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Abstract N°: 1

Efficacy and Safety of Oturkibart in Adults with Prurigo Nodularis: 52-Week Results from a Phase 3 Trial

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Introduction

Prurigo nodularis (PN) is a chronic, recurrent disease characterized by intensely pruritic and hyperkeratotic nodules. Oturkibart (R&D code: QX005N), a novel humanized anti-IL-4Rα IgG4 monoclonal antibody, has demonstrated clinically meaningful improvements in itch and skin lesions in adults with PN through Week 24 (findings to be presented soon as an e-poster at EADV 2026). Here, we report the first long-term open-label extension (OLE) data for an IL-4Rα inhibitor in PN, evaluating the efficacy and safety of oturkibart through Week 52 in a phase 3 OLE period to address this evidence gap.

Materials and Methods

Adults (18-75 years) with PN, who had an inadequate response or intolerance to topical corticosteroids (TCS), a

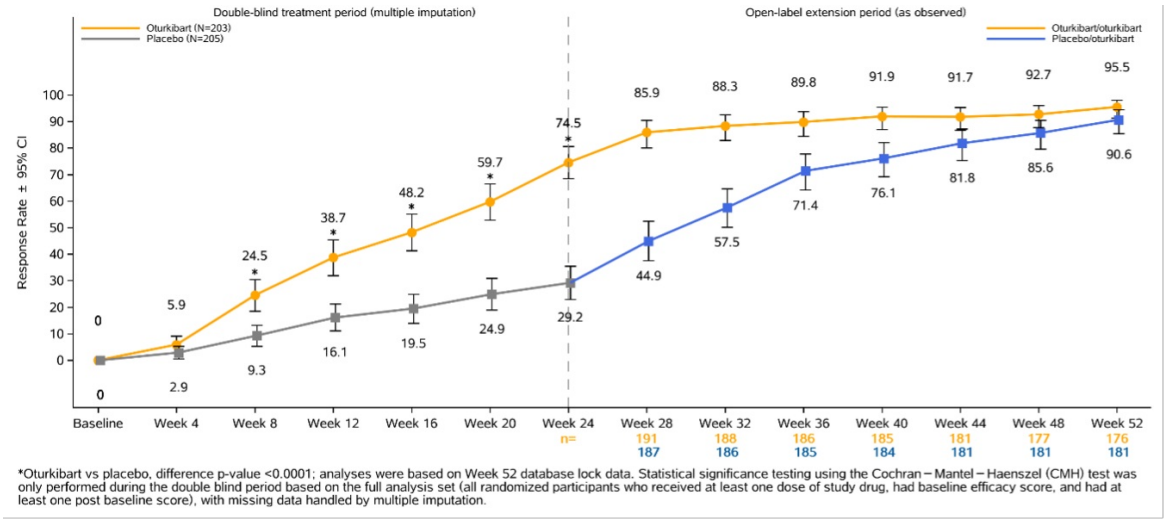
weekly average Worst Itch Numeric Rating Scale (WI-NRS) score ≥7, and an Investigator's Global Assessment for PN-Stage (IGA PN-S) ≥3 were randomized 1:1 to receive oturkibart 450 mg every 2 weeks (Q2W) or placebo for 24 weeks. This was followed by a 28-week OLE period, during which all patients received oturkibart 450 mg Q2W through Week 52, and a final 8-week follow-up. The primary endpoint was the proportion of participants achieving a ≥4-point reduction from baseline in the weekly average WI-NRS at Week 24. The key secondary endpoint was the proportion of participants with an IGA PN-S score 0/1 at Week 24. Other secondary endpoints included the proportion of patients achieving an Investigator's Global Assessment for PN-Activity (IGA PN-A) score 0/1, changes in Dermatology Life Quality Index (DLQI) and Hospital Anxiety and Depression Scale (HADS) scores, the use of rescue therapy. In addition, post-hoc analyses were performed on the proportion with a weekly average WI-NRS score ≤2, and the proportion with a weekly average WI-NRS score ≤1. For the OLE period, analyses were based on observed data, with no imputation for missing values. The safety of oturkibart was also evaluated.

Results

A total of 206 participants received oturkibart and 206 received placebo. Baseline demographics and disease characteristics were well balanced in two groups. At Week 52, responses were maintained among patients initially randomized to oturkibart (itch response, 95.5%(95% confidence interval [CI]: 91.24%, 98.02%); IGA PN-S 0/1, 66.9%(95% CI: 59.36%, 73.78%);IGA PN-A 0/1, 68.0%(95% CI: 60.54%, 74.84%)). Among patients who crossed over from placebo at Week 24, responses at Week 52 were substantially improved and similar to those achieved by patients initially randomized to oturkibart (itch response, 90.6%(95% CI: 85.39%, 94.43%);IGA PN-S 0/1, 49.2% (95% CI: 41.68%, 56.69%); IGA PN-A 0/1, 49.7%(95% CI: 42.22%, 57.24%)). Similar improvements in DLQI and HADS from Week 24 to Week 52 were reported in both groups (DLQI: oturkibart/oturkibart, -12.4; placebo/oturkibart, -11.1; HADS: oturkibart/oturkibart, -6.4; placebo/oturkibart, -5.3). Rescue therapy was used in 2.1% of the oturkibart/oturkibart group and 13.3% of the placebo/oturkibart group. Additionally, post-hoc analysis results showed: at Week 52, among patients initially randomized to the oturkibart, the proportion achieving a weekly average WI-NRS score ≤2 was 76.7%, and the proportion achieving a weekly average WI-NRS score ≤1 was 55.1%. The trends in the above endpoint for patients who crossed over from placebo were consistent with those in the oturkibart/oturkibart group. oturkibart was generally well tolerated during the extension period, with few grade ≥3 treatment-emergent adverse events (AEs) or serious AEs (oturkibart/oturkibart, 6.8% and 3.7%; placebo/oturkibart, 5.3% and 3.7%, respectively).

Conclusion

Oturkibart 450 mg Q2W for 52 weeks was well tolerated and demonstrated clear long-term efficacy in adult patients with PN, providing sustained and stable clinical benefits, including improvements in itch and skin lesions, as well as improvements in patients' quality of life and anxiety/depression.



Proportion of patients achieving a WI-NRS improvement of ≥4 points from baseline.

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Abstract N°: 3

Efficacy and Safety of MG-K10 Administered at 600 mg Every 8 Weeks Versus 300 mg Every 4 Weeks in Chinese Adults With Moderate-to-Severe Atopic Dermatitis: Results of a Randomized Phase 2 Study

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Introduction
MG-K10 is an innovative long-acting mAb that specifically binds to human IL-4Rα, and efficiently blocks the Th2 inflammatory signaling of IL-4 and IL-13. Following Fc mutation, MG-K10 allows long dosing interval owing to its prolonged half-life and demonstrated favorable efficacy and safety in adults with moderate-to-severe AD in a pivotal phase 3 trial which MG-K10 is administered at 300 mg every 4 weeks with 600 mg loading dose (MG-K10 300 mg Q4W). Herein, we report comparable efficacy and safety profiles of MG-K10 600 mg every 8 weeks (MG-K10 600 mg Q8W) and MG-K10 300 mg Q4W in Chinese adults with moderate-to-severe AD from a phase 2 trial of MG-K10 with 24 weeks' treatment.

Materials and Methods
This was a multicenter, randomized, double-blind, parallel, phase 2 study. 60 Chinese patients with moderate-to-severe AD were randomized 1:1 to subcutaneous dosing of MG-K10 300 mg Q4W or MG-K10 600 mg Q8W, both treatment regimens were administered over a 24-week treatment period. The co-primary endpoints were the proportion of patients achieving an EASI-75 response (≥75% improvement from baseline in Eczema Area and Severity Index score) and the proportion of patients achieving an IGA response (Investigator's Global Assessment score of 0 or 1 and a ≥2-point reduction from baseline) at week 24. Other efficacy endpoints included EASI-90, EASI-50, improvement from baseline in pruritus NRS, body surface area (BSA), Dermatology Life Quality Index (DLQI), and Patient Oriented Eczema Measure (POEM). Safety was assessed via adverse event (AE) and laboratory monitoring.

Results
At week 24, both MG-K10 600 mg Q8W and MG-K10 300 mg Q4W groups produced significant response rates from baseline at Week 24 on both co-primary endpoints (EASI-75 response: 88.5% % vs 83.3; IGA response: 73.1% vs 70.0%; both P>0.05). Both MG-K10 600 mg Q8W and MG-K10 300 mg Q4W groups demonstrated consistent potent efficacy over all efficacy endpoints, including EASI-90 and EASI-50 responses, as well as significant reductions in % BSA, and EASI score. Both groups achieved rapid and substantial reductions in pruritus and other

patient-reported symptoms of AD. The incidence of treatment-emergent adverse events (TEAEs) was similar between the two groups. Most TEAEs were grade 1 or 2. The incidence of conjunctivitis was low, and no injection-site reactions were reported.

Conclusion

The phase 2 trial has demonstrated that both MG-K10 600 mg Q8W and MG-K10 300 mg Q4W can rapidly and sustainably improve clinical manifestations in adults with moderate-to-severe AD. Compared to all commercially available anti-IL-4Rα therapeutics, MG-K10 features the longest dosing interval in the induction period. Further large-scale studies are warranted to confirm these findings.

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Abstract N°: 26

A Phase 2b Placebo-Controlled Study to Evaluate the Efficacy and Safety of Tulisokibart in Adults With Moderate to Severe Hidradenitis Suppurativa

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Introduction
Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by painful nodules and abscesses that can progress to tunnels, fibrosis, and scarring. Tumor necrosis factor–like cytokine 1A (TL1A) expressed by antigen-presenting cells signals by binding to death receptor 3 (DR3). TL1A is implicated in pathways that initiate and maintain chronic inflammation and may contribute to chronic fibrosis in HS. Tulisokibart is an investigational anti-TL1A monoclonal antibody that blocks TL1A-DR3 signaling, downregulating Th1, Th2, and Th17, thereby potentially disrupting the immuno-fibrotic loop in HS. This is the first study to evaluate the efficacy and safety of TL1A inhibition with tulisokibart in patients with HS.

Materials and Methods
This was a randomized, double-blind, placebo-controlled, multicenter trial in adults 18 to 75 years with HS (NCT06956235). Bayesian design was implemented to augment concurrent controls with historical placebo for the primary endpoint, the proportion of participants achieving Hidradenitis Suppurativa Clinical Response 50 (HiSCR50) at Week 16. Participants had moderate to severe HS defined as ≥5 abscesses and/or inflammatory nodules, lesions in ≥2 distinct anatomical areas, and Hurley Stage II or III in ≥1 area. Participants were randomized 2:2:1:2 (stratified by Hurley Stage [II or III] and concomitant systemic antibiotic [yes or no]) to subcutaneous tulisokibart 480 mg every 2 weeks (high dose), 480 mg every 4 weeks (medium dose), 240 mg every 4 weeks (low dose), or placebo, for 16 weeks, with a loading dose at day 1 (low dose group, 480 mg loading dose; medium and high dose groups, 960 mg loading dose). Secondary endpoints include proportion of participants with HiSCR75 response and change from baseline in Dermatology Life Quality Index (DLQI) total score at week 16.

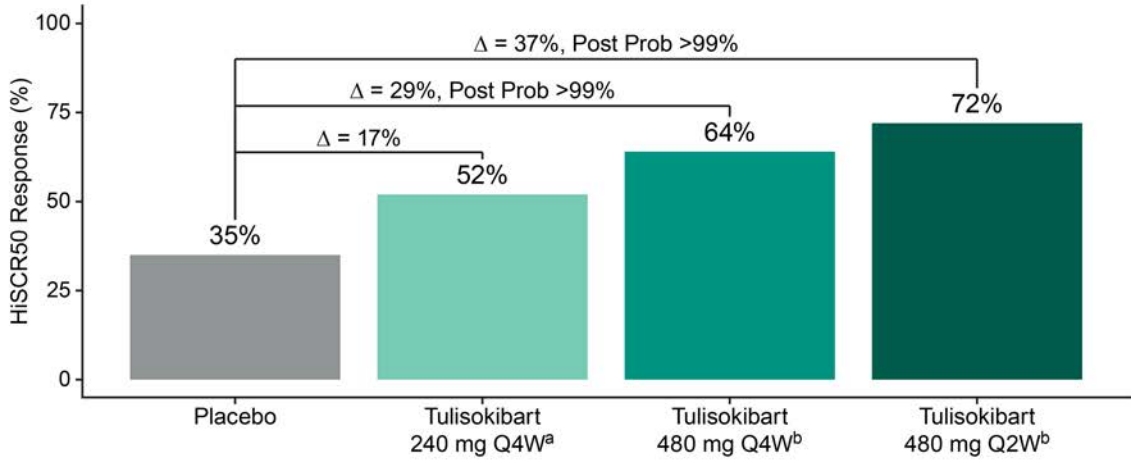
Results
Among 149 participants (tulisokibart high dose, N=42; tulisokibart medium dose, N=42; tulisokibart low dose, N=21; and placebo, N=44), baseline characteristics such as age, BMI, gender, Hurley stage, and systemic antibiotic

use, were balanced across the treatment groups. At Week 16, HiSCR50 response was achieved in 72.4% (high dose), 64.1% (medium dose), and 51.7% (low dose) of participants receiving tulisokibart compared with 35.1% of those receiving placebo (Bayesian treatment difference [95% credible interval] vs placebo: high dose, 37.3% [17.9, 54.9]; medium dose, 28.9% [9.0, 47.9]; low dose, 16.5% [-8.2, 41.0]; posterior probability of superiority >99% for high dose and medium dose) (figure). Treatment effects as measured by HiSCR50 were observed as early as Week 4. HiSCR75 was achieved at week 16 in 41.2% (high dose), 39.6% (medium dose), and 29.1% (low dose) of participants receiving tulisokibart compared with 15.1% receiving placebo (frequentist treatment difference [95% CI] vs placebo: high dose, 26.8% [9.1, 44.5], medium dose, 24.3% [6.9, 41.6]; and low dose, 13.0% [-5.9, 31.9]) (figure). LS mean change from baseline in DLQI at week 16 was -5.6 (high dose), -3.5 (medium dose), and 0.7 (low dose) in those receiving tulisokibart compared with -2.5 in those receiving placebo (treatment difference [95% CI] vs placebo: high dose, -3.2 [-5.6, -0.7], medium dose, -1.0 [-3.6, 1.5], and low dose, 3.1 [0.1, 6.1]) (figure). Adverse events (AEs) occurred in 42.9%, 47.6%, and 52.4% of those receiving tulisokibart high dose, medium dose, and low dose, respectively, compared with 40.9% of those receiving placebo. Serious AEs were infrequent and occurred at similar rates across the treatment groups (2.4%, 2.4%, and 4.8% for tulisokibart high dose, medium dose, and low dose, respectively, vs 2.3% for placebo). No serious or opportunistic infections were observed in the study.

