym for Hurley II–III. PIONEER I and II stratified the adalimumab comparison by

baseline Hurley II versus III, with baseline oral-antibiotic use also included in the PIONEER II stratification. SUNSHINE and SUNRISE likewise studied populations described as having moderate-to-severe HS. BE HEARD I and II studied moderate-to-severe HS, while their randomisation accounted for worst Hurley stage and baseline systemic-antibiotic use. These design choices make baseline anatomy important when interpreting trial results, but they do not establish an IHS4 cut-off that independently determines biologic candidacy. In particular, do not infer from these trials that all patients labelled “moderate” by either instrument have the same disease burden, treatment history or expected response.

The distinction also matters during follow-up. Hurley stage can remain unchanged while inflammatory lesions improve, because existing scars and tunnels do not disappear merely because new abscesses cease. IHS4 can register changes in inflammatory nodules, abscesses and draining tunnels; post hoc SUNSHINE and SUNRISE analyses have examined both IHS4 severity-category shifts and IHS4-based response at weeks 16 and 52. Those analyses support using IHS4 to *describe change*, not replacing the trials’ prespecified clinical-response endpoints or using a post hoc IHS4 shift as proof that a particular treatment should be started at a particular score. Evidence from an Australasian guideline similarly cautions that change in Hurley stage is not a validated treatment-response outcome; that recommendation is relevant to measurement but is not North American treatment guidance.

The practical classification is therefore two-dimensional: assign Hurley stage to identify **irreversible or slowly reversible structural involvement**, and measure IHS4 repeatedly to identify **current treatable inflammatory burden**. Where the two disagree, retain both findings in the assessment and determine which component is driving the decision. Neither the fair agreement between instruments nor the existence of separate IHS4 cut-offs justifies translating Hurley I, II and III mechanically into IHS4 mild, moderate and severe.

3. Which biologics are approved in the United States and Canada for hidradenitis, and for which stage or severity?

For treatment selection, the licensed biologic category is **moderate-to-severe hidradenitis suppurativa (HS)**, not a particular Hurley stage. Adalimumab, which inhibits TNF- α ; secukinumab, which inhibits IL-17A; and bimekizumab, which inhibits IL-17A and IL-17F, constitute the current approved biologic options in the United States. These agents also have Canadian HS indications for moderate-to-severe disease, but prescribing must follow the jurisdiction-specific product monograph, particularly for age eligibility. None has an HS indication defined simply as “Hurley stage II” or “Hurley stage III,” and a stage designation alone should not be treated as a substitute for current inflammatory severity.

Adalimumab: an established option across moderate-to-severe inflammatory disease

Adalimumab was the first biologic approved for HS and remains an approved option in the United States and Canada for moderate-to-severe disease. The pivotal PIONEER trials studied patients with Hurley stage II or III HS, establishing the treatment evidence chiefly in patients who had both active inflammatory lesions and established disease beyond Hurley stage I. Its regulatory indication is therefore broader in wording than a rule requiring a particular stage, while the trial population is narrower than *all* presentations a clinician might call moderate or severe.

This distinction matters most at the margins. A patient with predominantly fixed scars and inactive tunnels may be Hurley stage III, but the PIONEER population does not establish that TNF blockade will reverse that structural damage. Conversely, Hurley stage alone should not exclude consideration of systemic treatment when current inflammatory burden and its consequences are substantial. In the United States, adalimumab has an adolescent as well as an adult HS indication; age-specific authorization and dosing should be checked against the applicable national label rather than inferred from the adult PIONEER trials. The North American medical-management guideline identifies adalimumab as FDA-approved for moderate-to-severe HS, but its biologic discussion predates the later IL-17 approvals and is not an exhaustive list of current licensed agents.

Secukinumab and bimekizumab: approved IL-17-pathway alternatives

Secukinumab is an approved IL-17A inhibitor for moderate-to-severe HS in the United States and Canada. Its SUNSHINE and SUNRISE phase 3 programme studied moderate-to-severe disease; the published pooled pharmacokinetic and safety analysis describes its approval for **adults** with moderate-to-severe HS. In stage-based practice, it belongs among systemic options for patients with substantial ongoing inflammation, commonly including Hurley II and III disease. That placement describes the population in which treatment was tested; it does not make Hurley stage a stand-alone licensing criterion or imply that an individual tunnel will resolve with cytokine inhibition.

Bimekizumab adds simultaneous IL-17A and IL-17F inhibition and is an approved option for **adults** with moderate-to-severe HS in the United States and Canada. Its US HS indication appears in FDA labeling, and the BE HEARD I and BE HEARD II phase 3 trials enrolled adults with moderate-to-severe disease. It occupies the same broad severity category as adalimumab and secukinumab rather than a newly defined Hurley-stage niche. Its availability does not establish that dual IL-17A/F blockade should be preferred for every patient with stage III disease, nor does it establish efficacy for biologic treatment of isolated, minimally inflamed scarred areas.

