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Efficacy and Safety of Izokibep, a Novel IL-17A Inhibitor, in Moderate-to-Severe Hidradenitis Suppurativa: Week 12 Results from a Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 3 Study

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*At the time of the study.

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- All authors met the ICMJE authorship criteria and had full access to relevant data
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Background and Objective

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Hidradenitis Suppurativa

- Chronic, painful, systemic inflammatory disease characterized by deep-layer inflammatory nodules, skin abscesses, and draining tunnels, in which **dysregulated IL-17A** plays a key role[1,2]
- Unmet need for highly effective and safe treatments that deliver more complete and faster resolution of disease manifestations and improve quality of life[3-5]

Izokibep

- Small protein therapeutic (18.6 kDa) designed to **selectively inhibit IL-17A** with high potency through tight binding affinity; contains an albumin-binding domain that prolongs its half-life[6]

Primary Objective: to evaluate the efficacy and safety of izokibep through week 12 in a phase 3 study in patients with moderate-to-severe hidradenitis suppurativa (NCT05905783)

IL-17A, interleukin-17A.

1. Sabat R, et al. *Nat Rev Dis Primers*. 2020;6:18. 2. Kimball A, et al. *Exp Dermatol*. 2022;31:1522-32. 3. Kimball A, et al. *N Engl J Med*. 2016;375:422-34. 4. Frew J, et al. *Clin Exp Dermatol*. 2021;46:306-13. 5. Snyder CL, et al. *Clin Cosmet Investig Dermatol*. 2023;16:1833-41. 6. Klint S, et al. *MAbs*. 2023;15:2209920.

Izokibep: A Unique, Small-Protein Therapeutic

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Potency

Blocks IL-17A target with **high affinity of 0.3 pM**[1]

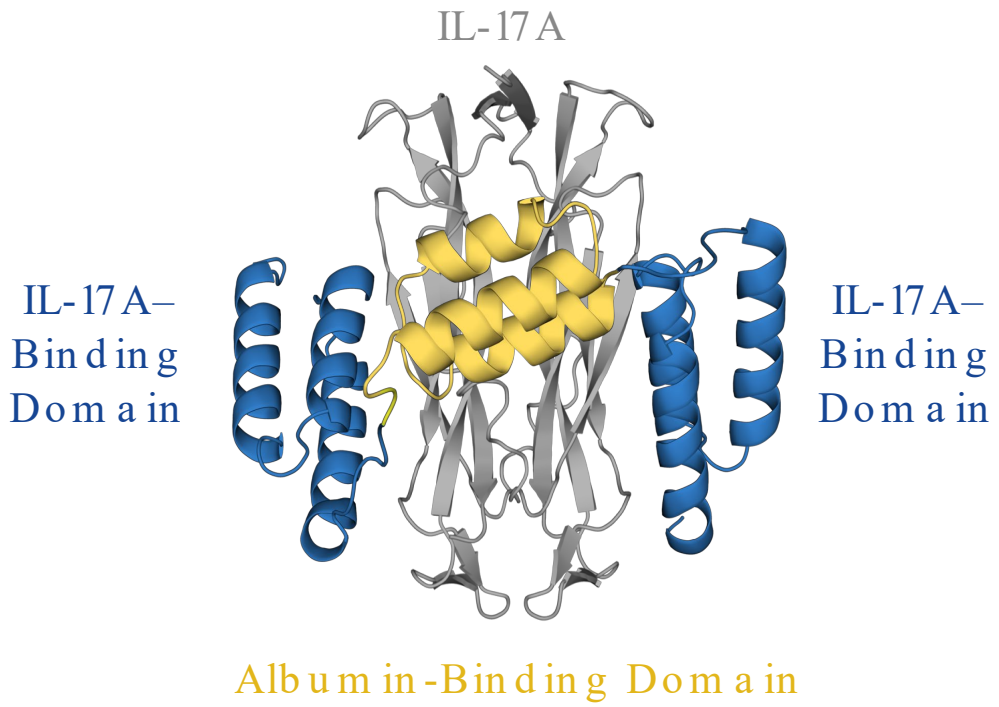
Size

~1/10th the size of a monoclonal antibody (18.6 kDa) potentially enabling izokibep to reach tissues difficult to access by monoclonal antibodies[1]

Albumin-Binding Domain

Extends plasma half-life and may **enhance targeting to sites of inflammation**[1]

Izokibep[1] (18.6 kDa)



IL-17A, interleukin-17A.