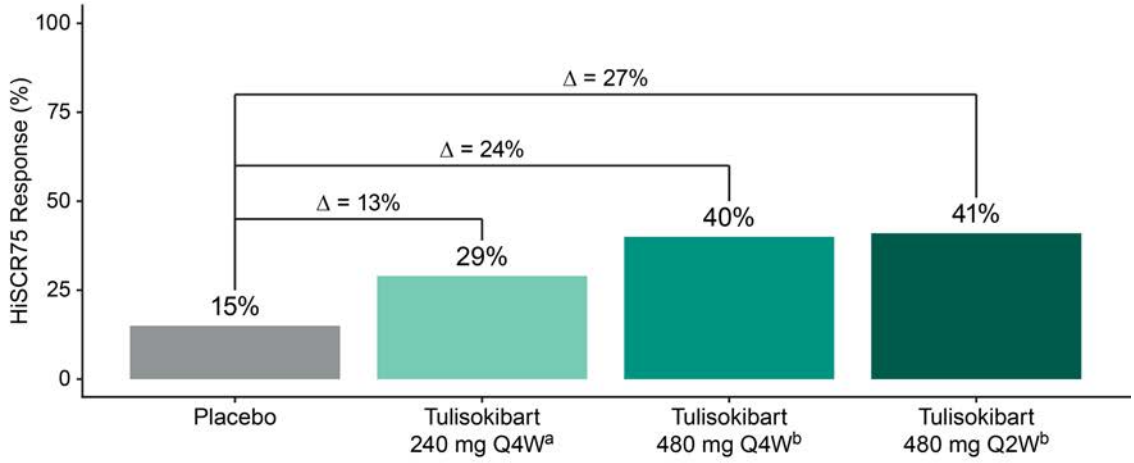
Conclusion

This Phase 2b study demonstrated dose-related efficacy of tulisokibart in the treatment of participants with moderate to severe HS through Week 16, with consistency across multiple endpoints. Tulisokibart was generally well-tolerated with no safety concerns identified.

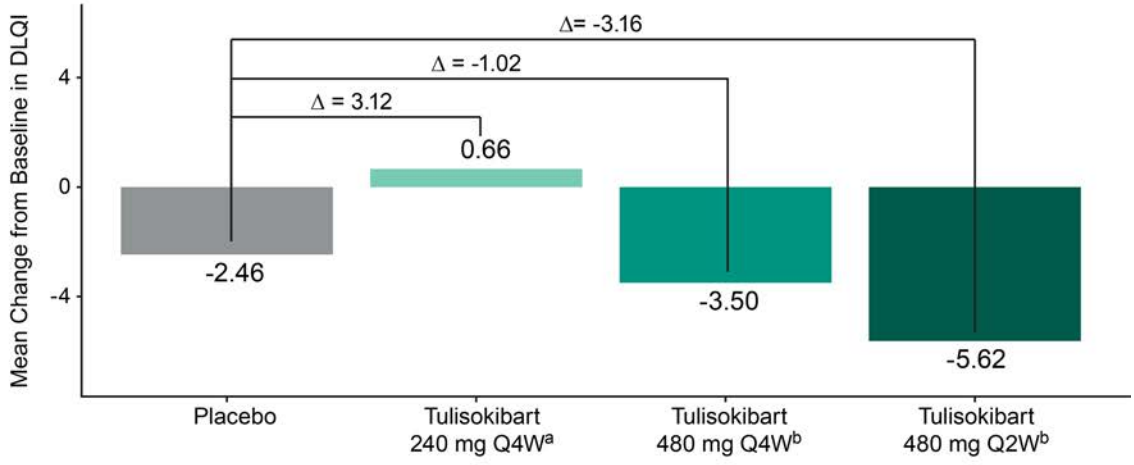
A. HiSCR50 Response



B. HiSCR75 Response



C. DLQI



[a]Loading dose: Tulisokibart 480 mg SC at Day 1/Week 0.
[b]Loading dose: Tulisokibart 960 mg SC at Day 1/Week 0.

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Abstract N°: 32

Positive Top-line Data from Phase 2a Proof-of-Concept Trial of EVO301, a Novel IL-18 Binding Protein, in Patients with Moderate-to-Severe Atopic Dermatitis.

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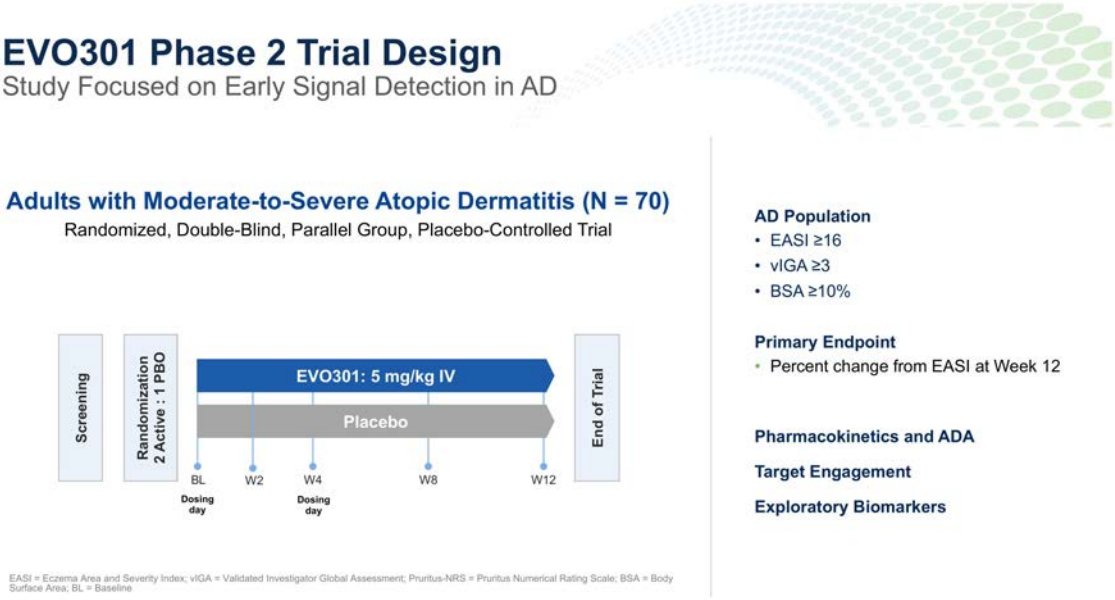
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Introduction

The EVO301-AD001 Phase 2 proof-of-concept trial evaluated EVO301, an IL-18–targeting biologic, in adults with moderate-to-severe atopic dermatitis (AD).

Materials and Methods

Investigators enrolled 70 biologic-naïve subjects across 12 sites in New Zealand and Australia and randomized subjects 2:1 to receive EVO301 5 mg/kg IV or placebo, with dosing administered on Day 1 and Day 28 and follow-up through Week 12. All subjects met standard AD severity thresholds (EASI ≥16, vIGA ≥3, BSA ≥10%). The trial aimed to detect early clinical signals of efficacy, safety, pharmacokinetics (PK), and target engagement.



Results

Efficacy: The study met its primary endpoint—percent change in EASI at Week 12 using a Bayesian analysis—after only two doses (Day 1 and Day 28). EVO301 demonstrated a mITT mean response at 12 Weeks of -31.7%

(placebo adjusted) in % change in EASI. Secondary endpoints showed early onset of effect by Week 2, with statistically meaningful separation from placebo beginning at Week 4 and sustained through Week 12 in both Bayesian and frequentist analyses.At Week 12, clinically relevant categorical responses favored EVO301. EASI-50 occurred in 62.5% of EVO301-treated subjects compared with 22.7% of placebo-treated subjects (p=0.0014). Higher-threshold responses (EASI-75 and EASI-90) demonstrated numerically favorable trends. Investigators observed vIGA 0/1 with ≥2-point improvement in 22.9% of EVO301-treated subjects versus 0% on placebo. Pruritus-NRS showed improvement over time, with statistically significant differences emerging at Week 8 (p=0.0021).Non-head-to-head comparative benchmarking suggests that Week 12 EASI improvements with EVO301 align broadly with those reported for marketed AD biologics, including dupilumab, lebrikizumab, tralokinumab, and nemolizumab, when compared with published Phase 3 trials of differing designs and durations.

Safety: EVO301 was well tolerated. No treatment-related serious or severe adverse events occurred, and no subjects discontinued treatment because of adverse events. No patients developed conjuntivitis. Infusion reactions occurred infrequently; 1 subject (2.1%) receiving EVO301 and 2 subjects (9.1%) receiving placebo experienced infusion reactions, none of which were severe. Atopic dermatitis flares occurred more frequently in the placebo group than in the EVO301 group (41% vs 21%). Other adverse events occurred at similar rates between groups, with upper respiratory infections and headache reported most commonly. Investigators identified no clinically significant laboratory or ECG abnormalities, and no cases of conjunctivitis occurred.

Pharmacokinetics and Immunogenicity: PK profiles remained consistent with Phase 1 data and supported both Q2W and Q4W dosing regimens for future development. Anti-drug antibody rates were low and showed no apparent impact on efficacy or PK in preliminary analyses.

Biomarkers and Target Engagement: EVO301 demonstrated target engagement, as shown by marked increases in serum total IL-18, consistent with pharmacological binding and extended IL-18 half-life when bound to drug. Treatment also down-modulated Th2-associated cytokines, including CCL-17 and CCL-22, and non-TH-2 biomarkers, supporting mechanistic plausibility and alignment with observed clinical improvements.

Phase 2 POC Trial in AD: Baseline Characteristics

	EVO301	Placebo
n	48	22
Age (SD)	30.5 (11.1)	33.1 (11.8)
Gender (female, %)	29 (60.4%)	13 (59.1%)
Weight (kg)	78.51 (18.69)	76.35 (17.50)
BMI (kg/m^2) (SD)	27.37 (5.99)	28.13 (6.30)
EASI (SD)	30.00 (11.79)	29.83 (10.48)
IGA (SD)	3.3 (0.5)	3.5 (0.5)
Pruritus-NRS (SD)	6.34 (1.51)	6.66 (2.14)
% BSA (SD)	47.10 (21.17)	49.26 (16.12)

Source: Table 14.1.3 (demographics), 14.2.2.3.3 (EASI), 14.2.2.6.3 (IGA) ,14.2.2.4.4 (NRS), 14.2.2.5.3 (BSA),

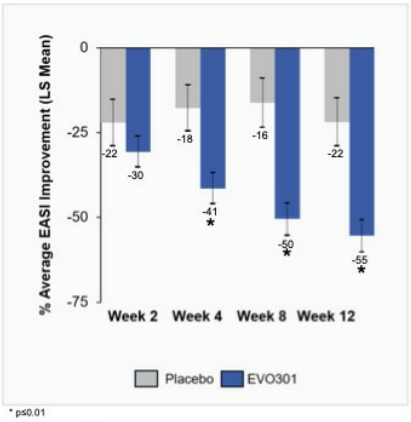
BMI: body mass index, EASI: Eczema Area and Severity Index, IGA: Investigator's global assessment, NRS: numeric rating score, BSA: body surface area, SD: standard deviation

Conclusion

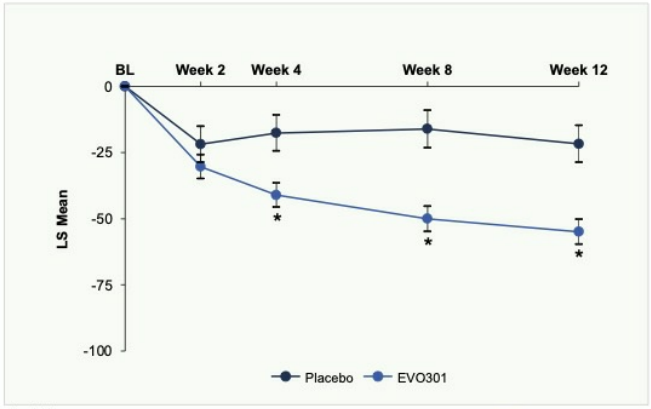
EVO301 met its primary and key secondary efficacy endpoints, produced rapid and sustained clinical improvements, demonstrated a favorable safety and tolerability profile, and showed clear biological activity. These results support further dose optimization and advancement into a Phase 2b dose-ranging study using a subcutaneous formulation.

Phase 2 POC Trial in AD: Efficacy

% Change in EASI by Study Visit: MMRM



* p≤0.01



* p≤0.01

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Abstract N°: 51

MELAPRED : A Parsimonious Clinical–Genetic Algorithm for Melanoma Risk Prediction

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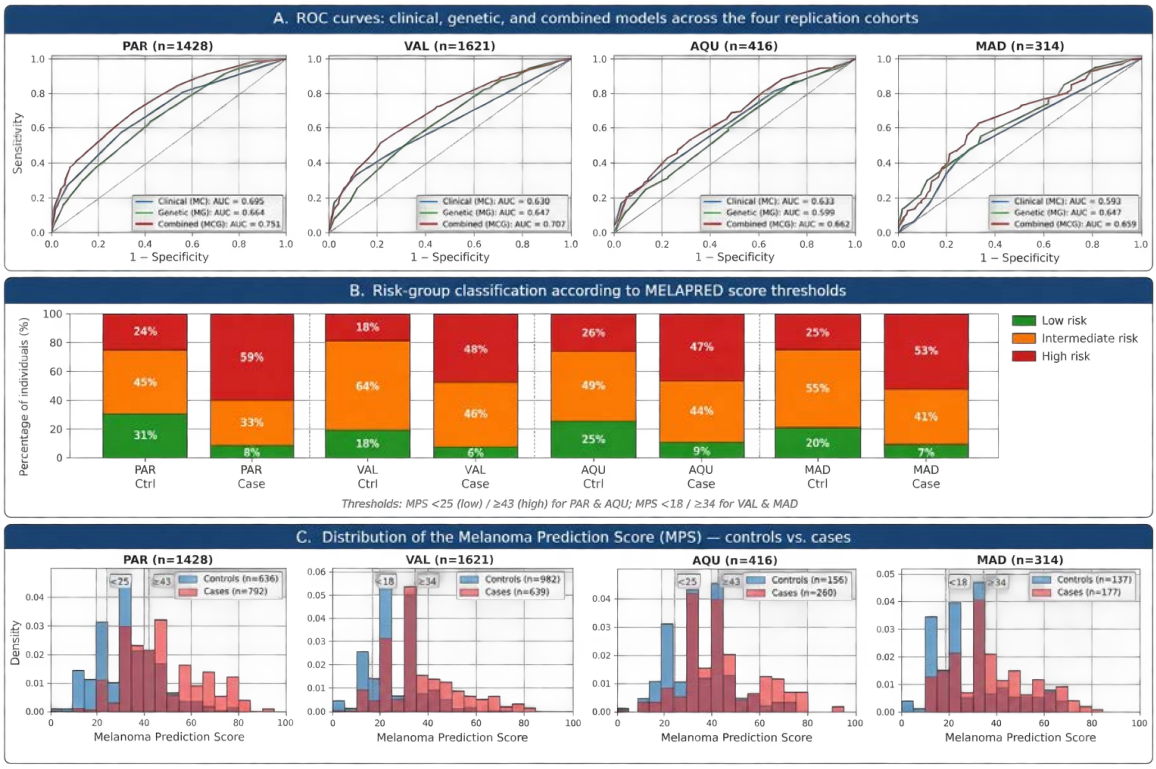
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Introduction
Accurate melanoma risk stratification may enable targeted surveillance while avoiding the complexity of large polygenic risk scores. We developed MELAPRED, a parsimonious clinical–genetic prediction model designed for routine clinical implementation.We aim to externally validate MELAPRED across independent European populations, quantify the incremental contribution of genetic information beyond clinical phenotype, and assess model calibration and geographical transportability.