What “approved for moderate-to-severe HS” does—and does not—resolve

Regulatory indications and clinical staging answer different questions. Hurley stage describes the presence and extent of tunnels and scarring, whereas active lesion counts capture a component of inflammatory burden that can change during treatment. The validated IHS4 incorporates inflammatory nodules, abscesses and draining tunnels, making it useful alongside Hurley stage when judging whether disease is currently moderate or severe. Neither an IHS4 category nor a Hurley category automatically confers a labeled indication: the prescribing decision must still account for the product's national indication and the patient's age.

The distinction also prevents an overreading of the phase 3 programmes. PIONEER, SUNSHINE/SUNRISE and BE HEARD support biologic treatment in their respective trial-defined moderate-to-severe populations, not routine biologic treatment of otherwise mild HS solely because a prior lesion left a scar. Equally, their approval status does not establish a head-to-head efficacy ranking among the three agents. Comparisons of response rates across programmes would confound treatment effects with differences in enrolled patients, concomitant treatment and trial methods; choosing among approved agents requires a separate assessment of the individual's inflammatory phenotype, comorbidities, contraindications and treatment goals.

Finally, chronology explains an apparent discrepancy in the literature. The North American guideline names adalimumab as the FDA-approved biologic because it was written before the IL-17 approvals; an earlier biologics review likewise describes only adalimumab and secukinumab while anticipating bimekizumab approval. Those statements accurately reflect their publication eras, but the subsequent US bimekizumab label and later reviews establish that they are not a current count of approved options.

4. What do the pivotal trials show for adalimumab and IL-17 inhibitors by baseline Hurley stage and HiSCR response?

What the trials establish across severity strata

The pivotal biologic trials establish reductions in inflammatory lesion activity in trial-defined moderate-to-severe hidradenitis suppurativa (HS), not reversal of established tunnels or scarring. Their common responder measure, HiSCR50, requires a $\geq 50\%$ reduction from baseline in the combined abscess and inflammatory-nodule count, with no increase in abscess or draining-tunnel count. That distinction matters when interpreting results by Hurley stage: a patient with extensive tunnel disease may meet HiSCR50 through improvement in nodules and abscesses without resolution of the structural disease that defines their stage. Conversely, stratification by Hurley stage tests whether treatment effects appear across baseline anatomical phenotypes; it does not make Hurley stage a sensitive measure of treatment

response.

Adalimumab: replicated benefit, without a demonstrated stage-specific restriction

In the placebo-controlled first periods of PIONEER I and PIONEER II, adalimumab produced higher week-12 HiSCR response rates than placebo: **41.8% vs. 26.0%, $P=0.003$** in PIONEER I and **58.9% vs. 27.6%, $P<0.001$** in PIONEER II. These are separate trial estimates, rather than interchangeable expectations for an individual patient. The PIONEER analyses were stratified by baseline Hurley stage II versus III; PIONEER II additionally stratified by baseline oral-antibiotic use. The investigators reported that adalimumab responses were similar regardless of baseline Hurley stage and, in PIONEER II, regardless of whether baseline antibiotic treatment continued. Thus, the pivotal evidence does not support withholding adalimumab solely because eligible inflammatory disease is Hurley III, nor does it establish a larger relative benefit in Hurley II.

That conclusion has limits. The reported stage comparison is an assessment within the enrolled trial population, not evidence that Hurley II and III lesions respond identically or that pre-existing tunnels disappear. A rank-ordered secondary endpoint concerning a very low residual abscess and inflammatory-nodule count among participants with Hurley II disease favoured adalimumab in PIONEER II ($P=0.01$), whereas the corresponding rank-ordered secondary results were not significant in PIONEER I. This difference should not be recast as proof of preferential efficacy in Hurley II: the replicated primary finding is the week-12 HiSCR benefit, and the stage-specific secondary finding was not replicated across the two trials. The stage-stratified results also cannot establish efficacy for isolated, low-activity Hurley I disease.

IL-17 inhibition: positive phase 3 programmes, but limited stage-specific effect estimates

SUNSHINE and SUNRISE tested secukinumab against placebo in two multicentre phase 3 trials of moderate-to-severe HS. The reported interpretation identifies secukinumab given every 2 weeks as clinically effective, with response sustained during treatment through week 52. Baseline Hurley II and III efficacy is a clinically important question, but an overall positive trial result should not be converted into a numerical stage-specific HiSCR estimate or a claim that one stage benefits more than the other. Post hoc analyses of these trials also assess change using IHS4, which includes draining tunnels, and report outcomes such as IHS4-55, IHS4-75 and IHS4-90. Those analyses address a different question from the prespecified HiSCR comparison; their observed-data presentation does not supersede the placebo-controlled primary result.