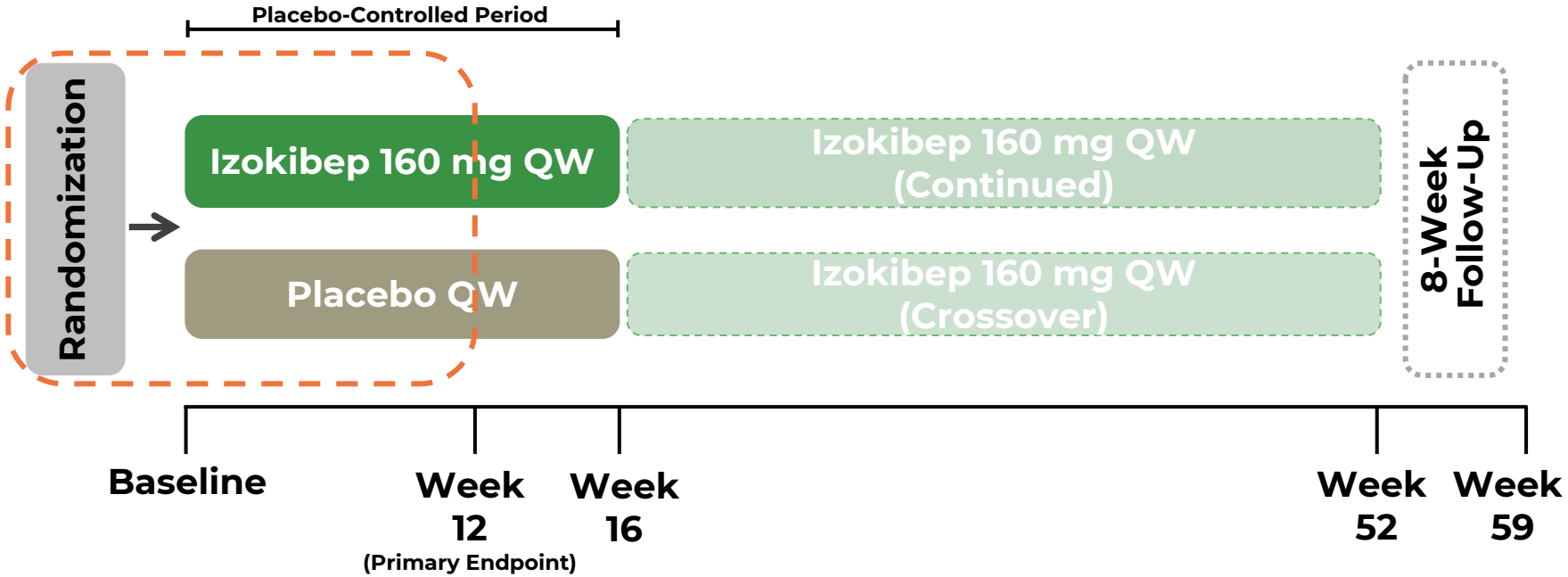
1. Klint S, et al. *MAbs*. 2023;15:2209920.

Study Design

Eligibility

- Moderate-to-severe HS
- Diagnosis of HS for ≥6 months
- HS lesions in ≥2 distinct anatomic areas (1 Hurley stage II or III)
- Total AN count ≥5
- Inadequate response, intolerance, or contraindication to oral antibiotics

Complete Trial Design



Endpoints (Week 12)