Materials and Methods
A clinical model (MC) and a combined clinical–genetic model (MCG, MELAPRED) were developed by logistic regression in a Paris discovery cohort and evaluated in four independent European replication cohorts from Valencia, Madrid, L'Aquila and a French familial/multiple-melanoma population. Analytic samples comprised 895 cases/858 controls in Paris, 731/1,101 in Valencia, 178/166 in Madrid, 260/156 in L'Aquila and 156/105 in the familial/multiple-melanoma cohort. Discrimination was assessed by area under the ROC curve (AUC), incremental performance by DeLong testing and continuous net reclassification improvement (cNRI), and calibration by Hosmer–Lemeshow and Cox calibration analyses. Population-specific logistic recalibration was performed when required.

Results
The final MELAPRED model retained only five predictors: naevus count, eye colour, MC1R genotype, rs16891982 in SLC45A2 and rs10757257 near MTAP. In Paris, adding genetic information increased AUC from 0.70 to 0.75

(DeLong $p=1.14\times10^{-10}$). Risk estimates were upgraded in 62.5% of melanoma cases and downgraded in 57.5% of controls, yielding a cNRI of 39.8%. The combined model outperformed the clinical model in all four replication cohorts, with AUCs of 0.71 in Valencia (95% CI 0.69–0.73), 0.69 in Madrid (0.63–0.74), 0.66 in L'Aquila (0.61–0.71) and 0.89 in the familial/multiple-melanoma cohort. Calibration was satisfactory in Valencia and the familial cohort but suboptimal in Madrid and L'Aquila. Cox analysis identified slope-dominated miscalibration, with calibration slopes of 0.57 (95% CI 0.36–0.87) in Madrid and 0.63 (0.40–0.87) in L'Aquila versus 0.89 (0.77–1.03) in Valencia. Two-parameter logistic recalibration restored adequate calibration in all replication cohorts (post-recalibration Hosmer–Lemeshow p=0.21–0.90) without altering discrimination.



Conclusion

MELAPRED demonstrates that substantial improvement in melanoma risk stratification can be achieved using only two clinical and three genetic predictors. Its performance replicated across independent European populations, while simple population-specific recalibration corrected geographical differences in calibration without loss of discrimination. As a clinical perspective, re-analysis of previously reported prospective high-risk follow-up yields an estimated number needed to screen of 10.3 over 6 years, supporting further evaluation of MELAPRED as a tool for risk-stratified dermatological surveillance.

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Abstract N°: 70

Lutikizumab Targets Neutrophilic Inflammation and Fibroblast Activation to Drive Response in Hidradenitis Suppurativa

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Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease, with multifactorial pathogenesis driven by neutrophil infiltration, interleukin (IL)-1 and IL-17 signalling, and specialised HS fibroblast states (CXCL13$^+$ and SFRP4$^+$) promoting tunnel formation. Lutikizumab (luti), a dual-variable domain immunoglobulin IL-1α/β antagonist, showed promising safety and efficacy in patients with moderate-to-severe HS. This study investigated the role of IL-1 in HS pathophysiology and characterised molecular mechanisms associated with clinical response to luti.

Materials and Methods

Samples were collected from two trials enrolling adults with moderate-to-severe HS: a 16-week, open-label biomarker (OLB) study (biologic-naïve and anti-tumour necrosis factor [TNF] inadequate responders [IR]) and a Phase 2, randomised, double-blind, placebo-controlled trial (NCT05139602; anti-TNF-IR). Patients in the Phase 2 trial received subcutaneous (SC) luti 300 mg every week (EW), 300 mg every other week (EOW), 100 mg EOW, or SC placebo EW. Spatial transcriptomic analysis was performed on non-lesional (Week 0) and lesional (Week 0 and 4) skin biopsies from patients in the OLB study using high-plex ribonucleic acid profiling. Peripheral samples from the Phase 2 trial were collected at Week 0, 2, 4, 8, 12, and 16, and analysed for serum proteomics and cell frequencies. Statistical differences were evaluated using a paired t-test, and biomarker median change from baseline (CFB) was analysed using a linear mixed model for repeated measures.

Results

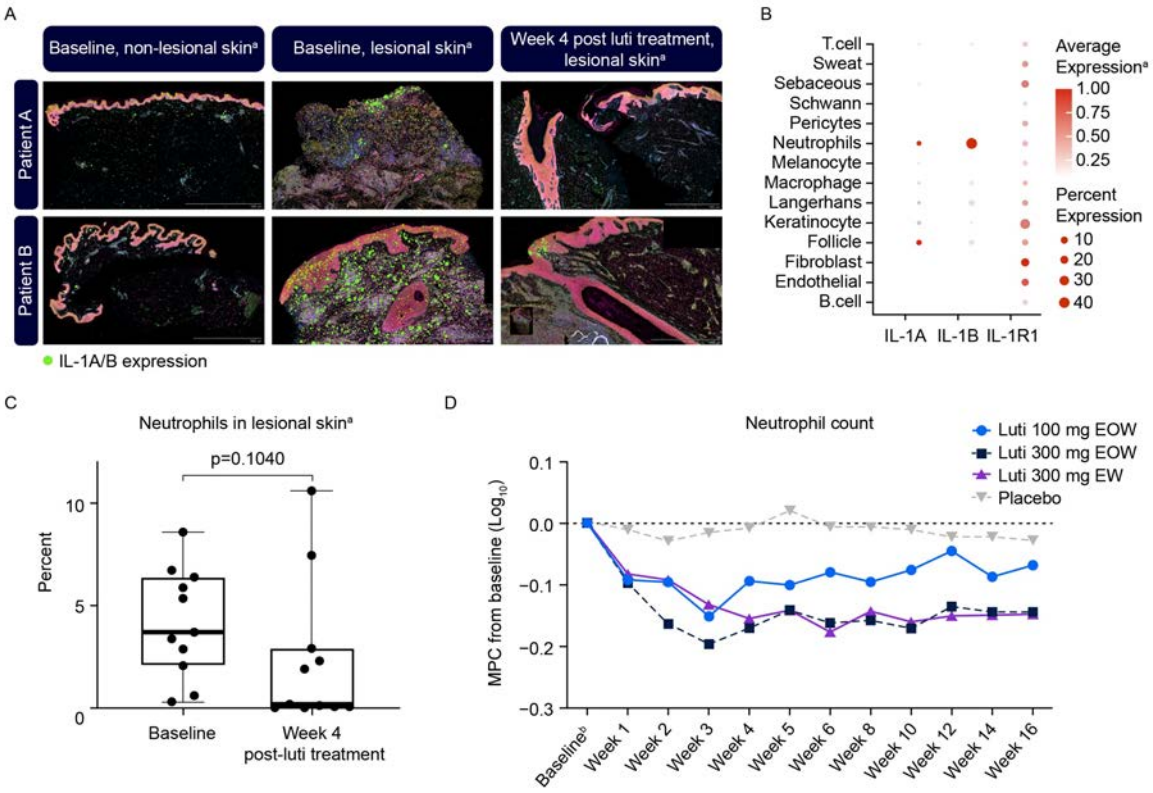
Samples were analysed from 14 patients in the OLB study (skin biopsy) and 64 patients in the Phase 2 trial (peripheral blood). At baseline, spatial transcriptomics showed increased lesional expression of IL-1A/B (**Figure A**) and significantly higher median percentage of neutrophils compared with non-lesional skin (3.7% vs 0.01%; p=0.004). IL-1A/B and IL-1 receptor-1 transcripts were predominantly expressed in neutrophils and fibroblasts, respectively (**Figure B**). At baseline, disease-specific CXCL13$^+$ fibroblasts were found exclusively in lesional skin. T cells were the primary source of IL-17A and IL-17F expression, with IL-17A–expressing T cells enriched in lesional compared with non-lesional skin (IL-17F was expressed at similar levels in both; data not shown). At Week 4, luti reduced IL-1A/B expression in HS lesions (**Figure A**), IL-17F expression in T cells (p≤0.01), and chemokine expression in fibroblasts (p≤0.01). Luti also decreased the percentage of infiltrating neutrophils in HS lesions at Week 4 compared with baseline (**Figure C**). Peripheral blood analysis showed luti led to greater mean percent

CFB in IL-1α (luti 300 mg EW: −17%; 300 mg EOW: −42%; 100 mg EOW: −6%; placebo: −14%), IL-1β (luti 300 mg EW: −54%; 300 mg EOW: −63%; 100 mg EOW: −72%; placebo: −19%), and neutrophil counts (**Figure D**) over 16 weeks compared with placebo. This coincided with greater mean percent CFB in IL-6 and C-reactive protein. Patients with ≥50% reduction from baseline in total abscess and inflammatory nodule count, with no increase in abscess or draining tunnel count relative to baseline (HS Clinical Response [HiSCR50] responders) at Week 16 also showed greater reductions in neutrophil counts compared with patients who did not achieve HiSCR50 (data not shown).

Conclusion

In patients with moderate-to-severe HS, lesions were characterised by elevated neutrophil counts, pathogenic fibroblast subsets, and IL-1α/β expression compared with non-lesional skin. Luti inhibited neutrophil-derived IL-1α/β expression and reduced fibroblast-derived chemokines and IL-17A/F in T cells. Luti disrupted neutrophil infiltration into the skin and reduced circulating neutrophils in patients who achieved HiSCR50 at Week 16. Therefore, luti may supress neutrophil and pathogenic fibroblast activity and mitigate aberrant extracellular matrix remodelling, thereby reducing fibrosis and tunnel formation.

Figure. IL-1A/B expression at baseline and Week 4 after treatment with luti (A), IL-1A/B expression by cell type at baseline (B), impact of treatment with luti on infiltrating neutrophils in the skin (C), and peripheral blood neutrophil counts over time in the Phase 2 trial in patients with moderate-to-severe HS (D).



[a]Tissues were sampled at baseline (lesional and non-lesional) and at Week 4 post-luti treatment (lesional). High-plex RNA profiling was executed using the 10x Genomics (Pleasanton, CA, USA) Xenium in situ platform with a 5100-gene panel. Following image acquisition, cell segmentation and transcript assignment were performed to generate cell-by-gene expression matrices. Downstream analysis included quality control filtering, cell-type clustering, and spatial differential expression to evaluate transcriptomic shifts across tissue microenvironments posttreatment.

[b]Baseline in the Phase 2 trial is at Week 0 prior to treatment with loading dose based on treatment group (luti [300 mg EW, 300 mg EOW, or 100 mg EOW] or placebo).

EW, every week; EOW, every other week; HS, hidradenitis suppurativa; IL, interleukin; luti, lutikizumab; MPC, mean percent change; RNA, ribonucleic acid.

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Abstract N°: 72

Efficacy and safety of lunsekimig in moderate-to-severe atopic dermatitis: Results from the phase 2b VELVET trial

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Introduction

Lunsekimig (SAR443765) is a novel, pentavalent, bispecific NANOBODY® molecule that blocks thymic stromal lymphopoietin (TSLP) and IL-13, two drivers of inflammation in atopic dermatitis (AD). This study evaluated the clinical efficacy and safety of lunsekimig in participants (pts) with moderate-to-severe AD.

Materials and Methods

VELVET (NCT06790121) was a phase 2b, multicentre, randomised, double-blind, placebo (pbo)-controlled, parallel-group, dose-ranging study. Eligible adults (aged 18–80 years) with moderate-to-severe AD who had an inadequate response to topical therapies or for whom topical therapies were inadvisable, were randomised 3:1:3:1:3:1 to: lunsekimig 300mg every 4 weeks (Q4W; n=37) or matching pbo, lunsekimig 300mg Q2W (n=36) or matching pbo, or lunsekimig 600mg Q4W (n=38) or matching pbo. The 3 pbo arms were analysed as 1 pooled pbo arm (n=39). The primary endpoint was % change in EASI score from baseline (BL) to W24. Key secondary endpoints included % of pts achieving EASI-75, a vIGA-AD score of 0 or 1 with a reduction from BL of ≥2 points, and a reduction of ≥4 points in the weekly average of daily PP-NRS scores from BL to W24. A multiplicity-controlled testing strategy was used to evaluate multiple dose regimens vs pbo on primary and key secondary endpoints, with significance determined by a prespecified hierarchical gatekeeping sequence at 1-sided α=0.025. Pts were considered non-responders after the use of mid- to very high-potency topical corticosteroids or prohibited medications/procedures that impact efficacy before W24, or after discontinuation of study intervention due to lack of efficacy. Missing data due to reasons other than lack of efficacy were handled with multiple imputation for the primary endpoint and non-responder imputation for the secondary endpoints.

Results

Demographics and disease characteristics were balanced across treatment arms. The primary endpoint did not reach statistical significance; however, there were numerically greater differences observed in lunsekimig treatment arms in EASI reductions vs pbo (Table). Mean % change in EASI from BL to W24 was -67.7%, -61.9%, and -53.8% for the 300mg Q4W, 300mg Q2W, and 600mg Q4W arms, respectively, compared with -43.7% in the pbo group. Key secondary endpoints are reported in the table. Pbo-adjusted (adj) EASI-75 responses at W24 were 44.5%, 41.1%, and 21.9% for the 300mg Q4W, 300mg Q2W, and 600mg Q4W arms, respectively; pbo-adj vIGA-AD 0/1 responses at W24 were 25.0%, 24.0%, and 8.9% for the 300mg Q4W, 300mg Q2W, and 600mg Q4W arms,

respectively (Table). Additional secondary endpoints demonstrated greater responses vs pbo (Table). There was no clinically meaningful difference observed in PP-NRS. Lunsekimig was well tolerated. In the combined lunsekimig group, incidence of less than 5% was seen for serious adverse events, severe treatment-emergent adverse events (TEAE), and TEAEs leading to discontinuation. The most common TEAE was injection site reaction.