Interpretation of durability likewise requires attention to the comparator. The SUNSHINE and SUNRISE presentation distinguishes analyses through week 16 from observed data between weeks 18 and 52,

when participants originally assigned placebo switched treatment. A sustained response among treated participants therefore supports persistence of benefit during treatment, but is not a continuous year-long placebo-controlled estimate. A subsequent correction identified mislabelling of the skin-pain response endpoint in the original trial report; skin-pain claims should be checked against the corrected account rather than used to strengthen an inference about stage-specific HiSCR efficacy.

BE HEARD I and BE HEARD II tested dual IL-17A/IL-17F inhibition with bimekizumab in two 48-week, randomised, placebo-controlled phase 3 trials of moderate-to-severe HS. Across the trials, bimekizumab improved the primary HiSCR50 outcome versus placebo, with maintained improvement reported through week 48; the programme also evaluated the more stringent HiSCR75 and HiSCR90 thresholds. Participants were stratified by their **worst baseline Hurley stage** and baseline systemic-antibiotic use, so stage was recognised in trial allocation rather than ignored. Stratification alone, however, is not an efficacy estimate. Without a reported stage-specific treatment contrast, the overall HiSCR finding cannot show that dual IL-17A/IL-17F inhibition is preferentially effective in Hurley II or III, or that it reverses tunnel-dominant disease.

Across the three pivotal programmes, **Hurley II and III identify the principal stage-stratified populations**, while HiSCR captures a change in active inflammatory lesions. There is no head-to-head comparison here from which to rank adalimumab, secukinumab and bimekizumab by HiSCR response within a Hurley stage. Cross-trial response percentages should not substitute for one: endpoint timing, concomitant-treatment rules, enrolled populations and handling of later follow-up differ. For treatment selection, the defensible inference is efficacy against active inflammation in moderate-to-severe trial populations, including patients assessed across Hurley II and III—not a demonstrated biologic-specific solution to irreversible structural disease or an established efficacy hierarchy by stage.

5. When should antibiotics, surgery, or adjuncts precede, accompany, or replace biologics under North American guidance?

Antibiotics before and alongside biologics

Under the North American medical-management guideline, systemic antibiotics can serve as primary treatment for mild hidradenitis suppurativa (HS). In more advanced disease, their lower response rates and frequent recurrence make them principally adjunctive rather than a durable substitute for control of inflammation. The guideline places topical and intralesional treatments alongside systemic antibiotics, hormonal therapy and immunomodulation in a treatment plan that often also requires procedures. Thus, an initial antibiotic course is reasonable when inflammatory disease is limited and a response can be reassessed. Repeated courses should not become a reason to defer escalation when substantial activity

persists, particularly in the presence of draining tunnels or progressive scarring.

The rationale for antibiotics is not that HS is ordinarily a primary bacterial infection: bacterial colonization can amplify inflammation after follicular disruption, but it is considered a secondary pathogenic factor. This distinction matters when evaluating apparent antibiotic failure. Persistent nodules, abscesses and tunnels after a course do not, by themselves, establish resistant infection or justify indefinite antimicrobial treatment; they prompt reassessment of the inflammatory disease and its structural burden. Conversely, clinical concern for a separate, treatable infection warrants its own assessment rather than assuming every draining lesion is only an HS flare.

Antibiotics may **accompany** biologic therapy when short-term control of active lesions is needed or when treatment is being coordinated with a procedure. Concomitant use is not evidence that antibiotics must be completed before a biologic can begin. In PIONEER II, baseline oral antibiotic use was accounted for in randomization, and the reported adalimumab response was similar whether baseline antibiotic therapy was continued or not. That comparison supports the feasibility of background antibiotics in the trial setting; it does not demonstrate that adding antibiotics improves biologic response, establish an optimal combination regimen, or justify prolonged antibiotic exposure. The guideline's distinction between antibiotic monotherapy in mild disease and an adjunctive role in advanced disease remains the more useful prescribing principle.

Surgery for persistent structural disease

Medical and procedural treatment address different components of HS. A biologic can suppress active inflammation without necessarily removing established tunnels and scarred, repeatedly affected tissue. Accordingly, persistent localized tunnels or recurrent lesions in a defined field warrant consideration of a tissue-directed procedure rather than successive antibiotic courses or an assumption that changing biologics alone will resolve the structural lesion. At the other end of the spectrum, extensive interconnected disease requires assessment for surgery alongside systemic inflammatory control; Hurley stage III is particularly useful for identifying patients likely to need an operative approach. North American guidance emphasizes that medical and surgical approaches often need to be combined for the best outcome.

Surgery may precede or replace a biologic as the principal treatment for a localized, surgically addressable site when inflammatory activity elsewhere does not warrant ongoing systemic immunomodulation. It may instead **accompany a biologic** when active disease extends beyond the operative field or ongoing inflammation threatens further lesions. This is a clinical distinction between treating a particular tunnel-bearing area and treating the patient's continuing inflammatory disease—not a rule that all patients must fail biologic therapy before referral for surgery.

