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Targeting the Pathway or the Cytokine? First Network Meta-Analysis Incorporating Phase 3 Povorcitinib Data: Comparative Efficacy of JAK1 vs. IL-17 Inhibitors in Moderate-to-Severe Hidradenitis Suppurativa

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Introduction

The therapeutic landscape of Hidradenitis Suppurativa (HS) has recently expanded beyond anti-TNF monotherapy. Two novel mechanistic classes have emerged as frontrunners: cytokine blockade targeting IL-17A and IL-17F (e.g., bimekizumab, secukinumab) and intracellular signaling inhibition via JAK1 (e.g., povorcitinib, upadacitinib). While these agents have demonstrated efficacy against placebo, head-to-head comparisons are lacking to guide treatment algorithms and emerging "upgrade criteria" [1]. This study aims to conduct the first Bayesian Network Meta-Analysis (NMA) incorporating the newly released Phase 3 data of povorcitinib (September 2025) and Phase 2 data of upadacitinib to establish a comparative efficacy hierarchy among these novel therapeutic options.

Materials and Methods

A systematic literature search was conducted to identify randomized, double-blind, placebo-controlled trials (RCTs) evaluating JAK inhibitors, IL-17 inhibitors, and TNF inhibitors in adults with moderate-to-severe HS. The primary endpoint was the proportion of patients achieving Hidradenitis Suppurativa Clinical Response (HiSCR50) at the end of the induction period (Week 12–16). The analysis integrated the most recent Phase 3 data for povorcitinib (STOP-HS1/2) [2] and bimekizumab (BE HEARD I/II) [3], alongside pivotal Phase 3 data for secukinumab (SUNSHINE/SUNRISE) [4] and adalimumab (PIONEER I/II) [5]. Additionally, Phase 2 data for upadacitinib was included as an exploratory arm [6] to comprehensively evaluate the class effect of JAK1 inhibition. A Bayesian NMA was performed to estimate Odds Ratios (OR) and Surface Under the Cumulative Ranking (SUCRA) scores.

Results

Eight pivotal RCTs involving over 4,000 patients were included in the network. In the comparative analysis for HiSCR50 achievement, bimekizumab (320mg Q2W) demonstrated the highest probability of being the most effective treatment (SUCRA: 0.88), followed by adalimumab (40mg QW) and povorcitinib (75mg QD). Specifically, bimekizumab showed HiSCR50 rates of 48–52% [3], while povorcitinib demonstrated rates of 40.6–42.3% in Phase 3 trials [2]. Upadacitinib (30mg QD) exhibited consistent efficacy signals (HiSCR50: 38.3% - Phase 2 data) [6], reinforcing the potential of the JAK1 pathway, though slightly lower than the confirmatory Phase 3 data of povorcitinib. Indirect comparison between the JAK1 inhibitor class and IL-17A/F inhibitors revealed no statistically significant difference in efficacy (OR: 0.72, 95% CrI: 0.37–1.43), suggesting comparable short-term efficacy between the two mechanisms.

Table 1. Summary of Key Efficacy Data Included in the Network Meta-Analysis (Induction Period: Week 12–16)

Treatment Agent	Mechanism of Action	Administration Route	Key Trials Included	HiSCR50 Response Rate (%) at Induction
Bimekizumab (320mg Q2W)	IL-17A & IL-17F Inhibitor	Subcutaneous (SC)	BE HEARD I & II (Phase 3)	**48% – 52%**
Povorcitinib (75mg QD)	JAK1 Inhibitor (Small Molecule)	**Oral (PO)**	STOP-HS1 & 2 (Phase 3)	**40.6% – 42.3%**
Upadacitinib (30mg QD)	JAK1 Inhibitor (Small Molecule)	**Oral (PO)**	Phase 2 RCT (Ackerman et al.)	**38.3%** *(Phase 2 Data)*
Secukinumab (300mg Q2W)	IL-17A Inhibitor	Subcutaneous (SC)	SUNSHINE & SUNRISE (Phase 3)	**42% – 45%**
Adalimumab (40mg QW)	TNF-alpha Inhibitor	Subcutaneous (SC)	PIONEER I & II (Phase 3)	**41.8% – 58.9%**

Abbreviations: Q2W: Every 2 weeks; QD: Once daily; QW: Once weekly; HiSCR50: Hidradenitis Suppurativa Clinical Response 50.

Conclusions

This is the first NMA to statistically position povorcitinib within the biologic landscape using Phase 3 data, while supporting the class effect with upadacitinib findings. Our results suggest that oral JAK1 inhibitors offer a viable, non-injectable alternative with comparable efficacy to potent IL-17 biologics in the induction phase. While IL-17A/F inhibition numerically leads the ranking, the lack of significant superiority over JAK1 inhibition supports a patient-centered approach, where comorbidity profiles and delivery preferences (oral vs. injectables) drive the therapeutic choice.

References: [1] Nikolakis G, et al. J Eur Acad Dermatol Venereol. 2024;38(11):e1205. [2] Kimball AB, et al. EADV Congress 2025, Late Breaking News. [3] Kimball AB, et al. Lancet. 2024;403(10443):2504-19. [4] Kimball AB, et al. Lancet. 2023;401(10378):747-61. [5] Kimball AB, et al. N Engl J Med. 2016;375(5):422-34. [6] Ackerman L, et al. JAAD. 2022;87(1):52-61.