Conclusion

In the VELVET phase 2b dose-ranging study, while the primary endpoint was not achieved, lunsekimig showed clinically meaningful, numerical improvements across multiple measures of skin clearance and disease severity among pts with moderate-to-severe AD and was well tolerated at all doses. Further research may be warranted on the role of dual TSLP/IL-13 inhibition in AD.

Table. Efficacy of lunsekimig at Week 24

	Pooled Placebo (n=39)	300 mg Q4W (n=37)	300 mg Q2W (n=36)	600 mg Q4W (n=38)
Primary endpoint				
EASI score[a]	**37**	**36**	**35**	**38**
LS mean change from baseline, %	-43.7	-67.7	-61.9	-53.8
LS mean difference vs placebo,[b] % (95% CI)	-	23.9 (3.1, 44.7)	18.2 (-2.6, 39.0)	10.1 (-10.4, 30.5)
P value	-	.012	.044	.168
Adjusted *P*[c]	-	.036	.105	.252
Key secondary endpoints				
EASI-75[a]	**39**	**37**	**36**	**38**
Responders,[d] n (%)	7 (17.9)	23 (62.2)	21 (58.3)	15 (39.5)
Rate difference vs placebo,[e] % (95% CI)	-	44.5 (22.6, 61.2)	41.1 (19.0, 58.3)	21.9 (1.5, 40.3)
P value	-	< .001	< .001	.018
vIGA-AD 0/1[a]	**39**	**37**	**36**	**38**
Responders,[d] n (%)	4 (10.3)	13 (35.1)	12 (33.3)	7 (18.4)
Rate difference vs placebo,[e] % (95% CI)	-	25.0 (5.7, 42.3)	24.0 (4.6, 41.5)	8.9 (-7.8, 25.4)
P value	-	.005	.006	.136
PP-NRS ≥4[a]	**38**	**35**	**36**	**38**
Responder,[d] n (%)	9 (23.7)	7 (20.0)	13 (36.1)	10 (26.3)
Rate difference vs placebo,[e] % (95% CI)	-	-5.6 (-23.9, 13.9)	12.4 (-8.2, 32.1)	2.3 (-17.0, 21.6)
P value	-	.726	.123	.409
Secondary endpoints				
EASI-90 response[a]	**39**	**37**	**36**	**38**
Responders,[d] n (%)	5 (12.8)	18 (48.6)	12 (33.3)	10 (26.3)
Rate difference vs placebo,[e] % (95% CI)	-	35.6 (14.8, 52.8)	21.3 (1.6, 39.3)	14.1 (-4.3, 31.5)
P value	-	< .001	.015	.060
vIGA-AD 0/1 with BPE[a]	**39**	**37**	**36**	**38**
Responders,[d] n (%)	4 (10.3)	10 (27.0)	9 (25.0)	6 (15.8)
Rate difference vs placebo,[e] % (95% CI)	-	17.7 (-0.7, 34.9)	15.3 (-2.8, 32.7)	6.1 (-10.1, 22.3)
P value	-	.024	.042	.218

[a]N represents the number of participants included in the model. [b]LS mean difference in reduction vs placebo determined using ANCOVA model that includes treatment, randomisation strata (AD severity, prior systemic medications) as fixed effects, and baseline EASI as covariate. [c]Adjusted P value accounts for the testing hierarchy and adjusted P < .025 indicates statistical significance of the treatment effect. For endpoints after the hierarchy breaks and secondary endpoints not in the testing hierarchy, only nominal P values are presented. [d]MH. [e]MH common rate difference vs placebo, adjusting for randomisation strata (AD severity, prior systemic medications).

ANCOVA, analysis of covariance; AD, atopic dermatitis; BPE, barely perceptible erythema; CI, confidence interval; EASI, Eczema Area and Severity Index score; LS, least squares; MH, Mantel-Haenszel; PP-NRS, Peak Pruritus Numerical Rating Scale; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

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Abstract N°: 74

Safety of dupilumab in pregnancy: final results of the dupilumab prospective pregnancy registry

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Introduction
As many as 10-12% of women of reproductive age are estimated to have asthma or atopic dermatitis, many of whom may require treatment for moderate to severe disease. However, there are limited published data on the safety of dupilumab in pregnancy. To address this gap, a pregnancy registry (NCT04173442) was conducted to study the safety of dupilumab in pregnant women who were being treated for asthma or atopic dermatitis or both.

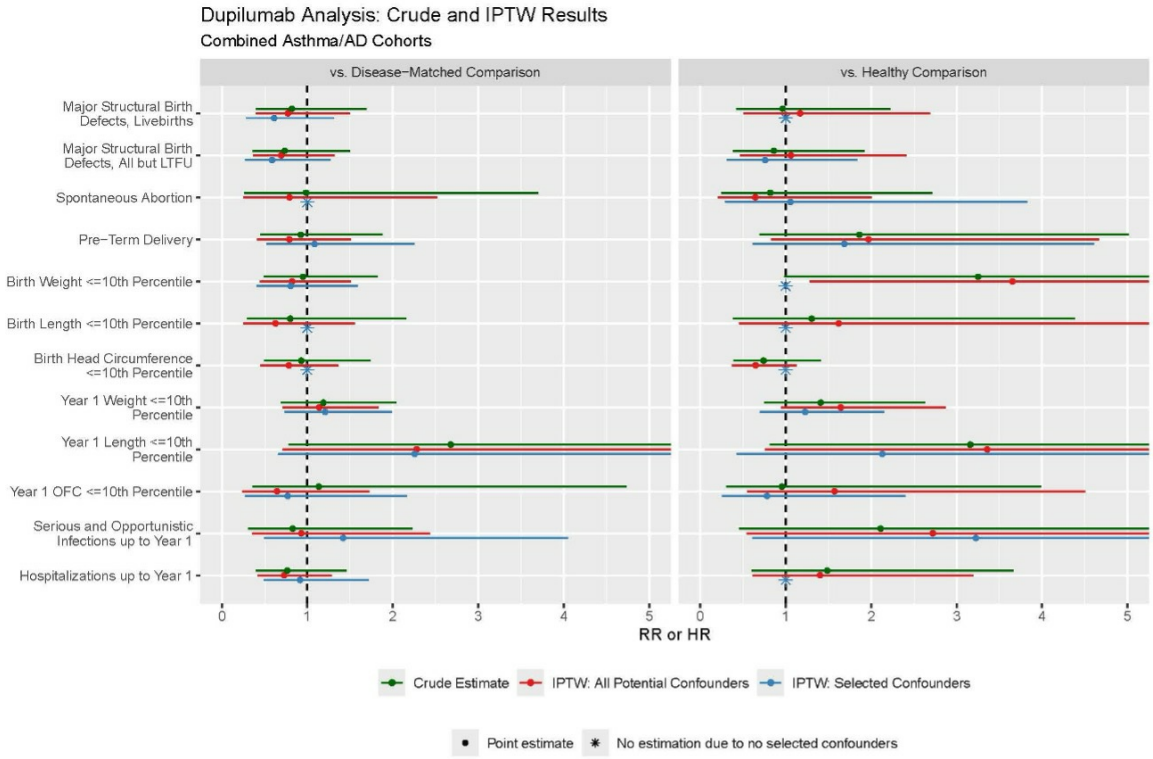
Materials and Methods
A prospective study was conducted by the Organization of Teratology Information Services (OTIS) Research Center between 2018 and 2025. Pregnant women in the U.S. or Canada were enrolled in a dupilumab-exposed group, a disease-matched group that was not exposed to dupilumab, or a non-diseased unexposed group. Outcomes included major birth defects, spontaneous abortion, preterm delivery, pre- and postnatal infant growth, and serious or opportunistic infections or hospitalizations in the child's first year of life. Data were collected from multiple telephone interviews on maternal demographics, pregnancy and medical history, and any exposures to prescription and over-the-counter medications, vaccines, and recreational substances throughout pregnancy. Medical records from the pregnant woman and her infant's health care providers as well as the delivery hospital were obtained and abstracted. Classification of major birth defects was performed by an expert in teratology. Inverse probability of treatment weighted (IPTW) risk or hazard ratios (RRs or HRs) and their 95% confidence intervals (CIs) were calculated including all potential confounders and secondarily using only selected confounders. Primary comparisons were made between the dupilumab-exposed group and the disease-matched group for each outcome, and secondary comparisons were made to the non-diseased group.

Results
A total of 539 pregnant participants enrolled in the study. Of these, 238 were in the dupilumab-exposed group (95 with atopic dermatitis alone; 143 with asthma with or without atopic dermatitis), 175 were in the disease-matched group (33 with atopic dermatitis alone; 142 with asthma with or without atopic dermatitis) and 126 were in the non-diseased group. A total of 14.1% were lost to follow-up. In group comparisons including all potential confounders, the weighted RR for major structural birth defects among liveborn infants was 0.77 (95% CI 0.40, 1.50) in dupilumab-exposed vs disease-matched, and 1.17 (95% CI 0.51, 2.69) vs non-diseased. In the atopic dermatitis alone subset, the weighted RR in dupilumab-exposed vs disease-matched was 0.90 (95% CI 0.10, 8,04),

and 0.66 (95% CI 0.22, 2.01) vs non-diseased. Moreover, there was no evidence of a pattern of birth defects in the dupilumab-exposed group. For spontaneous abortion, the weighted HR was 0.79 (95% CI 0.25, 2.52) for dupilumab-exposed vs disease-matched, and 0.64 (95% CI 0.21, 2.01) vs non-diseased. In the atopic dermatitis alone subset, the HR was not estimated for the primary comparison due to no events in the disease-matched group, and was 0.60 (95% CI 0.16, 2.24) in dupilumab-exposed vs non-diseased. For preterm delivery in the overall cohort, the weighted HR was 0.79 (95% CI 0.41, 1.51) for dupilumab-exposed vs disease-matched, and 1.97 (95% CI 0.83, 4.67) vs non-diseased. In the atopic dermatitis alone subset, the HR was not estimated for the primary comparison due to no events in the disease-matched group, and was 2.28 (95% CI 0.82, 6.35) in dupilumab exposed vs non-diseased. As shown in the figure, there were no significant differences between groups for infant growth, serious or opportunistic infections or hospitalizations with the exception of infants ≤10th centile on birth weight in the dupilumab-exposed vs non-diseased groups.

Conclusion

The findings of this registry were consistent with the limited previous literature and did not suggest an increased risk with dupilumab use in pregnancy for the outcomes studied.



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Abstract N°: 120

Efficacy and safety of Telikibart, a novel anti-IL-4Rα monoclonal antibody, for moderate-to-severe atopic dermatitis: 52-week outcomes and prespecified subgroup analyses from a randomized, placebo-controlled phase III trial

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Introduction
Telikibart (GR1802) is a fully human monoclonal antibody that targets the interleukin-4 receptor alpha (IL-4Rα) subunit with high affinity and potent capability of inhibiting IL-4/IL-13 signaling pathway to suppress Th2-driven inflammation. Its Fc region has been engineered with triple mutations (L234F/L235E/P331S) to eliminate antibody-dependent cell-mediated cytotoxicity, leading to a favorable safety profile. A previous phase II trial has preliminarily demonstrated promising efficacy of telikibart in moderate-to-severe atopic dermatitis. Here, we report the results of a randomized, placebo-controlled, phase III trial (NCT06216392) to evaluate the 52-week efficacy and safety of Telikibart in a larger adult cohort, with prespecified subgroup analyses to assess consistency of therapeutic effects.

Materials and Methods
Eligible patients with moderate to severe atopic dermatitis were randomized 2:1 to receive either telikibart 300 mg (600 mg on day 1) or placebo every 2 weeks during the 16-week induction period. Subsequently, all participants received telikibart 300 mg every 2 weeks until week 52 in the maintenance period (placebo group received telikibart 600 mg at the first dose). Coprimary endpoints were the proportions of patients achieving a ≥75% improvement in Eczema Area and Severity Index (EASI-75) and an Investigator's Global Assessment (IGA) score of 0 or 1 with a ≥ 2-point reduction from baseline at week 16.

Results
Between January 2024 and August 2025, a total of 450 patients were randomized to receive either telikibart

(n=299) or placebo (n=151). At week 16, the proportion of patients achieving an EASI-75 response was significantly higher in the telikibart group than in the placebo group (69.6% vs. 22.5%; difference, 47.1% [95% CI, 38.62-55.50]; P <0.0001; Figure 1A). A higher proportion of IGA 0/1 with a ≥ 2-point reduction from baseline was also observed in the telikibart group (33.1% vs. 6.6%; difference, 26.5% [95% CI, 19.86-33.15]; P <0.0001; Figure 1B). Consistently, telikibart yielded higher rates of EASI-90, ≥4-point reduction in weekly average daily Peak Pruritus Numerical Rating Scale (PP-NRS), as well as greater least squares (LS) mean improvements in Dermatology Life Quality Index (DLQI) versus placebo (all P <0.0001; Figure 1C-E). At week 52, EASI-75 was achieved in 94.3% of patients who continued telikibart treatment and 95.9% of those switched from placebo to telikibart. Corresponding the proportion of IGA 0/1 with a ≥ 2-point reduction from baseline were 65.4% and 58.5%, respectively. 76.0% and 76.7% of patients in the two groups achieved a ≥4-point reduction in the weekly average of the daily PP-NRS score, respectively. The consistency of treatment effects was further supported by subgroup analyses, which showed higher EASI-75 response rates with telikibart versus placebo across all prespecified subgroups at Week 16 (all P <0.01), including patients with prior exposure to IL-4Rα inhibitors and immunosuppressants. During the doubleblind period, treatment-emergent adverse events (TEAEs) were reported in 64.5% of the telikibart group and 57.6% of the placebo group. Overall, 82.2% of patients who received at least one dose of Telikibart experienced TEAEs during the study, the majority of which were graded as Grade 1-2 according to the CTCAE 5.0.

Conclusion

Telikibart demonstrated promising efficacy in patients with moderate to severe atopic dermatitis at week 16 with significant improvement observed across all prespecified subgroups. Efficacy were consistent throughout 52-week treatment. The safety profile was mild and tolerable.