A consensus panel outside North America describes combined biologic treatment and surgery as feasible and reports that biologic interruption is unnecessary in most cases; it also quotes the North American guideline's judgment that surgical complications are likely a greater concern with poorly controlled disease than with medication. That consensus is supportive but indirect for a North American recommendation, and "most cases" should not be read as a universal perioperative rule. The operative field, active infection, wound status and the patient's immunomodulatory risks still require individual assessment. Neither that consensus nor the North American medical-management guideline establishes that surgery plus a biologic is superior to either strategy for every pattern of HS.

Adjuncts and reassessment

Topical therapy, intralesional treatment and hormonal therapy retain roles alongside—or, for appropriately limited disease, instead of—systemic biologics in the North American treatment framework. A focal inflamed lesion may call for local symptom control while the broader regimen is reassessed; hormonally influenced disease may warrant consideration of a hormonal approach. These are complementary decisions, not evidence that an adjunct can reliably reverse established tunnels or replace systemic control of widespread active disease. Wound care, pain assessment and attention to treatment burden likewise remain necessary even when an anti-inflammatory drug reduces lesion activity.

The practical sequence is therefore conditional rather than a rigid antibiotic-to-biologic-to-surgery ladder: use local measures and, where appropriate, antibiotics for limited inflammatory disease; do not prolong antibiotics as the sole strategy for persistently active advanced HS; assess localized persistent tunnels for procedures; and combine tissue-directed treatment with systemic inflammatory control when both problems coexist. Reassessment should distinguish continuing inflammatory lesions from residual structural disease. The first may require adjustment of medical treatment, whereas the second may remain an operative problem despite improvement in inflammatory counts. Trial evidence permitting background antibiotics and expert consensus supporting combined surgery and biologics inform those choices, but neither establishes that every patient needs concurrent treatment or identifies a single sequence that fits all disease distributions.

Guidelines

The United States and Canadian Hidradenitis Suppurativa Foundations' North American guidelines organize management around disease severity and the need to combine medical and procedural treatment, rather than around a fixed sequence in which every patient must fail antibiotics before

receiving a biologic. Their medical-management guideline identifies adalimumab at its approved hidradenitis suppurativa dosing as a treatment for moderate-to-severe disease. It also describes systemic antibiotics as potential monotherapy in mild disease but principally as adjuncts in advanced disease, where responses are less durable and recurrence is more frequent. This distinction matters clinically: antibiotics can address active inflammatory lesions without being an adequate substitute for sustained control of extensive inflammatory disease or for removal of established tunnels.

The North American guideline was published before the phase 3 secukinumab and bimekizumab programs and therefore cannot be read as a comparative recommendation among all currently approved biologic targets. Subsequent regulatory labeling and randomized evidence extend the treatment landscape beyond TNF inhibition: the US bimekizumab label includes moderate-to-severe hidradenitis suppurativa, while SUNSHINE and SUNRISE evaluated secukinumab and BE HEARD I and II evaluated bimekizumab in trial-defined moderate-to-severe populations. A recommendation established in the earlier North American guideline for adalimumab should thus be distinguished from a claim that it has been shown superior to the IL-17 inhibitors; the pivotal programs compared each agent with placebo, not with another approved biologic.

Severity assessment should inform, but not mechanically determine, that decision. Hurley stage describes structural disease and is particularly useful for recognizing extensive tunnel-bearing disease likely to require a procedural plan. Its inter-rater reliability is moderate, and it is not a dynamic treatment-response measure. The validated IHS4 instead weights current inflammatory nodules, abscesses and draining tunnels; scores of ≤ 3 , 4–10 and ≥ 11 designate mild, moderate and severe inflammatory activity, respectively. Consequently, a patient's Hurley classification, current inflammatory burden and surgically addressable lesions answer different questions. Neither an IHS4 category nor Hurley stage alone should be treated as identical to a pivotal trial's eligibility criteria or to the wording of a biologic indication.

North American guidance recognizes that medical and surgical approaches often need to be combined. An informative difference in emphasis comes from the Australasian guideline, which uses a modified Hurley classification and explicitly considers systemic management at stage 2B or above; that threshold is a regional treatment framework, **not** a North American regulatory criterion. For special populations, the more recent North American guidance addresses biologic decisions separately from the general treatment algorithm. In pregnancy, it notes that HS-specific biologic safety studies are lacking and that reassurance is drawn largely from use in other conditions; decisions therefore require an indication-specific assessment rather than an unqualified extension of routine moderate-to-severe HS recommendations.