Efficacy

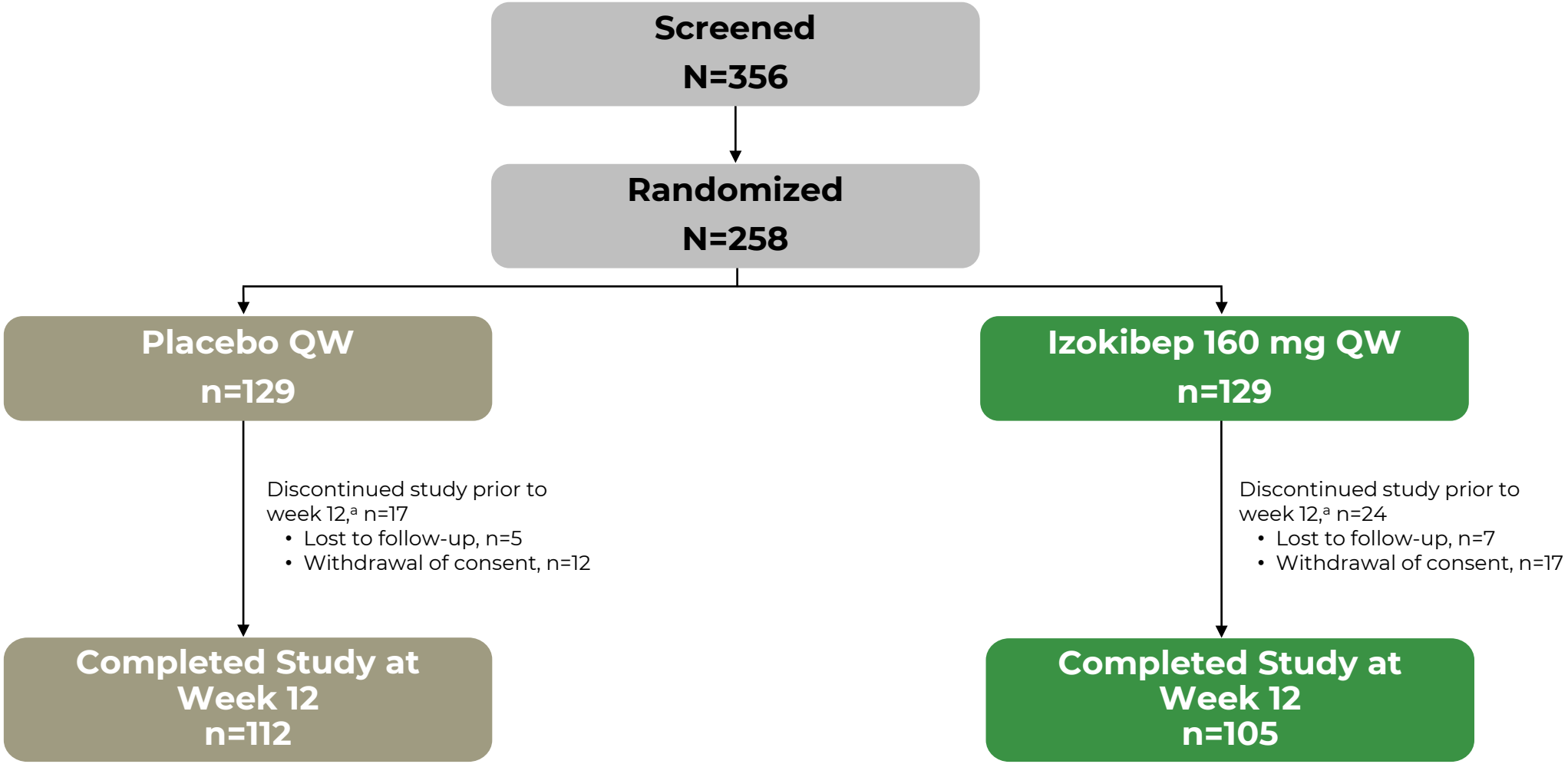
- *Primary*:
  - HiSCR75
- *Secondary:*
  - HiSCR90/100/50
  - DLQI
  - AN count of 0, 1, or 2[a]
  - ≥3-point reduction in skin pain NRS[b]
  - ≥1 HS flare

Safety

- TEAEs, AESIs, SAEs, laboratory assessments, vital signs

Randomization was stratified by any prior TNFi use for HS (yes/no) and Hurley stage (II or III).
[a]In patients with baseline Hurley stage II. [b]In patients with baseline skin pain NRS ≥4.
AE, adverse event; AESI, AE of special interest; AN, abscess and inflammatory nodule; DLQI, Dermatology Life Quality Index; HiSCR50/75/90/100, ≥50%/≥75%/≥90%/100% improvement in HS Clinical Response (≥50%/≥75%/≥90%/100% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count); HS, hidradenitis suppurativa; NRS, numeric rating scale; QW, once weekly; SAE, serious AE; TEAE, treatment-emergent AE; TNFi, tumor necrosis factor inhibitor.

Patient Disposition



[a]Prior to the primary efficacy assessment and prior to study day 98 (last day of the week 12 analysis visit window).
QW, once weekly.