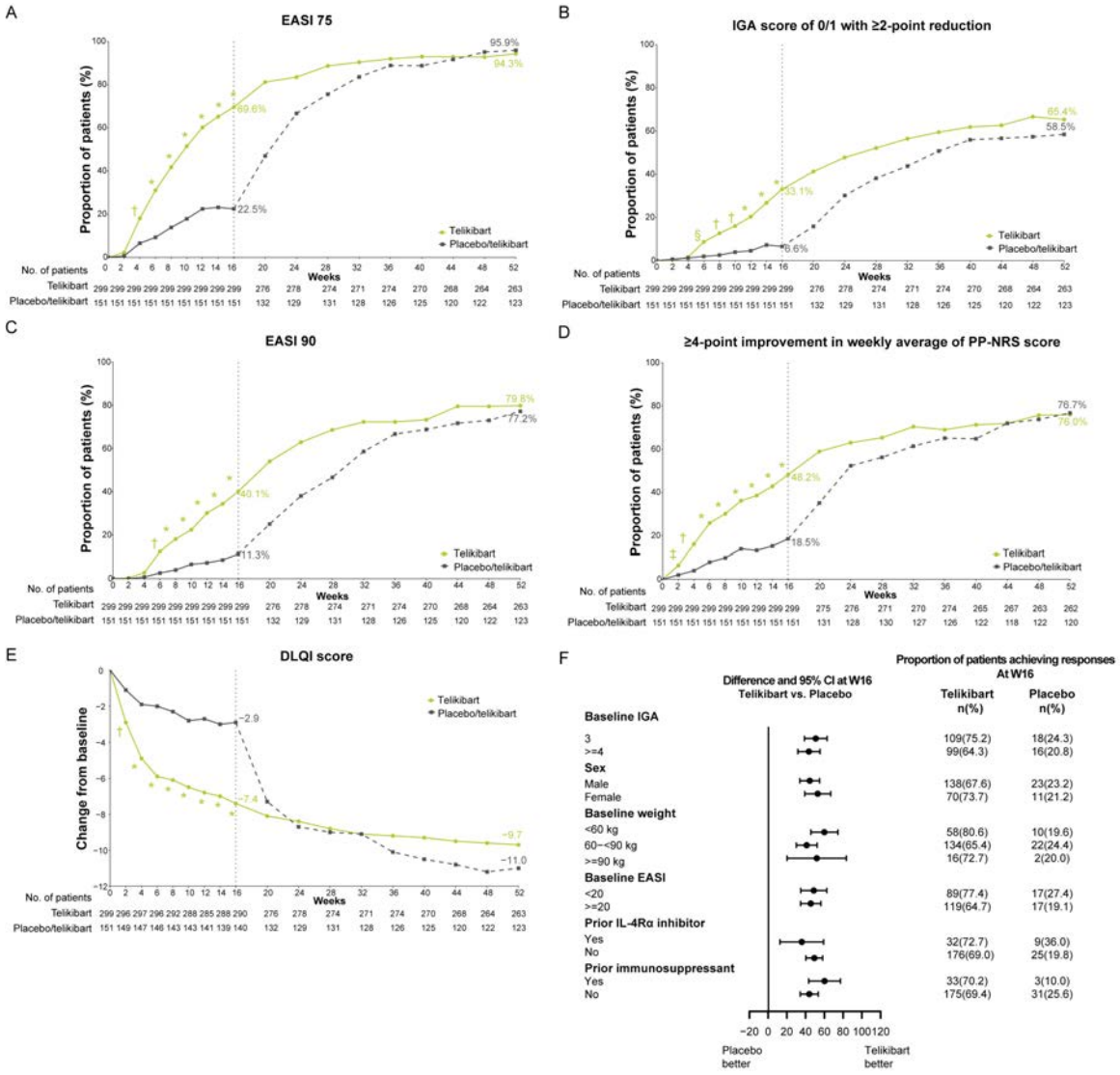


Figure 1 Efficacy of telikibart versus placebo over 52 weeks. Proportions of patients achieving (A) EASI-75 response, (B) IGA score of 0/1 with a ≥2-point reduction, (C) EASI-90 response, and (D) ≥4-

point improvement in weekly average of PP-NRS score. (E) Changes from baseline in DLQI scores, presented as LS mean for Weeks 0-16 and mean for Weeks 20-52. (F) Prespecified subgroup analyses. *p <0.0001, †p <0.001, §p <0.01, ‡p <0.05 vs. placebo.

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Abstract N°: 125

Results from the 2025 British National Teledermatology Standards Audit

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Introduction
Teledermatology has become a vital tool in enhancing access to dermatology services. The aim of the british national audit was to assess compliance with the 2024 British Association of Dermatologists (BAD) Teledermatology Standards: evaluating pathway performance, response time, image acquisition and quality of clinical history and response.

Materials and Methods
In September 2025, BAD members from the United Kingdom (UK) were invited to submit data on either 50 consecutive departmental teledermatology cases or 20 individual cases on both the urgent suspected skin cancer (USSC) or advice and guidance (A&G) pathways. Mann-Whitney test was used for group comparisons.

Results
2,436 cases from 55 UK centres across the UK were submitted: 929 on A&G and 1,507 on USSC referrals.
Median response time was significantly shorter for the USSC pathway (A&G 9 days, USSC 5 days, U = 522,682, p< .001).
The most common source of images was in GP setting for the A&G (651 (71%)), and hospital setting for USSC pathway 772 (51.2%). USSC pathway showed superior image quality scores (U = 371,523.5, p < .001). Images taken in secondary care community hubs achieved the highest image quality and fastest turnaround times. Hospital-acquired photos followed in image quality but showed some delayed clinician response to referral. Only 3.5% of images were unusable.
Clinical history was generally good; however, frailty scores were only documented in 26.8% of referrals, no reporting of bleeding altering medications in 21.8% or implantable devices in 32.1% of cases.
Overall, 4.4% were confirmed as melanoma, melanoma in situ, or squamous cell carcinoma (1.8% A&G, 6.1% USSC).
The median time for diagnosing melanoma/melanoma in situ via A&G was 9 days (range 0-162, n=9) vs. 3 days

via USSC (range 2-39, n=45); the difference was not significant.

Conclusion

The first national audit of teledermatology services provides an important benchmark and preliminary assessment. Improvement is needed in history documentation and standardising A&G response times to adhere to national guidance.

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Abstract N°: 128

Hypogammaglobulinemia, Late-Onset Neutropenia and Infection After Rituximab in Pemphigus, with Divergent Desmoglein Antibody and Immunoglobulin Kinetics: A Retrospective Cohort Study

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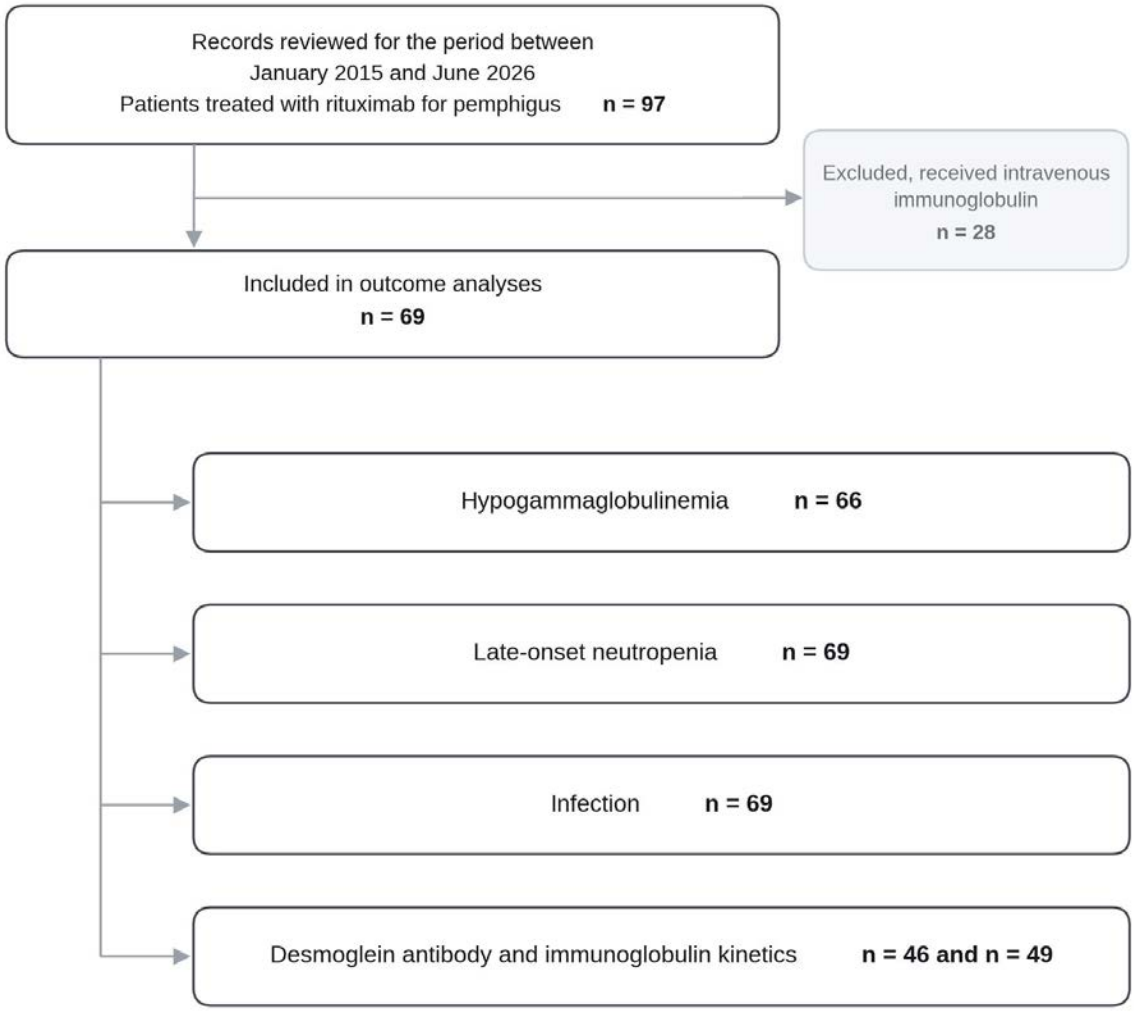
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Introduction

Pemphigus is a rare autoimmune blistering disease treated first-line with rituximab. Reduction of B lymphocytes lowers pathogenic desmoglein antibodies but may also suppress the synthesis of protective immunoglobulin, leading to hypogammaglobulinemia, and late-onset neutropenia is another uncommon adverse effect, both of which may increase infection risk. Most safety data derive from lymphoma, rheumatoid arthritis and vasculitis cohorts. In pemphigus, where cycles are repeated less often, the frequency of hypogammaglobulinemia and late-onset neutropenia, the baseline markers of risk, and whether desmoglein antibody titers and total immunoglobulin fall together have not been defined; we therefore conducted a single-center retrospective cohort study of pemphigus patients treated with rituximab to assess hypogammaglobulinemia, late-onset neutropenia and infection during rituximab treatment, the baseline predictors of hypogammaglobulinemia, and whether desmoglein antibody titers and total immunoglobulin fall together.

Materials and Methods

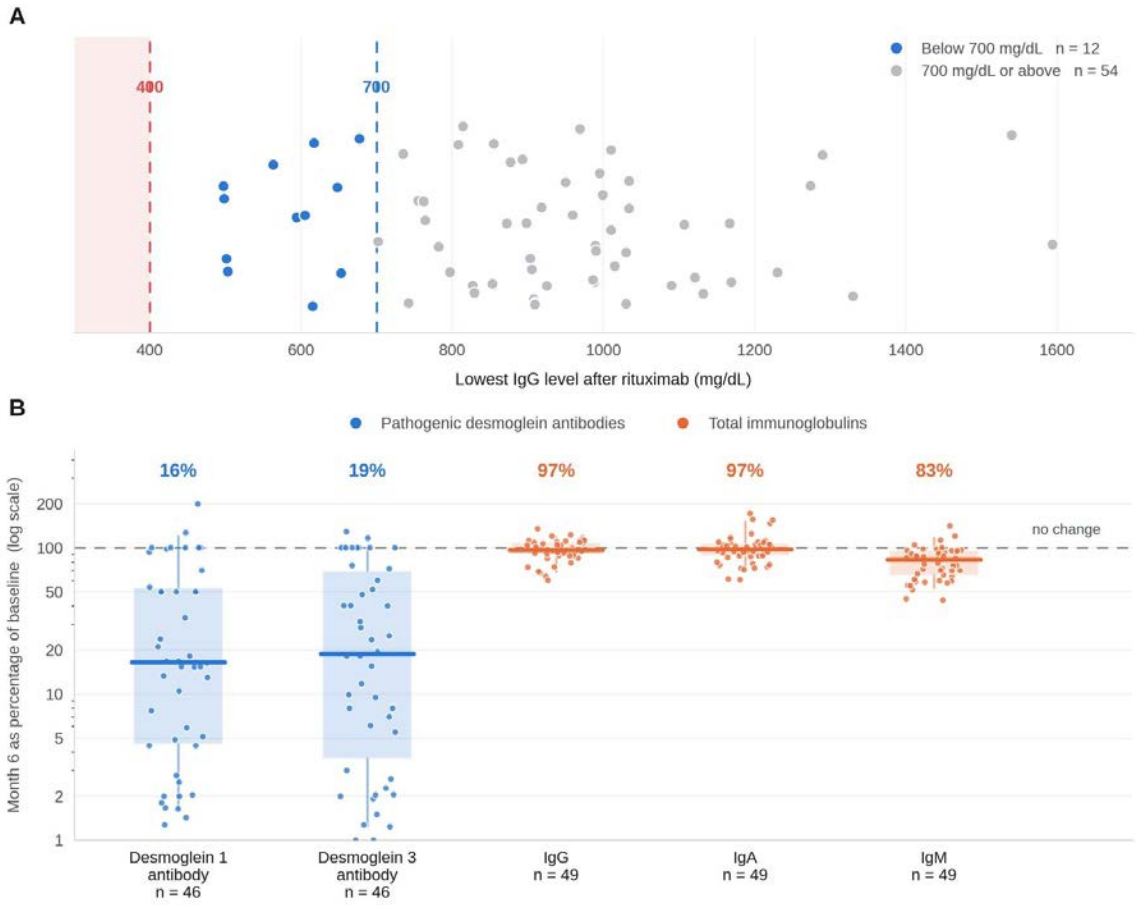
Single-center retrospective cohort study of 97 patients given rituximab for pemphigus between January 2015 and June 2026. IgG, IgA and IgM levels, absolute neutrophil count, desmoglein antibody titers and the methylprednisolone dose were recorded before each cycle and at months 3 and 6. Hypogammaglobulinemia was defined as an IgG level below 700 mg/dL at any measurement after rituximab, the pretreatment value being used only as a predictor, and severe hypogammaglobulinemia as a level below 400 mg/dL. Late-onset neutropenia was defined as a neutrophil count below 1.5x10^3/uL at least four weeks after the last infusion. Patients receiving intravenous immunoglobulin were excluded, leaving 69 (Figure 1).