Certainty and limitations

Confidence is highest that TNF and IL-17 inhibition can reduce inflammatory lesion activity in appropriately selected patients with moderate-to-severe HS. That conclusion rests on replicated, randomized, placebo-controlled phase 3 programs, rather than solely on pathway expression or expert consensus. At week 12, HiSCR response with adalimumab versus placebo was **41.8% vs. 26.0% in PIONEER I (P=0.003)** and **58.9% vs. 27.6% in PIONEER II (P<0.001)**. The investigators reported similar adalimumab responses regardless of baseline Hurley stage or continuation of baseline antibiotics, but that finding does not establish identical benefit for every structural phenotype. SUNSHINE and SUNRISE provide randomized evidence for secukinumab, and BE HEARD I and II provide randomized evidence for dual IL-17A/IL-17F inhibition with bimekizumab; both programs studied moderate-to-severe disease rather than isolated, limited Hurley I disease. These trials directly support treatment of inflammatory activity in their enrolled populations, not a conclusion that biologics reverse established scarring or replace tunnel surgery.

The evidence is less decisive when choosing *between* approved biologics, extrapolating to an individual Hurley stage, or forecasting long-term structural outcomes. Trial definitions, background treatment, dosing schedules and assessment timepoints differ across programs; a larger response percentage in one placebo-controlled trial cannot be interpreted as superiority over an agent tested in another. Baseline Hurley stage is useful for subgroup interpretation, but trials were not designed primarily as head-to-head tests of biologic strategies within each stage. HiSCR chiefly captures change in abscesses and inflammatory nodules while requiring no worsening in abscesses or draining tunnels; it does not fully characterize the burden or reversibility of tunnels and scars. Post hoc analyses using IHS4 add information about tunnel-weighted inflammatory severity, although their observed-data and exploratory character makes them less conclusive than prespecified randomized comparisons. Hurley stage itself has only moderate inter-rater reliability, further limiting fine distinctions based on a single stage assignment.

Duration and safety also temper certainty. The controlled portions of pivotal trials establish efficacy against placebo over their specified primary assessment periods, whereas later follow-up is less protected against treatment-switching and selective retention. The pooled bimekizumab extension reports outcomes extending to two years, but an open-label extension preferentially observes people who enter and remain in follow-up; it cannot supply an untreated long-term comparator. In the 48-week BE HEARD trials, serious treatment-emergent adverse events were reported in **40 (8%)** bimekizumab-treated patients in BE HEARD I and **24 (5%)** in BE HEARD II; those figures describe treated trial populations and do not, by themselves, establish comparative safety against other biologics. Interpretation of ancillary outcomes also requires care: a published correction identified mislabeling of a skin-pain response endpoint in the secukinumab trial report, without replacing its primary HiSCR comparison.

Finally, mechanistic plausibility is not clinical proof of target selection for a particular patient. Follicular

disruption, inflammatory cytokines, neutrophils and altered microbial communities form a credible account of persistent HS inflammation, but the relative contribution of each pathway varies and cannot currently be read from Hurley stage or IHS4 as a validated predictor of response to TNF versus IL-17 blockade. The practical evidence-based distinction is therefore between **demonstrated population-level efficacy** for approved biologics in moderate-to-severe inflammatory HS, **structural assessment** that identifies where surgery remains necessary, and **unproven individual-level biomarker selection** among biologic mechanisms.

Clinical reasoning

The clinical decision is whether a person with hidradenitis suppurativa (HS) needs treatment directed primarily at current inflammation, a procedure directed at persistent tunnels, or both—and, if systemic immunomodulation is warranted, whether an approved TNF or IL-17 inhibitor is appropriate. For North American practice, the relevant standards are the United States and Canadian HS Foundations' management guidance and the current indication and safety information for each product. The North American guideline describes medical and surgical treatment as complementary rather than mutually exclusive; it also distinguishes antibiotics used as monotherapy in mild disease from their predominantly adjunctive role in advanced disease. A biologic indication for *moderate-to-severe HS* should not be read as an instruction to treat every lesion in a person assigned Hurley stage II or III with a biologic.

First establish what is driving morbidity now. Document the distribution of inflammatory nodules, abscesses and draining tunnels; distinguish active drainage from residual scarring; and establish whether the problem is localized or present across several regions. Hurley stage describes the pattern of established tissue damage and is useful for recognizing disease that may require surgery, particularly stage III disease, but is less suited to measuring a short-term treatment response. Calculate IHS4 from the current counts of nodules $\times 1$, abscesses $\times 2$ and draining tunnels $\times 4$. Its validated categories are mild at ≤ 3 , moderate at 4–10 and severe at ≥ 11 . Record both assessments rather than translating one into the other: agreement between IHS4 and Hurley classification was only fair in the validation study ($\kappa = 0.32$). Thus, a high current inflammatory count and a localized network of longstanding tunnels can raise different treatment questions even when both are described broadly as “severe HS.”