Patient Demographics and Baseline Characteristics

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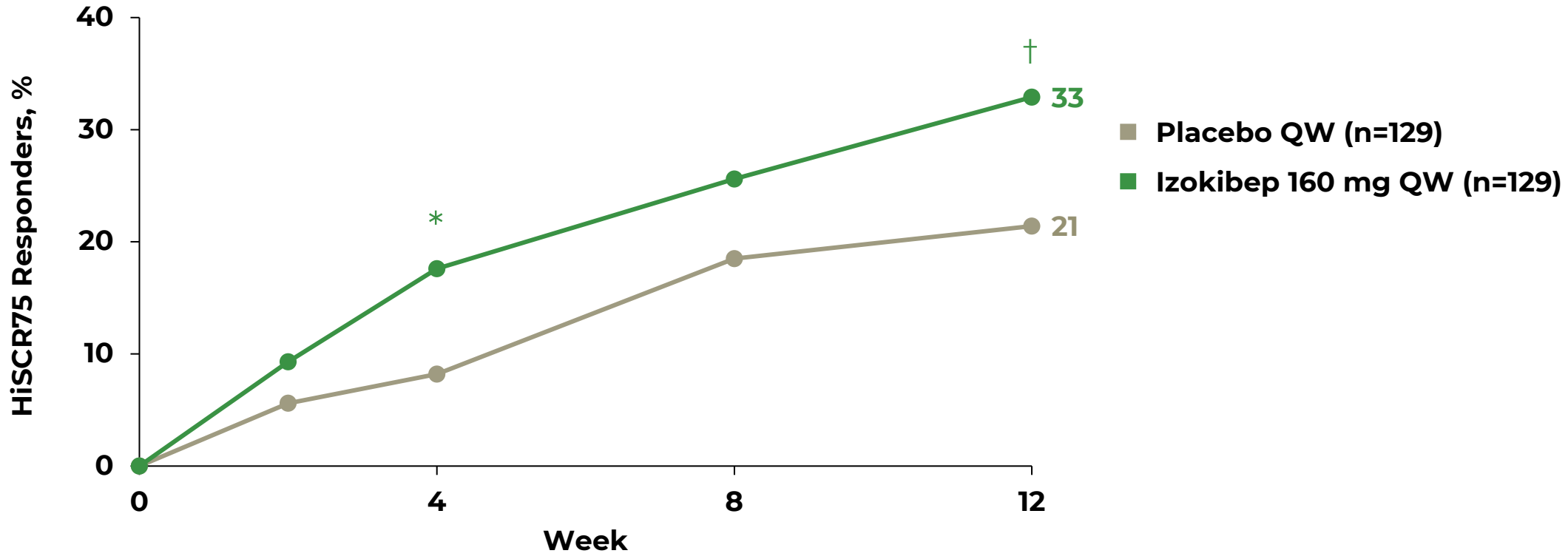
	Placebo n=129	Izokibep 160 mg QW n=129	Overall N=258
Age, mean (SD), years	37.4 (12.9)	37.1 (11.9)	37.3 (12.4)
Race, n (%)			
White	90 (70)	91 (71)	181 (70)
Black or African American	28 (22)	21 (16)	49 (19)
Asian	10 (8)	8 (6)	18 (7)
Other[a]	1 (1)	9 (7)	10 (4)
Female, n (%)	89 (69)	89 (69)	178 (69)
BMI, mean (SD), kg/m^2	34.1 (9.6)	34.0 (7.6)	34.0 (8.7)
Smoking status, current, n (%)	58 (45)	53 (41)	111 (43)
Disease duration, mean (SD), years	10.2 (8.4)	10.2 (8.9)	10.2 (8.7)
AN count, mean (SD)	13.2 (11.5)	13.5 (13.3)	13.4 (12.4)
Abscess count, mean (SD)	2.7 (3.2)	2.4 (4.0)	2.5 (3.6)
Inflammatory nodule count, mean (SD)	10.5 (11.1)	11.1 (12.2)	10.8 (11.6)
Draining tunnels, mean (SD)	2.2 (3.3)	2.2 (3.5)	2.2 (3.4)
Hurley stage, n (%)			
Stage II	82 (64)	78 (60)	160 (62)
Stage III	47 (36)	51 (40)	98 (38)
DLQI score, mean (SD)	11.4 (7.2)	12.3 (7.3)	11.9 (7.2)
Prior TNFi, n (%)	20 (16)	18 (14)	38 (15)

[a]Includes n=3 American Indian or Alaska Native in the izokibep arm, n=1 Native Hawaiian or Other Pacific Islander in the izokibep arm, and n=1 and n=5 Other in the placebo and izokibep arms, respectively.
AN, abscess and inflammatory nodule; BMI, body mass index; DLQI, Dermatology Life Quality Index; QW, once weekly; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.

Primary Endpoint of HiSCR75 at Week 12 Was Achieved

Izokibep treatment showed early separation from placebo, and one-third of patients receiving izokibep achieved HiSCR75 at week 12



Response rates were determined using NRI for patients who received antibiotic therapy that could affect HS and for patients with missing data who discontinued treatment for reason of adverse event or lack of efficacy, with multiple imputation for all other patients with missing data. Statistical significance per the prespecified testing hierarchy: †*P*<0.05 vs placebo. Nominal *P*-value: **P*<0.05 vs placebo.
HS, hidradenitis suppurativa; HiSCR, HS Clinical Response; NRI, nonresponse imputation; QW, every week.