Flow of the patients through the study.

Results

Of the 97 patients, 60 were women and 37 men, the mean age was 59.1 years, 87 had pemphigus vulgaris and 10 foliaceus, and the median number of cycles was 1 (1-6). Post-treatment IgG could be assessed in 66 patients. Hypogammaglobulinemia occurred in 12 patients (18%, 95% CI 11-29), the lowest value was 497 mg/dL and no patient developed severe hypogammaglobulinemia (Figure 2A). Among the 51 patients whose baseline IgG was 700 mg/dL or above, 5 (10%) developed new-onset hypogammaglobulinemia and baseline IgG discriminated them comparably (AUC 0.83 vs 0.90). The cumulative number of cycles was not associated with IgG levels (rho=-0.11, p=0.37). Median age was higher and median baseline IgG and IgM were lower in patients who developed hypogammaglobulinemia, whereas baseline IgA was similar. Areas under the curve were 0.90 for IgG (cut-off 800 mg/dL), 0.83 for IgM (60 mg/dL) and 0.71 for age (60 years). Baseline IgG and IgM retained significance after false discovery rate correction. Late-onset neutropenia was not detected in any of the 97 patients and the lowest count was 1.68x10^3/uL. Infection occurred in 5/69 patients (7%) and severe infection in 2/69 (3%), both pneumonia and one with hypogammaglobulinemia. Infection occurred in 3/12 patients with hypogammaglobulinemia (25%) and in 2/54 without (4%), a risk difference of 21 percentage points (exact odds ratio 8.2, 95% CI 0.8-111.7). Six months after induction, desmoglein 1 and desmoglein 3 antibody titers had fallen to 16% and 19% of baseline whereas IgG and IgA remained at 97%, with the most pronounced decline seen in IgM (83%, Figure 2B). In the 41 patients with both measurements the ratio to baseline was lower for desmoglein antibodies than for total immunoglobulin ($p<0.001$), and this ratio was unrelated to hypogammaglobulinemia and to the IgG ratio.



A, lowest IgG level after rituximab in each patient. B, month 6 desmoglein antibody titers and total immunoglobulin levels as a percentage of baseline.

Conclusion

Hypogammaglobulinemia remained mild, severe hypogammaglobulinemia and late-onset neutropenia were not observed and severe infection was rare. The fall in desmoglein antibodies was not accompanied by a fall in total immunoglobulin, so the two are not interchangeable measures. Advanced age and low baseline IgG and IgM levels emerged as candidate markers of risk, which supports measuring immunoglobulin levels before treatment.

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Abstract N°: 136

Daxdilimab in Moderate-to-Severe Discoid Lupus Erythematous: Efficacy and Safety Results from a Phase 2, Randomised, Placebo-controlled Trial

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Introduction

Discoid lupus erythematosus (DLE) is the most prevalent form of chronic cutaneous lupus erythematosus (CCLE). It is clinically characterised by erythematous scaly lesions occurring on the scalp, face, and ears that may progress to permanent scarring, alopecia and facial disfigurement, negatively impacting quality of life [1]. Plasmacytoid dendritic cells (pDCs) are increased in the lesional skin of patients with cutaneous lupus erythematosus and are key mediators of disease immunopathogenesis through their association with type I interferon biology [2]. Daxdilimab is a human IgG1 monoclonal antibody targeting immunoglobulin-like transcript 7 (ILT7), a cell-surface protein exclusively expressed on pDCs. Binding of daxdilimab to ILT7 results in targeted reduction in the number of pDCs in the tissue and blood [2]. Here, we report results from a phase 2 trial (NCT05591222) evaluating the efficacy and safety of two doses of daxdilimab in patients with DLE.

Materials and Methods

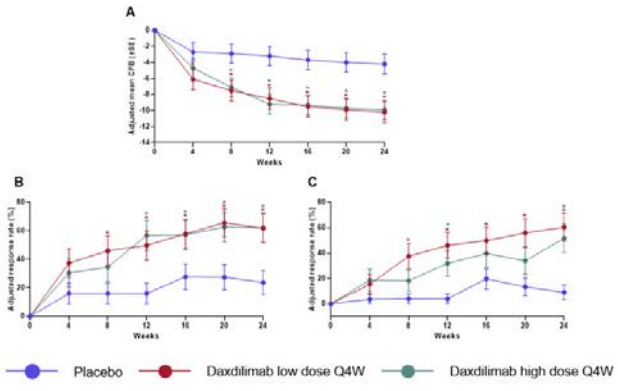
A multicentre, randomised, double-blind, placebo-controlled, parallel-group study enrolled patients aged 18–75 years with chronic, moderate-to-severe, treatment-refractory DLE for ≥ 6 months with active disease at baseline (Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity [CLASI-A] ≥ 8) and without systemic features. Patients were randomised 1:1:1 to receive low dose (LD) daxdilimab, high dose (HD) daxdilimab, or placebo for 24 weeks, with dosing every 4 weeks from Day 1 through Week 20. The primary efficacy endpoint was mean change in CLASI-A score from baseline to Week 24. Secondary endpoints included the proportion of patients achieving ≥ 50% reduction in CLASI-A score (CLASI-50) and those achieving a score of 0 or 1 on the Cutaneous Lupus Activity Investigator's Global Assessment (CLA-IGA) scale (CLA-IGA 0/1) at Week 24. Safety was assessed up to Week 24. Primary endpoint was analysed in the full analysis set (all randomised patients who received any dose of trial treatment) using a mixed model for repeated measures.

Results

Overall, 72 patients were randomised to LD daxdilimab (n = 24), HD daxdilimab (n = 23), or placebo (n = 25). Baseline demographics and disease characteristics were generally comparable across treatment groups (mean ± SD age, 48.8 ± 12.0 years; 69.4% female). At baseline, the overall mean ± SD CLASI-A and CLA-IGA scores were 15.2 ± 6.30 and 3.1 ± 0.63, respectively. Both doses of daxdilimab met the primary and secondary endpoints. Significant reductions in CLASI-A vs placebo were observed at Week 24, with treatment response evident as early as Week 4. At Week 24, the LS mean difference in change from baseline in CLASI-A vs placebo was –6.0 (90% confidence interval [CI]: –8.7, –3.2; P = 0.0005) for LD daxdilimab and –5.7 (90% CI: –8.5, –2.9; P = 0.0012) for HD daxdilimab (Figure 1A). At Week 24, adjusted response rates (standard error [SE]) were significantly increased for

CLASI-50 (Placebo: 23.7% [8.5]; LD: 61.7% [10.1], P = 0.0037; HD: 62.1% [10.3], P = 0.0044) and CLA-IGA 0/1 (Placebo: 8.9% [5.6]; LD: 60.3% [11.0], P < 0.0001; HD: 51.6% [11.2], P = 0.0007) compared with placebo (Figures 1B and 1C). Daxdilimab was well tolerated, with no serious adverse events or death reported. Overall treatment related adverse events occurred in 58.3%, 56.5% and 60.0% of patients in the LD, HD, and placebo groups, respectively. One patient in the HD group discontinued the study due to arthralgia (Table 1).

Figure 1. (A) LS mean change from baseline in CLASI-A score through Week 24[a], (B) Patients achieving CLASI-50 response through Week 24[b] and (C) Patients achieving CLA-IGA 0/1 response through Week 24[c]



*P<0.05 vs Placebo (two sided).
[a]Results are from MMRM analysis with treatment, visit, visit by treatment interaction, and baseline CLASI-A score included in the model; [b]Results are from logistic regression analysis with treatment and baseline CLASI-A score included in the model; [c]Results are from logistic regression analysis with treatment, baseline CLASI-A (<13, ≥13) and baseline CLA-IGA score included in the model. The CLA-IGA scale ranges from 0 (clear) to 4 (severe).
CFB, change from baseline; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity; CLASI-50, ≥ 50% reduction in CLASI-A score; CLA-IGA, Cutaneous Lupus Activity Investigator's Global Assessment; CLA-IGA 0/1, patients achieving 0 (clear) or 1 (almost clear) on the CLA-IGA scale; LS, least squares; MMRM, mixed model for repeated measures; Q4W, every 4 weeks; SE, standard error.

Table 1: Summary of the key safety findings

n (%)*	Placebo (N = 25)	Daxdilimab LD (N = 24)	Daxdilimab HD (N = 23)	Total Daxdilimab (N = 47)
At least one event	15 (60.0)	14 (58.3)	13 (56.5)	27 (57.4)
At least one investigational product related event	3 (12.0)	6 (25.0)	5 (21.7)	11 (23.4)
At least one event of ≥ grade 3 severity[a,b]	0 (0.0)	0 (0.0)	1 (4.3)	1 (2.1)
At least one event leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	1 (4.3)	1 (2.1)
Most Frequent TEAEs (≥5%)				
Headache	0 (0.0)	4 (16.7)	1 (4.3)	5 (10.6)
Cough	0 (0.0)	2 (8.3)	1 (4.3)	3 (6.4)
Diarrhoea	0 (0.0)	0 (0.0)	3 (13.0)	3 (6.4)
Upper respiratory tract infection	1 (4.0)	3 (12.5)	0 (0.0)	3 (6.4)
Injection site pain	0 (0.0)	2 (8.3)	0 (0.0)	2 (4.3)
Nausea	0 (0.0)	0 (0.0)	2 (8.7)	2 (4.3)
Nasopharyngitis	4 (16.0)	1 (4.2)	0 (0.0)	1 (2.1)
Seasonal allergy	2 (8.0)	1 (4.2)	0 (0.0)	1 (2.1)
Hypertension	2 (8.0)	0 (0.0)	1 (4.3)	1 (2.1)
Influenza	2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Participants are counted once for each category regardless of the number of events.
[a]Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal.
[b]Grade 3, non-serious severe event of arthralgia was reported in 1 patient (4.3%) in daxdilimab HD group on Day 42 after the patient had received two doses of study treatment. The patient did not receive specific treatment for the event and was referred to a rheumatologist. The investigator considered the event related to daxdilimab, and study treatment was permanently discontinued.
HD, high dose daxdilimab; LD, low dose daxdilimab; TEAEs, treatment emergent adverse events.

Conclusion

Daxdilimab demonstrated significant improvement in the primary endpoint of CLASI-A and consistent efficacy across secondary endpoints, with a favourable safety profile in patients with moderate-to-severe DLE. These findings support the role of pDCs in disease pathogenesis of DLE and the potential of targeting this pathway.

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Abstract N°: 145

Efficacy and Safety of Brepocitinib in Cutaneous Sarcoidosis: Results from the Phase II Portion of the Randomized, Double-Blind, Placebo-Controlled BEACON Trial

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Introduction

Cutaneous sarcoidosis (CS) is a highly morbid, granulomatous skin disease with no approved therapies. Current treatment relies on off-label antimalarials, conventional disease-modifying antirheumatic drugs (DMARDs), and other immunomodulatory therapies, often in combination with systemic glucocorticoids; however, complete and durable disease control remains uncommon. Several key cytokines implicated in CS, including IFNγ, IL-6, and IL-12, signal through tyrosine kinase 2 (TYK2) and/or Janus kinase 1 (JAK1), providing a mechanistic rationale for selective TYK2/JAK1 inhibition.

Materials and Methods

BEACON (NCT06978725) is an ongoing, global, multicenter, randomized, double-blind, placebo-controlled Phase 2/3 trial. This prespecified interim analysis evaluated the 16-week, dose-ranging, Phase 2 portion of the study. Adults with biopsy-proven active CS (Cutaneous Sarcoidosis Activity and Morphology Instrument-Activity [CSAMI-A] ≥ 10; range 0–165) were randomized 3:2:2 to once-daily oral brepocitinib 45 mg, brepocitinib 15 mg, or placebo. Stable background antimalarial, tetracycline, and/or DMARD therapy was permitted. Participants receiving oral corticosteroids at baseline underwent a protocol-mandated taper, with complete discontinuation required by Week 8. The primary efficacy endpoint was change from baseline in CSAMI-A at Week 16. Additional endpoints included achievement of Cutaneous Sarcoidosis Activity – Investigator Global Assessment (CSA-IGA) "Clear" or "Almost Clear" with ≥ 2-category improvement, CSAMI-A response (≥ 50% improvement), ≥ 10-point CSAMI-A reduction, achievement of CSAMI-A < 5, patient-reported outcomes (PROs), and safety.

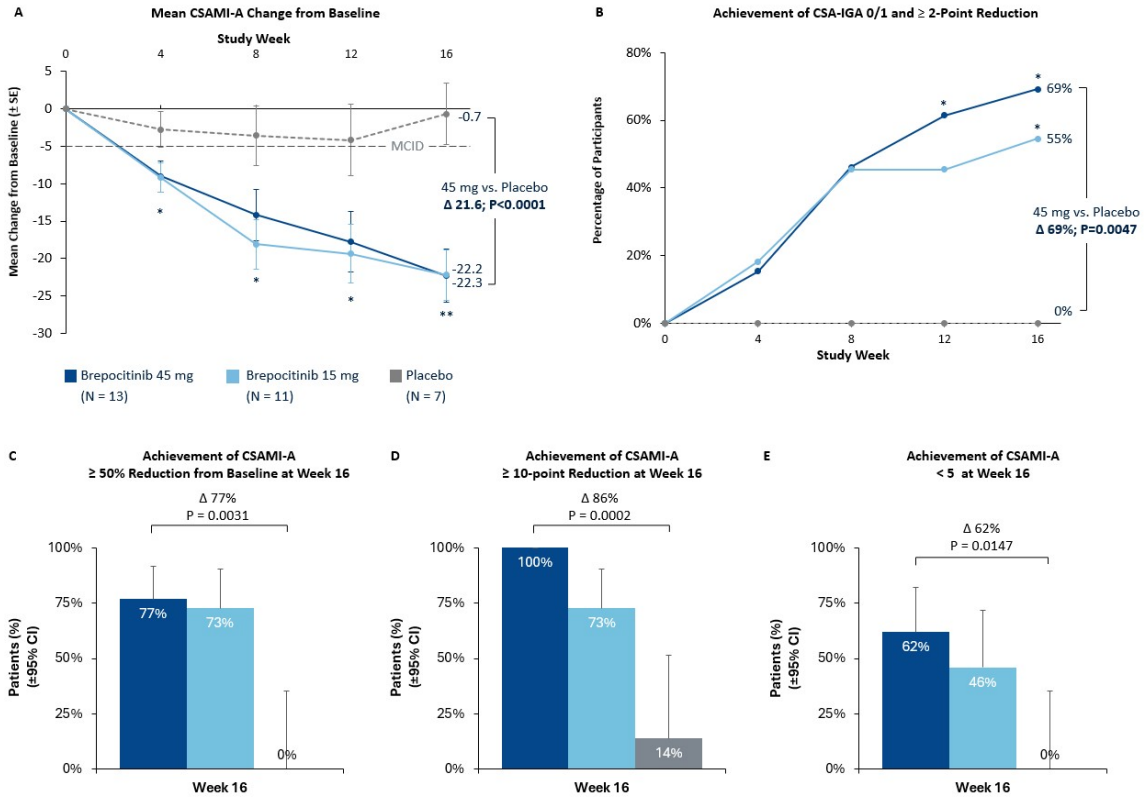


Figure 1. Cutaneous Sarcoidosis Disease Activity and Remission-Oriented Outcomes with Brepocitinib. (A) Mean change from baseline in CSAMI-A and (B) achievement of CSA-IGA 0/1 with a ≥ 2-category improvement over time. Proportion of participants achieving (C) ≥ 50% reduction in CSAMI-A (D) ≥ 10-point reduction in CSAMI-A and (E) CSAMI-A < 5 at Week 16. *P < 0.05; **P < 0.0001.
Abbreviations: CSAMI-A, Cutaneous Sarcoidosis Activity and Morphology Instrument-Activity; MCID, Minimal Clinically Important Difference; SE, standard error; CSA-IGA, Cutaneous Sarcoidosis Activity Investigator Global Assessment