The biological rationale helps identify *which component is treatable by which means*. Follicular obstruction and rupture can expose dermal tissue to keratin and bacteria, recruiting neutrophils and sustaining inflammation; lesional TNF and IL-17 signaling supply rational targets for adalimumab, secukinumab and bimekizumab. That model does not establish that blocking a cytokine will remove a mature epithelialized tunnel. Nor does bacterial involvement make all HS lesions a primary infection requiring repeated antibiotics: colonization and altered local microbial communities can amplify the inflammatory process without being its sole cause. In practice, count inflammatory lesions when judging a systemic drug and

map persistent tunnels separately when planning a procedure.

Next match the individual's disease to the populations in which benefit was tested. The strongest direct evidence for approved biologics comes from randomized trials in moderate-to-severe HS, not from trials of isolated mild lesions. PIONEER I and II tested adalimumab in patients stratified by baseline Hurley stage II or III; at week 12, HiSCR was achieved by 41.8% versus 26.0% with placebo in PIONEER I ($P=0.003$), and by 58.9% versus 27.6% in PIONEER II ($P<0.001$). Reported adalimumab responses were similar across those baseline Hurley stages, and continued baseline antibiotic treatment in PIONEER II did not account for the response pattern. These are trial-level comparisons, not probabilities assignable to an individual. They support use against active inflammatory disease in either studied stage; they do not show that adalimumab reverses scarring or makes excision unnecessary.

SUNSHINE and SUNRISE tested secukinumab against placebo in moderate-to-severe HS, with HiSCR assessed at week 16 and follow-up to week 52. The replicated efficacy conclusion is strongest for the every-two-week regimen; the every-four-week results should not be treated as identical across the two trials. BE HEARD I and II similarly tested dual IL-17A/IL-17F inhibition with bimekizumab against placebo in adults with moderate-to-severe HS and found improvement in the HiSCR50 endpoint. These trials establish alternatives to TNF inhibition, but they are **not head-to-head trials** against adalimumab or one another. Differences in trial entry, allowed background treatment, timing and placebo response preclude ranking the three agents simply by juxtaposing HiSCR percentages. Post hoc IHS4 analyses can add information about tunnel-weighted response, but should not replace the prespecified trial endpoint when judging the strength of efficacy evidence.

Weigh the expected gain against the specific treatment burden and hazard. HiSCR captures reduction in abscesses and inflammatory nodules without worsening in abscess or draining-tunnel counts. It is therefore a useful measure of inflammatory control, not proof of tunnel clearance or restoration of damaged skin. The PIONEER placebo responses—26.0% and 27.6% at week 12—also make clear why improvement noticed during an uncontrolled treatment course cannot, by itself, identify a drug effect. Conversely, a patient may obtain meaningful relief of inflammation while retaining a tunnel that remains a source of drainage and needs procedural assessment.

Screen and counsel for infection risk before immunomodulation, and review prior serious infection, tuberculosis and hepatitis risk, vaccination status, pregnancy intentions, malignancy history, inflammatory bowel disease, previous biologic exposure and concomitant immunosuppression before choosing an agent. These factors can change both eligibility and the preferred target. IL-17 blockade warrants particular attention to mucocutaneous fungal events: across 48 weeks of bimekizumab treatment, serious treatment-emergent adverse events were reported in 40 (8%) patients in BE HEARD I and 24 (5%) in BE HEARD II; oral candidiasis was among the frequently reported treatment-emergent events in BE HEARD II. Those 48-week treated-group figures are not a placebo-controlled estimate of excess risk.

Special-population decisions require an individual assessment rather than extrapolation from the typical trial participant; North American guidance specifically considers pregnancy, breastfeeding and major infectious comorbidity separately.

Then choose the least intensive approach that addresses the dominant problem without delaying needed escalation. For limited inflammatory disease without troublesome tunnels, local measures, topical or intralesional therapy, and an appropriate course of systemic antibiotics may be a reasonable initial strategy. North American guidance allows antibiotic monotherapy in mild HS but describes antibiotics in advanced disease chiefly as adjuncts because response is less reliable and recurrence is common. Repeated courses should not become a substitute for reassessing stage, current activity and the presence of a surgically addressable tract. For persistent moderate-to-severe inflammatory disease, an approved biologic becomes a treatment consideration; selection among TNF and IL-17 inhibition depends on the complete medical history, previous response, contraindications, tolerability and the applicable national product authorization—not Hurley stage alone. Adalimumab has randomized evidence in baseline Hurley II and III disease and a defined HS induction and maintenance regimen in PIONEER; a regimen used for another indication should not be assumed equivalent for HS.

Where a discrete persistent tunnel is the principal residual problem, assess it for a local procedure rather than escalating systemic immunosuppression solely because the person retains a high structural stage. Where widespread active lesions coexist with tunnels, coordinate anti-inflammatory treatment and surgical planning: systemic control does not eliminate the need to address established tract-bearing tissue, and surgery does not necessarily control activity at other sites. Hurley stage III is especially useful as a prompt to assess surgical needs. The decision to continue a biologic around a procedure should be individualized with the treating teams rather than governed by an assumption that all biologic therapy must stop; the North American guidance emphasizes the potential harm of poorly controlled disease when considering surgical medication decisions, as discussed in a subsequent surgical consensus.