Significant HiSCR90 and HiSCR100 Responses with Izokibep at Week 12

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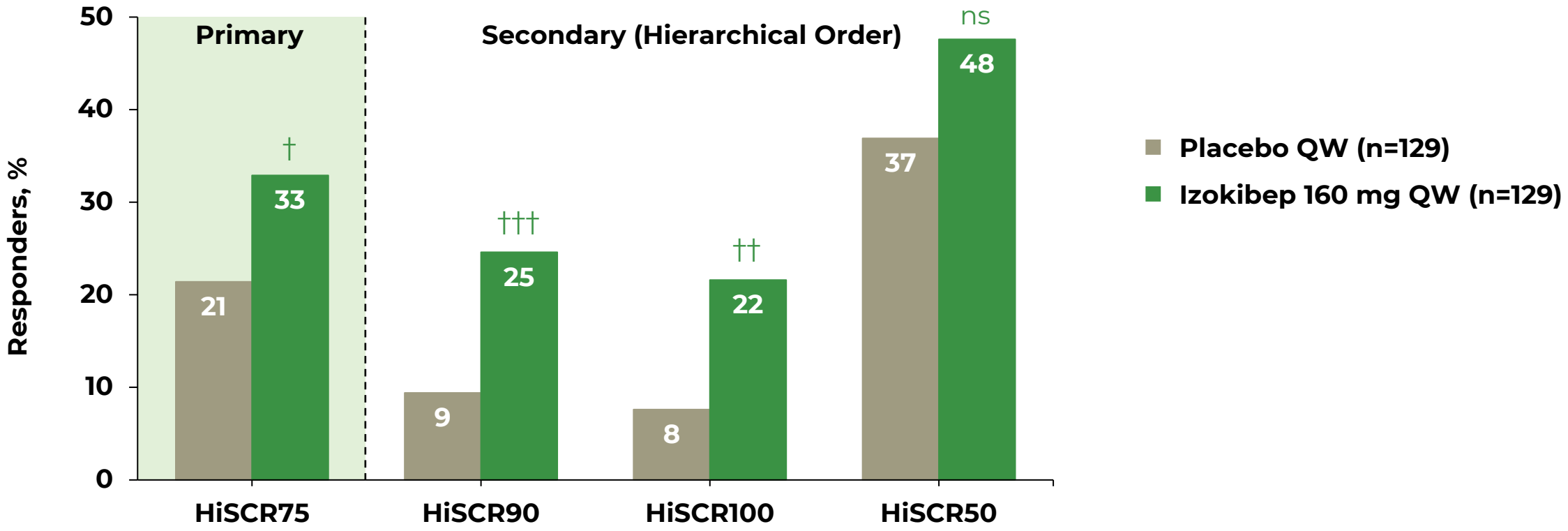
Approximately 1 in 4 patients achieved HiSCR90/100 by week 12 with izokibep



Response rates were determined using NRI for patients who received antibiotic therapy that could affect HS and for patients with missing data who discontinued treatment for reason of adverse event or lack of efficacy, with multiple imputation for all other patients with missing data. Statistical significance per the prespecified testing hierarchy: †$P<0.05$, ††$P<0.01$, †††$P<0.001$ vs placebo.
HS, hidradenitis suppurativa; HiSCR, HS Clinical Response; NRI, nonresponse imputation; ns, not significant; QW, every week.