Results

Thirty-one participants (58% female; mean age 53.3 years) were randomized to brepocitinib 45 mg (n=13), brepocitinib 15 mg (n=11), or placebo (n=7). Despite prior and/or concomitant use of off-label systemic therapies, participants had longstanding and highly active skin disease at baseline (mean [SD] disease duration, 8.1 [7.5] years; CSAMI-A, 33.6 [17.6]; CSA-IGA, 3.0 [0.6]). Overall, 52% were receiving at least one CS-directed systemic therapy at baseline. Both brepocitinib doses produced rapid improvements in CS disease activity, with treatment effects evident by Week 4 and increasing through Week 16 (Figure 1A). At Week 16, mean CSAMI-A reduction was 22.3 points with brepocitinib 45 mg versus 0.7 with placebo ($p < 0.0001$) (Figure 1A). Across responder-based and remission-oriented endpoints, efficacy consistently favored brepocitinib 45 mg, supporting a dose-dependent treatment effect. Compared with placebo, brepocitinib 45 mg resulted in higher rates of CSA-IGA "Clear" or "Almost Clear" (69% vs 0%; p=0.0047), CSAMI-A response (77% vs 0%; p=0.0031), ≥ 10-point CSAMI-A reduction (100% vs 14%; p=0.0002), and CSAMI-A < 5 (62% vs 0%; p=0.0147) (Figure 1B-E). Clinical improvements were accompanied by significant benefits in skin-related quality of life (Figure 2A-C). Brepocitinib was well tolerated; no deaths or serious adverse events occurred, and there were no malignancies, major adverse cardiovascular events, venous thromboembolic events, or viral reactivations (Table 1).

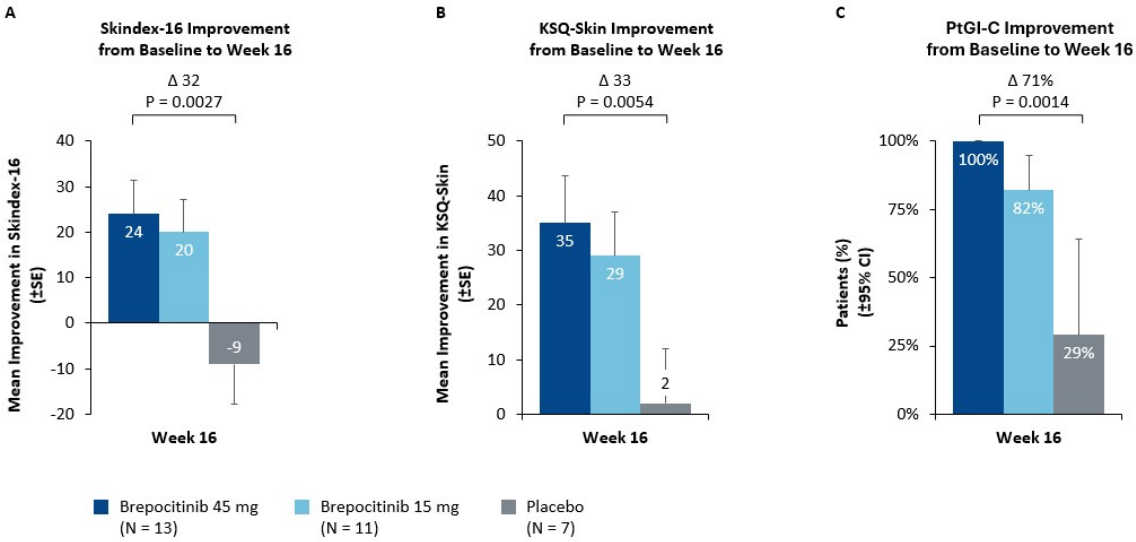


Figure 2. Improvements in Skin-Related Quality of Life and Patient Perception of Disease Activity with Brepocitinib Mean improvement from baseline to Week 16 in Skindex-16 (A) and KSQ Skin (B). Proportion of participants reporting improvement on Patient Global Impression of Change at Week 16 (C). Abbreviations: KSQ, King's Sarcoidosis Questionnaire; PtGI-C, Patient Global Impression of Change; SE, standard error; CI, confidence interval

Conclusion

In the Phase 2, dose-ranging portion of the BEACON trial, brepocitinib 45 mg produced rapid, dose-dependent, and clinically meaningful improvements in CS disease activity, with corresponding improvements in skin-related quality of life and an acceptable safety profile. As the first positive, randomized, placebo-controlled trial to demonstrate efficacy of a targeted therapy in CS, these findings support selective TYK2/JAK1 inhibition as a promising therapeutic strategy and provide a strong rationale for evaluation of brepocitinib 45 mg in the ongoing Phase 3 portion of the BEACON trial.

References: [1] Noe MH, et al. JAMA Dermatol. 2020;156(1):98-99.

Table 1. Summary of Safety Events During the 16-Week BEACON Trial

	Brepocitinib, 45 mg (N=13)	Brepocitinib, 15 mg (N=11)	Placebo (N=7)
	number of patients (percent)		
Adverse events (AEs)	12 (92%)	9 (82%)	6 (86%)
Death	0	0	0
Serious adverse events (SAEs)	0	0	0
AEs leading to treatment discontinuation	1 (8%)	1 (9%)	1 (14%)
AEs leading to study discontinuation	0	0	0
Adverse events of special interest (AESI)[1]			
Creatine kinase (CK) elevation[2]	1 (8%)	0	0
Anemia[3]	1 (8%)	0	0
Viral reactivation	0	0	0
Malignancy	0	0	0
Major adverse cardiovascular event	0	0	0
Venous thromboembolism	0	0	0
Liver enzyme elevation	0	0	0

[1]Both AESIs were moderate in severity.
[2]CK elevation was asymptomatic, did not result in study drug discontinuation, and improved with continued treatment.
[3]Anemia represented worsening of baseline anemia and improved following study drug discontinuation.

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Abstract N°: 146

Golidocitinib Plus Brentuximab Vedotin for Brentuximab Vedotin-Refractory/Relapsed Advanced Folliculotropic Mycosis Fungoides and Sézary Syndrome: A Retrospective Cohort Study

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Introduction
Advanced folliculotropic mycosis fungoides (FMF) and Sézary syndrome (SS) represent aggressive subtypes of cutaneous T-cell lymphoma (CTCL) with limited therapeutic options after brentuximab vedotin (BV) failure. Aberrant JAK/STAT signaling contributes to CTCL pathogenesis, and golidocitinib, a selective JAK1 inhibitor, has shown activity in relapsed/refractory T-cell lymphomas. This study aimed to evaluate the efficacy and safety of golidocitinib plus brentuximab vedotin (Go-BV) in BV-refractory/relapsed advanced FMF and SS.

Materials and Methods
We conducted a retrospective cohort study of 10 patients with histologically confirmed FMF (n=7) or SS (n=3), all with stage ≥IIB disease and prior BV failure. BV refractoriness/relapse was defined as progressive disease after ≥2 cycles, failure to achieve response after ≥3 cycles, or relapse within 12 months after discontinuation. Patients received golidocitinib (150 mg daily, adjustable to every other day) in combination with BV (1.8 mg/kg every 3 weeks). Primary endpoint was objective response rate (ORR). Secondary endpoints included ORR at 4 months (ORR4), progression-free survival (PFS), duration of response (DoR), time to response (TTR), pruritus numeric rating scale (NRS), and treatment-related adverse events (TRAEs).

Results
At a median follow-up of 36.7 weeks, the ORR was 70% (7/10), including 1 complete response and 6 partial responses. ORR4 was 40%. Response rates were higher in SS compared with FMF (100% [3/3] vs 57.1% [4/7]). Organ-specific responses were observed in skin (70%), lymph nodes (40%), and blood (100% in SS patients). Median TTR was 6.6 weeks, median DoR was 15.6 weeks, and median PFS was 20.6 weeks. Patients with low skin CD30 expression (≤5%) demonstrated higher ORR than those with higher expression (100% vs 40%，P=0.058) and significantly longer PFS (38.6 vs 10.1 weeks; HR=9.97, P=0.013). Pruritus improved markedly, with median NRS decreasing from 8 to 0.5 (P=0.006).A total of 15 treatment-emergent adverse events occurred in 8 patients. The most common were cytomegalovirus infection (n=4, including 1 grade ≥3 event), peripheral neuropathy (n=3), leukopenia, anemia, thrombocytopenia, and hypertriglyceridemia. No treatment-related deaths occurred.

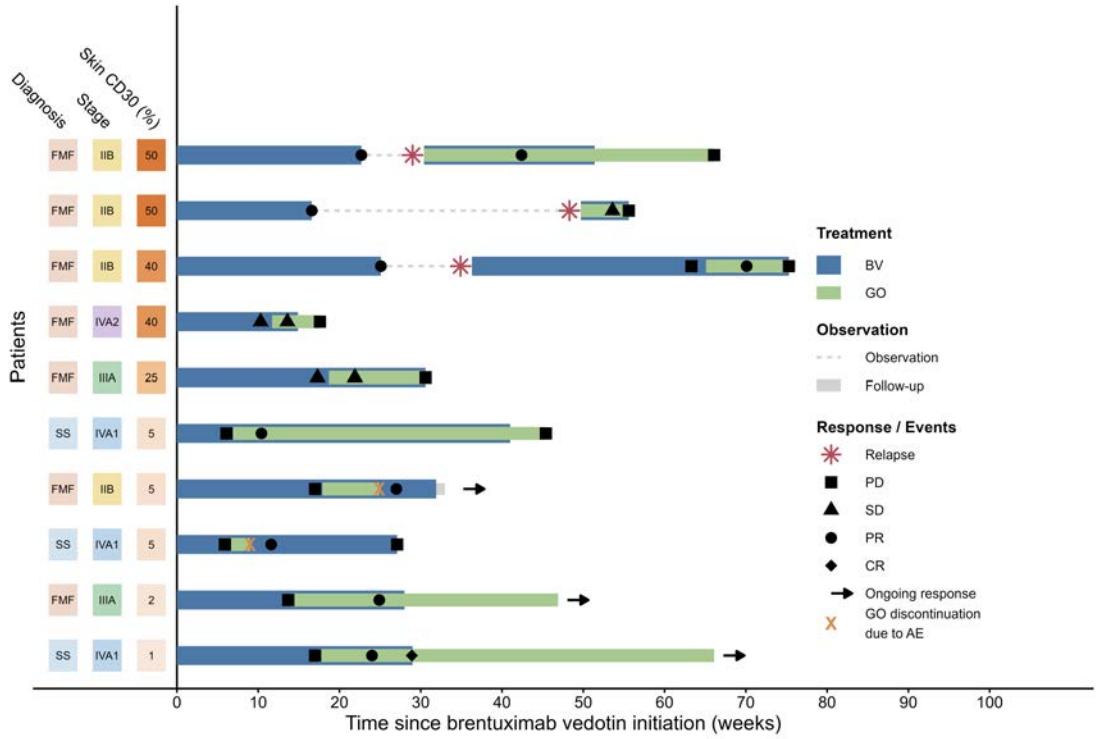


Fig 1. Responses to golidocitinib plus brentuximab vedotin and response duration since brentuximab vedotin initiation. FMF, folliculotropic mycosis fungoides; SS, Sézary syndrome; BV, brentuximab vedotin; Go, golidocitinib; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; AE, adverse event.

Conclusion

The combination of golidocitinib and BV demonstrated encouraging clinical activity with manageable toxicity in patients with BV-refractory/relapsed advanced FMF and SS, achieving a high ORR and pruritus improvement. Responses appeared more pronounced in patients with low CD30 expression, suggesting a potential role of JAK1 inhibition in overcoming BV resistance. These findings support further prospective studies to validate Go-BV as a therapeutic strategy in advanced CTCL.

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Abstract N°: 155

JAKPPPOT: a feasibility trial assessing upadacitinib in palmoplantar pustulosis

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Introduction
Background

Palmoplantar pustulosis (PPP) is a rare, disabling inflammatory skin disease with substantial unmet need: no therapies are currently licensed in the UK or Europe, and existing off-licence systemic and biologic options show only modest, inconsistent efficacy. Janus kinase inhibitors (JAKi) are mechanistically attractive, targeting multiple inflammatory pathways implicated in PPP, but prospective trial data are lacking. Regulatory safety warnings around cardiovascular and malignancy risk with JAKi, combined with the high smoking prevalence and cardiometabolic comorbidity seen in PPP, may limit their use and complicate future trial recruitment.

Objective

To determine the feasibility of a definitive randomised controlled trial (RCT) of JAKi therapy in PPP and generate an exploratory estimate of treatment effect to inform future sample size calculations.

Materials and Methods
This single-centre, open-label, assessor-blinded feasibility trial (JAKPPPOT) enrolled adults (≥18 years) with dermatologist-confirmed moderate-to-severe PPP at a UK specialist dermatology centre. Participants received upadacitinib 30 mg once daily for 8 weeks (15 mg in higher-risk individuals, per MHRA guidance). Prespecified feasibility endpoints were recruitment (consent rate), adherence (≥80% proportion of days covered), and acceptability (5-point Likert scale: 'completely unacceptable' to 'completely acceptable'). Traffic-light progression criteria (green/amber/red) were prespecified for each domain, requiring ≥40% recruitment, ≥80% adherence (PDC), and ≥80% acceptability to support progression to a definitive trial.