Apply explicit response checks. Before starting, record the lesion counts needed for HiSCR and IHS4, the location and character of tunnels, symptoms and functional burden, concurrent HS treatment, and the treatment objective. Reassess at a time aligned with the chosen pivotal endpoint—week 12 for the PIONEER adalimumab comparison or week 16 for the secukinumab comparison—while accounting for the licensed regimen and any additional time warranted for an individual decision. Recount lesions and revisit the tunnel map rather than recording only a global impression of “better.” If inflammatory lesions remain uncontrolled despite an adequate trial, check dosing and adherence, intercurrent infection and concomitant treatment before deciding whether to change biologic target. If inflammatory counts improve but localized drainage persists, reconsider a procedure rather than automatically declaring systemic treatment failure. Extension observations can inform durability, but outcomes among people who remain on treatment should not be mistaken for the probability that every person starting treatment will maintain response.

Several misreadings would lead to poor selection. Hurley III is neither synonymous with a high *current* inflammatory count nor an automatic reason to replace surgery with a biologic. A low IHS4 does not erase the importance of a persistently draining tunnel, because the score and the anatomical assessment answer different questions. Similarly, mechanistic evidence for TNF and IL-17 is not comparative efficacy evidence; randomized outcomes, product indications and the person's contraindications must govern drug choice. Finally, establish the precise country-specific indication and current label before prescribing, particularly when age or prior treatment may affect the choice. The original North American medical guideline predates the IL-17 inhibitor approvals, so its adalimumab-era biologic discussion must be read alongside later trials and current regulatory information.

Illustrative scenario: A person has limited recurrent inflammatory lesions, no clinically evident tunnel and an IHS4 in the validated mild category (≤ 3). The initial choice is local treatment and, if clinically warranted, a time-limited antibiotic strategy rather than starting a biologic solely because HS has been diagnosed. The feature to recheck is whether lesions persist or become more extensive despite that approach.

Illustrative scenario: Keep the same absence of a clinically evident tunnel, but change current activity to an IHS4 in the moderate category (4–10). Persistent, consequential inflammation now makes systemic treatment—including assessment for an approved biologic—more pertinent. Confirm whether the overall presentation meets the product's moderate-to-severe indication, review previous treatments and contraindications, and establish baseline lesion counts against which to judge response.

Illustrative scenario: Keep the moderate current inflammatory category but add a discrete draining tunnel. That single anatomical change raises IHS4 because a draining tunnel contributes 4 points, and it adds a procedural question that the inflammatory score alone cannot settle. Consider systemic control if the broader inflammatory disease warrants it, while separately evaluating the tunnel for a local surgical approach; a favorable HiSCR assessment should not be interpreted as proof that the tract has resolved.

What this means in practice

Stage structural damage and measure current inflammatory activity separately. Hurley stage records the pattern of recurrent lesions, tunnels and scarring; it is most useful for identifying disease that needs a procedural plan, particularly extensive stage III disease. IHS4 is a dynamic count: inflammatory nodules + 2 × abscesses + 4 × draining tunnels, with scores of ≤ 3 classified as mild, 4–10 as moderate and ≥ 11 as severe. Agreement between IHS4 and Hurley classification was only fair in the validation study ($\kappa = 0.32$), so one should not be used as a substitute for the other. At assessment and follow-up, document the worst affected sites, draining tunnels, inflammatory lesion counts, pain and functional impact. A low

current lesion count does not erase established tunnels or scarring; conversely, substantial inflammatory activity merits attention even when fixed structural damage is limited. This is a clinical use of complementary measures, not a validated rule that any single score mandates a particular drug.

Match treatment to the component most likely to change. For limited, predominantly inflammatory disease without extensive tunnels, topical or intralesional treatment and an appropriate course of systemic antibiotics can be proportionate initial measures. The North American medical guideline allows antibiotic monotherapy in mild disease but characterizes antibiotics in advanced disease principally as adjuncts because responses are less frequent and recurrence is common. Repeated antibiotics should therefore not become a substitute for reassessing persistently active moderate-to-severe disease. For a persistent localized tunnel, consider deroofing or excision as a structural intervention; for widespread, interconnected stage III disease, develop a surgical strategy alongside control of surrounding inflammation. Hurley staging is particularly reliable for recognizing stage III disease relevant to surgical assessment. Biologic suppression of inflammatory lesions should not be presented as proof that established scarred tunnel networks will disappear.