Improved Quality of Life and Skin Pain Reduction with Izokibep at Week 12

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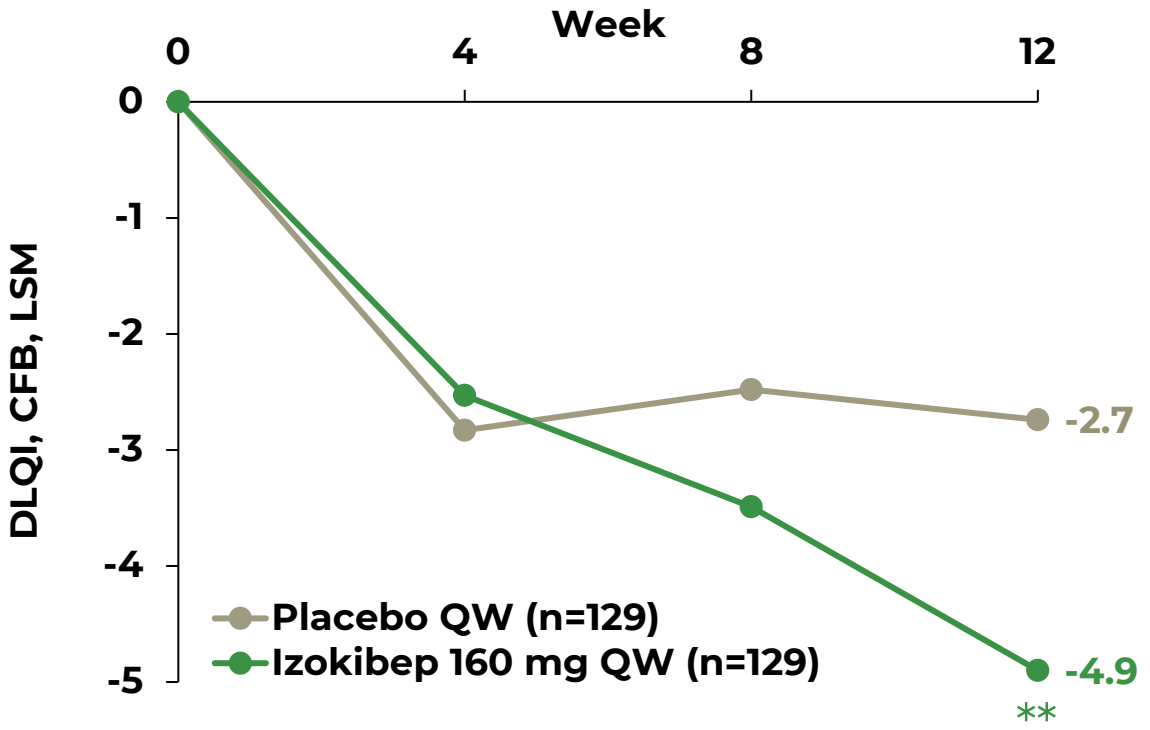
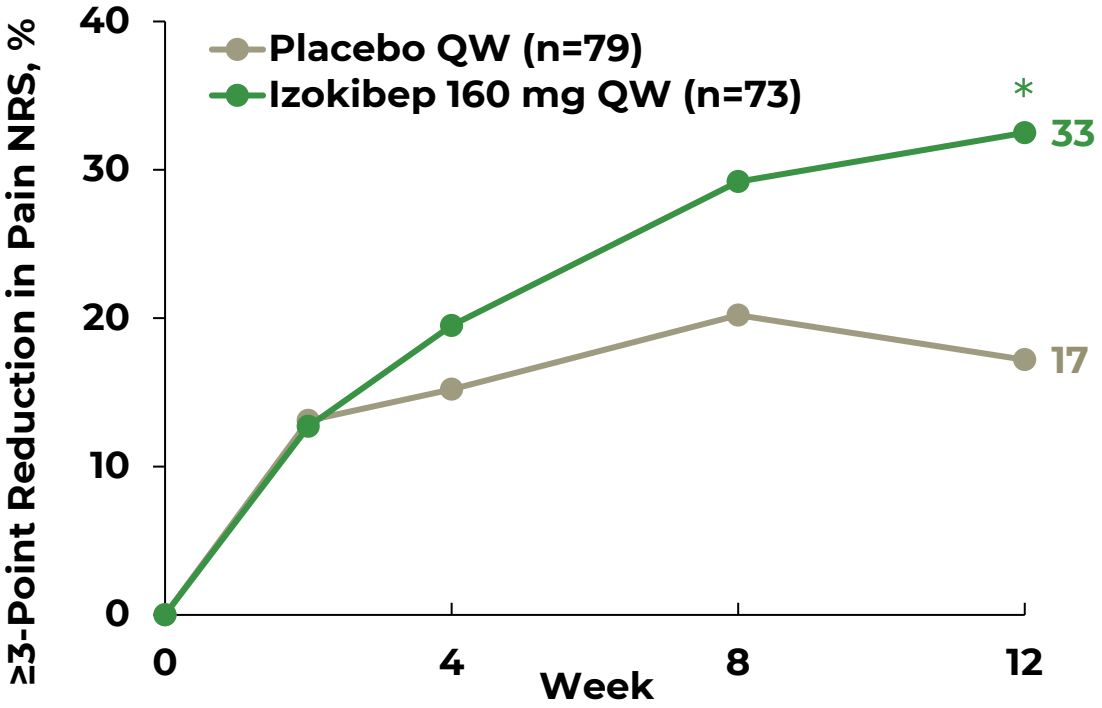
Patients receiving izokibep showed greater improvement in DLQI[a] at week 12 vs placebo



A higher percentage of patients receiving izokibep achieved a ≥3-point reduction in skin pain NRS[b] at week 12 vs placebo



Nominal *P*-value: **P*<0.05, ***P*<0.01 vs placebo.

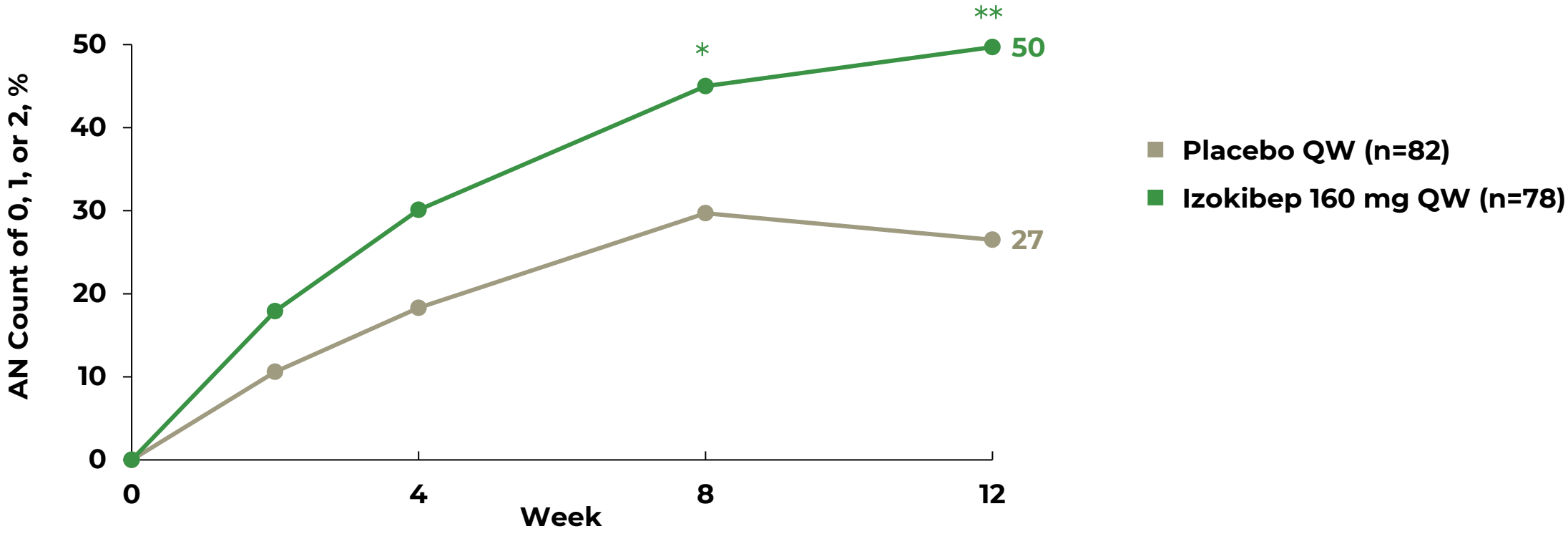
[a]LSM using MMRM; the model included treatment, baseline DLQI, stratification factors, visit week, and treatment by visit week interaction as covariates. The number of evaluable patients at week 12 was n=112 for placebo and n=102 for izokibep.

[b]In patients with baseline skin pain NRS ≥4. Response rates were determined using NRI for patients with missing data who discontinued treatment for reason of adverse event or lack of efficacy and patients who received prohibited analgesic therapy for hidradenitis suppurativa within 28 days of the visit, with multiple imputation for all other patients with missing data.

CFB, change from baseline; DLQI, Dermatology Life Quality Index; LSM, least squares mean; MMRM, mixed model repeated measures; NRI, nonresponse imputation; NRS, numeric rating scale; QW, every week.