Use approved biologics for the population in which benefit was demonstrated, rather than for a Hurley number alone. Randomized phase 3 evidence supports adalimumab in moderate-to-severe HS: week-12 HiSCR was 41.8% versus 26.0% with placebo in PIONEER I ($P=0.003$) and 58.9% versus 27.6% in PIONEER II ($P<0.001$). Responses were reported as similar across baseline Hurley II and III groups, but that does not establish that stage III structural disease can be managed without surgery. Secukinumab's SUNSHINE and SUNRISE trials and bimekizumab's BE HEARD I and II trials likewise evaluated moderate-to-severe HS, providing randomized evidence for IL-17-pathway inhibition rather than an evidence-based sequence among the approved agents. In the United States, the bimekizumab prescribing information includes an HS indication; its labeling and the relevant jurisdiction's current product information should govern eligibility, precautions and dosing, rather than extrapolation from another indication. The North American guideline's statement that adalimumab was the FDA-approved biologic reflects its publication-era treatment landscape and should not be read as a current inventory of approvals.

Assess response against the treatment objective, not merely whether a trial endpoint was met. HiSCR measures reduction in abscesses and inflammatory nodules without worsening of abscesses or draining tunnels; it is useful for judging anti-inflammatory treatment, but it does not fully describe persistent tunnel burden, pain or disability. Record both a dynamic measure such as IHS4 and the sites still requiring procedural treatment. A meaningful reduction in inflammatory lesions can justify continuing a biologic while operating on a residual tunnel; conversely, continued new lesions despite treatment warrants reassessment of the drug strategy and adherence rather than surgery alone. Medical and surgical management often need to be combined under North American guidance.

Select an agent through comorbidity and safety review as well as efficacy. Before TNF or IL-17 inhibition,

review infection risk and relevant contraindications, and apply product-specific screening and monitoring. Oral candidiasis was among the frequently reported treatment-emergent adverse events in BE HEARD II; serious treatment-emergent adverse events over 48 weeks were reported in 40 (8%) bimekizumab-treated patients in BE HEARD I and 24 (5%) in BE HEARD II. These observations inform counselling, but cross-trial event rates should not be treated as a head-to-head safety comparison. Pregnancy, breastfeeding and other special populations require a separate risk assessment because HS-specific biologic safety evidence in pregnancy is limited.

Open questions

Which approved biologic should be first, and which should follow failure of another? PIONEER, SUNSHINE/SUNRISE and BE HEARD tested their agents against placebo under different protocols and at different primary assessment times. Their response percentages cannot rank adalimumab, secukinumab and bimekizumab. A pragmatic randomized head-to-head trial, stratified by prior biologic exposure, baseline Hurley stage, draining-tunnel burden and concomitant antibiotics, would address initial selection. A second randomization among primary nonresponders and patients losing response would address sequencing more directly.

Can inflammatory control prevent irreversible structural progression? Current efficacy endpoints principally capture changing inflammatory lesions. Hurley stage describes accumulated anatomical damage and is poorly suited to measuring short-term treatment response, while IHS4 incorporates draining tunnels but remains a count-based assessment. Longitudinal studies beginning before extensive tunnelling, with standardized imaging or clinical mapping and prespecified incident-tunnel and surgery endpoints, could test whether earlier targeted treatment changes the course of structural disease rather than only current activity. Such a claim should not be inferred from short-term HiSCR improvement.

How should biologics and surgery be timed together? North American guidance recognizes that medical and surgical approaches often must be combined, but it does not establish a single optimal sequence for every inflammatory and tunnel phenotype. A randomized strategy trial comparing biologic initiation before planned surgery with surgery followed by biologic initiation—while standardizing the procedure and measuring recurrence at operated and non-operated sites—would be more informative than comparing postoperative outcomes in selectively treated cohorts. It should include patients with localized persistent tunnels as well as those with extensive stage III disease.

What is durable benefit beyond the controlled trial period, and for whom? SUNSHINE/SUNRISE reported outcomes through week 52, and BE HEARD I and II through week 48; longer bimekizumab follow-up includes an open-label extension, which cannot preserve the original placebo-controlled comparison.

Prospective comparative registries with consistent definitions of loss of response, treatment switching, tunnel outcomes, infection and patient-reported burden would complement longer randomized follow-up. Prespecified analyses by baseline Hurley stage and IHS4 components are essential: a treatment effect on nodules must not be assumed to be an equivalent effect on established draining tunnels.

Which biological features predict response? Follicular disruption, TNF- and IL-17-associated inflammation, neutrophil recruitment and altered microbial communities offer a coherent rationale for treatment development, but the relative contribution of these processes varies across lesions and patients. Neither pathway expression nor a microbiome result is established here as a treatment-selection test. Prospective biomarker studies embedded in randomized trials—sampling comparable lesion types before treatment and testing a prespecified treatment-by-biomarker interaction—would be needed before these mechanistic observations could guide choice between TNF and IL-17 inhibition.