AN Count at Week 12

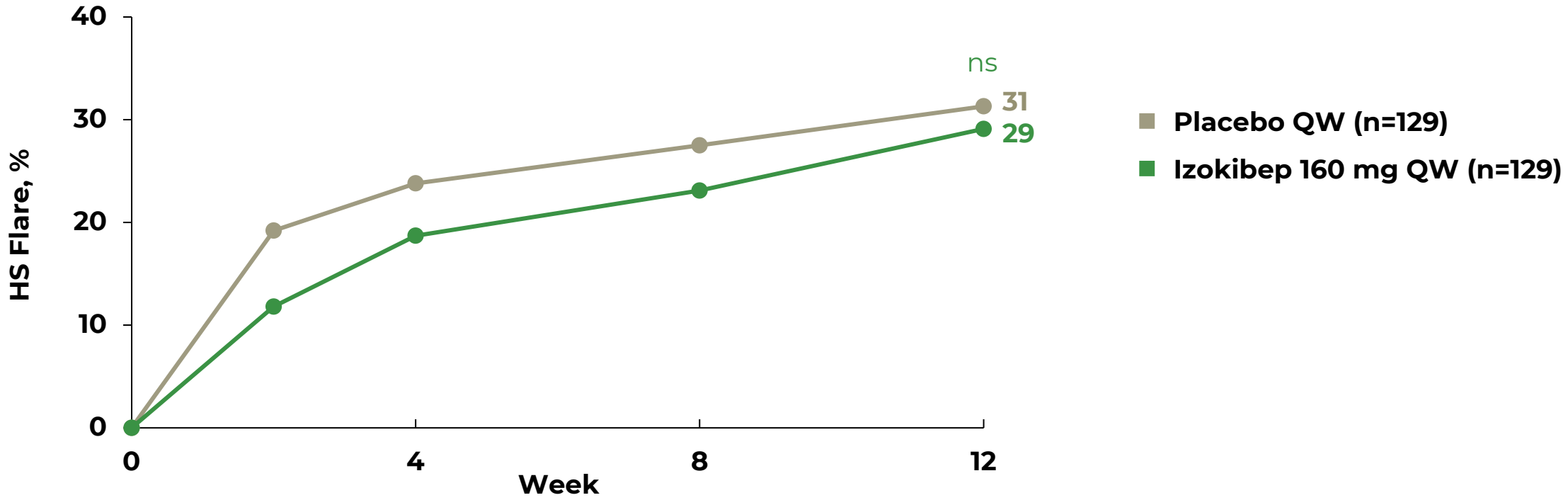
Half of patients with baseline Hurley stage II disease receiving izokibep achieved an AN count of 0, 1, or 2 by week 12



In patients with baseline Hurley stage II. Response rates were determined using NRI for patients who received antibiotic therapy that could affect HS and for patients with missing data who discontinued treatment for reason of adverse event or lack of efficacy, with multiple imputation for all other patients with missing data. Nominal *P*-value: *$P<0.05$, **$P<0.01$ vs placebo.
AN, abscess and inflammatory nodule; HS, hidradenitis suppurativa; NRI, nonresponse imputation; QW, every week.

HS Flare at Week 12

The percentages of patients with ≥1 flare[a] at any time through week 12 were similar between treatment arms



Response rates were determined using NRI for patients who received antibiotic therapy that could affect HS and for patients with missing data who discontinued treatment for reason of adverse event or lack of efficacy, with multiple imputation for all other patients with missing data.
[a]Disease flare defined as ≥1 flare (≥25% increase in AN count with a minimum increase of 2 AN relative to baseline) at any time through week 12.
AN, abscess and inflammatory nodule; HS, hidradenitis suppurativa; NRI, nonresponse imputation; ns, not significant; QW, every week.

Summary of Safety Through Week 12

n, %	Placebo QW n=129	Izokibep 160 mg QW n=129
Any TEAE	68 (52.7)	102 (79.1)
Serious TEAE	4 (3.1)	1 (0.8)
TEAE leading to discontinuation of study treatment	4 (3.1)	10 (7.8)
Injection-site reactions	0	6 (4.7)
Death	0	0
Infections and infestations	31 (24.0)	27 (20.9)
TEAE preferred term (≥5% in either treatment arm)		
Injection-site reactions	10 (7.8)	84 (65.1)
Headache	12 (9.3)	13 (10.1)
Nasopharyngitis	9 (7.0)	9 (7.0)
Fatigue	3 (2.3)	7 (5.4)
Diarrhea	2 (1.6)	7 (5.4)
AE of special interest	3 (2.3)	1 (0.8)
Candidiasis[a]	3 (2.3)	0
Hypersensitivity	0	1 (0.8)
Inflammatory bowel disease	0	0
Suicidal ideation	0	0

[a]Two vulvovaginal, 1 undefined.
AE, adverse event; QW, once weekly; TEAE, treatment-emergent AE.

- Serious TEAEs
  - Placebo: abdominal pain lower, pelvic fracture, hepatic enzyme increased, urinary retention, hidradenitis
  - Izokibep: vasculitis
- Injection-site reactions
  - Grade 1 or 2 in all but 1 patient

Conclusions

- The primary endpoint of this phase 3 study was met, with one-third of patients receiving izokibep 160 mg QW achieving HiSCR75 at week 12, a significant improvement over placebo
- Approximately 1 in 4 izokibep-treated patients achieved HiSCR90/100
- Izokibep-treated patients demonstrated notable improvements over placebo in patient-reported quality of life and pain
- Izokibep treatment was well tolerated, with no new safety signals and a safety profile generally consistent with that of other IL-17A–selective inhibitors

HS, hidradenitis suppurativa; HiSCR, HS Clinical Response; IL-17A, interleukin-17A; QW, every week.