Secondary outcomes included the Palmoplantar Pustulosis Area and Severity Index (PP-PASI), Investigator Global Assessment (PPP-IGA), Dermatology Life Quality Index (DLQI), and safety. Individual patient-level historic placebo data from APRICOT, a closely matched UK multicentre RCT of the IL-1 antagonist anakinra in PPP, provided an exploratory comparator.

Results

Of 67 individuals approached, 28 (41.8%) consented and 20 (71.4%) started treatment (mean age 46.0 years; 85% female; 90% smoking history). Adherence ≥80% was achieved by 19/20 (95%; mean 95.7%, SD 9.7), and 18/19 (94.7%) rated treatment as 'acceptable/completely acceptable'. All pre-specified feasibility progression criteria were therefore met.

Mean PP-PASI fell from 20.3 (SD 10.6) to 4.6 (SD 4.5) at week 8 with upadacitinib, versus 18.0 (10.4) to 15.4 (10.1) with historic placebo (baseline-adjusted difference −12.3, 95% CI −15.8 to −8.9; Figure 1). PP-PASI75 was achieved by 65.0% vs 3.2%, and PPP-IGA clear/almost clear by 45.0% vs 7.1%. DLQI improved from 15.8 (8.2) to 4.6 (5.3) with upadacitinib, versus 13.9 (7.2) to 10.1 (7.1) with placebo (adjusted difference −6.8, 95% CI −9.9 to −3.7). Sensitivity analyses using inverse-probability-of-treatment weighting to adjust for baseline differences between cohorts produced consistent treatment-effect estimates, supporting the robustness of these findings. Following treatment discontinuation, mean PP-PASI rose to 12.2 (SD 8.5) by week 12, suggesting continued therapy may be needed to sustain response.

Upadacitinib was well tolerated: the most common adverse events were headache, acne and upper respiratory tract infection; one unrelated serious adverse event occurred (retinal detachment) and one participant discontinued treatment (weight gain). No participant required rescue topical corticosteroids during the 8-week treatment period, versus 6% with historic placebo.

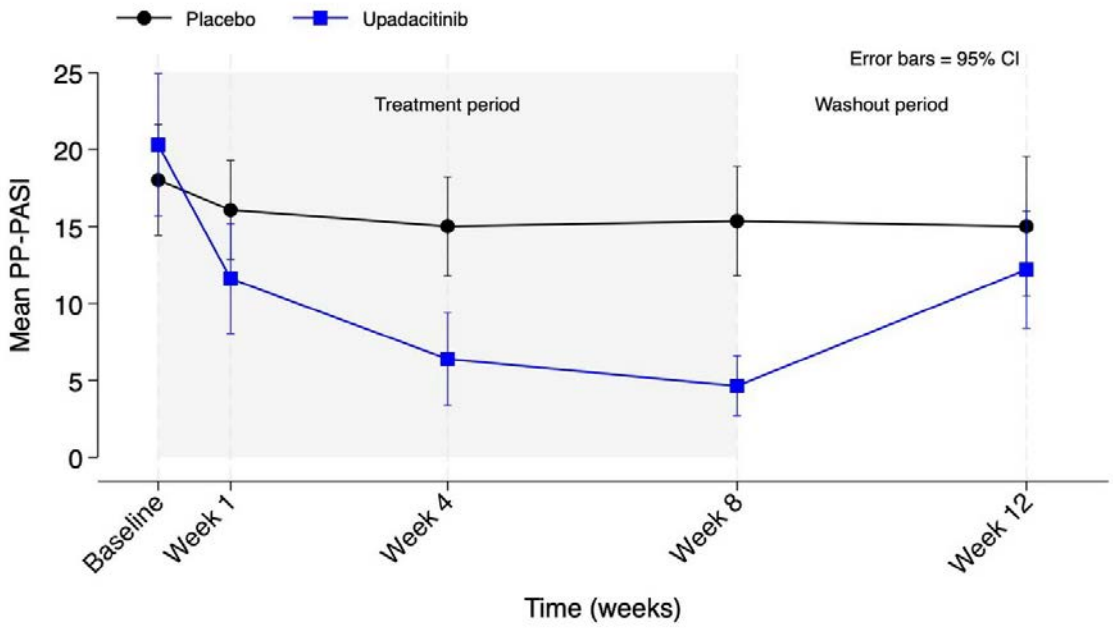


Figure 1: Mean PP-PASI over time in the JAKPPPOT and historic placebo cohorts. PP-PASI: Palmoplantar Pustulosis Psoriasis Area and Severity Index

Conclusion

A definitive trial of JAKi therapy in PPP is feasible, and upadacitinib produced a substantial improvement in disease severity and quality of life relative to historic placebo, albeit in a non-randomised comparison. These findings support progression to a multicentre, active-comparator RCT and position JAK inhibition as a promising strategy to address the considerable unmet therapeutic need in PPP.

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Abstract N°: 159

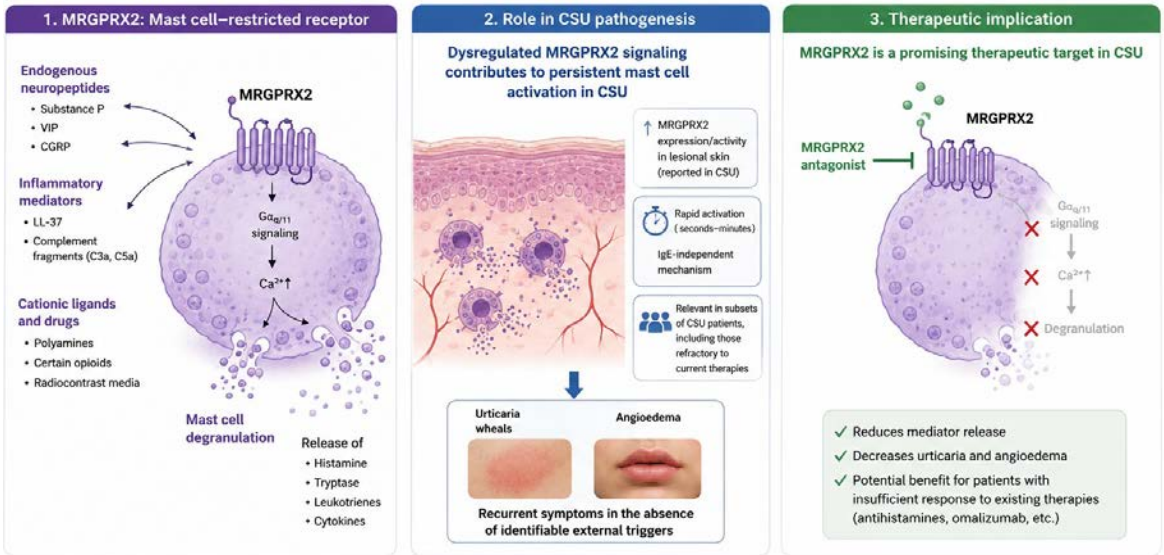
Rapid Dose-Related Responses to an Oral MRGPRX2 Partial Inverse Agonist in Chronic Spontaneous Urticaria

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Introduction

Mas-related G protein-coupled receptor X2 (MRGPRX2) is a mast cell–restricted receptor that mediates IgE-independent mast cell activation in response to diverse endogenous neuropeptides, inflammatory mediators, and cationic ligands. Increasing evidence implicates MRGPRX2 in the pathogenesis of chronic spontaneous urticaria (CSU), a mast cell–driven disease characterized by recurrent wheals and/or angioedema in the absence of an identifiable external trigger. MRGPRX2 expression and activity may be enhanced in lesional skin and can promote rapid mast cell degranulation and release of histamine, proteases, and other inflammatory mediators, providing a mechanistic pathway complementary to the classical FcεRI–IgE axis. These observations suggest that dysregulated MRGPRX2 signaling may contribute to persistent mast cell activation in subsets of patients with CSU, including those inadequately controlled by existing therapies. Accordingly, pharmacological inhibition of MRGPRX2 represents a promising mechanism-based therapeutic strategy for CSU.



MRGPRX2 mediates rapid, IgE-independent mast cell activation in response to diverse endogenous and exogenous ligands. Dysregulated MRGPRX2 signaling may contribute to persistent mast cell degranulation and the development of wheals and angioedema in CSU. Targeting MRGPRX2 therefore represents a promising mechanism-based therapeutic strategy for patients with CSU.

Materials and Methods

Patients were enrolled in an ongoing 28-day multiple-ascending-dose study. Each dose cohort included eight patients using a 6 active + 2 placebo allocation. Oral once-daily doses of 50 mg and 125 mg were evaluated. Clinical activity was assessed using the 7-day Urticaria Activity Score (UAS7), 7-day Itch Severity Score (ISS7), 7-

day Hives Severity Score (HSS7), Dermatology Life Quality Index (DLQI), Urticaria Control Test (UCT), and Peak Pruritus Numerical Rating Scale (PP-NRS). Safety was additionally informed by a completed Phase 1a single-ascending-dose study.

Results

At 50 mg once daily, active-treated patients showed improvement across disease activity, itch, hives, quality of life, and disease control within 7-14 days. By Day 14, UAS7 decreased by 50-70% in most patients; individual reductions in ISS7, HSS7, and DLQI ranged from 30-56%, 40-63%, and 40-68%, respectively. PP-NRS also decreased, while UCT improved, consistent with better overall urticaria control. Preliminary results at 125 mg once daily showed a faster and greater response. By Day 7, UAS7 had decreased by 58-88% and ISS7 by 50-86% in evaluable active-treated patients. The completed Phase 1a study evaluated single oral doses up to 1000 mg without observed adverse events, and no adverse events have been observed to date in the ongoing multiple-dose study.

Conclusion

Oral MRGPRX2 inverse agonism produced rapid, multi-domain clinical improvement in CSU, with preliminary evidence of an earlier and deeper response at 125 mg than at 50 mg once daily. Together with the favourable early safety profile, these findings provide emerging clinical evidence supporting MRGPRX2 as a therapeutic target in CSU and warrant further evaluation in larger controlled studies.

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Abstract N°: 161

Efficacy and safety of ritlecitinib in patients with nonsegmental vitiligo (NSV): results from the Tranquillo 2 Part Ia and Tranquillo Phase 3 randomized, double-blind, placebo-controlled, multicenter clinical trials

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Introduction

NSV is an autoimmune skin disease characterized by pigment loss due to melanocyte destruction. In a Phase 2b study of NSV treatment, ritlecitinib, an oral JAK3/TEC family kinase inhibitor, was efficacious & well-tolerated over 48 wk. The Phase 3 Tranquillo 2 (NCT06072183) Part Ia & Tranquillo (NCT05583526) studies evaluated the efficacy, safety, & tolerability of ritlecitinib 100 mg (R100) & ritlecitinib 50 mg (R50) vs placebo (PBO) (Tranquillo 2 Part Ia) and R50 vs PBO (Tranquillo) in patients with NSV over 52 wk.

Materials and Methods

Patients aged ≥18 y (Tranquillo 2) or ≥12 y (Tranquillo) with a diagnosis of active or stable NSV for ≥3 mo, body surface area (BSA) involvement 4%-60%, facial BSA ≥0.5%, Facial Vitiligo Area Scoring Index (F-VASI) ≥0.5 & Total (T)-VASI ≥3 were included. In Tranquillo 2 Part Ia, patients were randomized 3:1:1 to receive R100, R50, or PBO for 52 wk; in Tranquillo, patients were randomized 2:1 to receive R50 or PBO for 52 wk. In both trials,

coprimary endpoints were the proportion of patients achieving ≥75% improvement in F-VASI from baseline (F-VASI75) & T-VASI50 at Wk 52 in the R100 group (Tranquillo 2) or the R50 group (Tranquillo) vs PBO. Key secondary endpoints included % change from baseline (%CFB) in F-VASI/T-VASI at Wk 24/36/52, the proportion of patients achieving F-VASI75/T-VASI50 at Wk 24/36 & T-VASI75 at Wk 52, & Patient Global Impression of Severity–Face/Vitiligo (PGIS–F/V) response at Wk 52. In Tranquillo 2, R50 vs PBO comparisons were not alpha-controlled. Safety was monitored throughout both studies.

Results

The overall Tranquillo program included 2174 patients with NSV across 271 sites worldwide. In Tranquillo 2 Part Ia, 622, 206, & 208 patients received R100, R50, and PBO, respectively. Mean age was 47.5 years. A significantly higher proportion of patients receiving R100 vs PBO achieved F-VASI75 (21.9% vs 2.4%; *P*<0.000001) & T-VASI50 (13.0% vs 2.4%; *P*<0.000001) at Wk 52 (**Fig 1A**). %CFB in F-VASI at Wk 24/36/52 & F-VASI75 response at Wk 24/36 were significantly greater for R100 vs PBO (*P*<0.05; **Table**). %CFB in T-VASI at Wk 24/36/52 & T-VASI50 response at Wk 36 were significantly greater for the R100 group vs PBO (*P*<0.05; **Table**). PGIS−F/V responses at Wk 52 for R100 vs PBO, respectively, were 42.9% vs 18.3% & 32.3% vs 17.3% (*P*<0.05). In the R100, R50, vs PBO groups, treatment-emergent adverse events (TEAEs) occurred in 67.7%, 60.0%, & 62.0% of patients; treatment-emergent serious AEs (TESAEs) occurred in 3.4%, 2.9%, & 3.4% of patients. The most common TEAEs across R100, R50, & PBO were upper respiratory tract infection (URTI, 8.9%, 6.8%, 3.4%), nasopharyngitis (7.9%, 6.3%, 7.3%) & headache (4.0%, 3.4%, 5.4%). In Tranquillo, 401 patients (26 adolescents) received R50 & 202 (13 adolescents) received PBO. Mean age was 44.8 years. A significantly higher proportion of patients receiving R50 vs PBO achieved F-VASI75 (12.5% vs 2.5%; *P*<0.000001) & T-VASI50 (9.0% vs 2.0%; *P*=0.000073) at Wk 52 (**Fig 1B**). %CFB in F-VASI and %CFB in T-VASI for R50 were significantly greater vs PBO as early as Wk 24 and continued through Wk 52 (*P*<0.05; **Table**). PGIS−F/V responses at Wk 52 for the R50 vs PBO groups, respectively, were 35.0% vs 12.2% & 23.3% vs 16.6% (*P*<0.05). In the R50 & PBO groups, TEAEs occurred in 81.0% & 77.1% of patients (TESAEs: 2.0% & 2.5% of patients). The most common TEAEs across R50 & PBO were URTI (14.0% & 10.9%), blood creatinine phosphokinase increased (11.0% & 8.0%) & nasopharyngitis (10.5% & 9.5%).

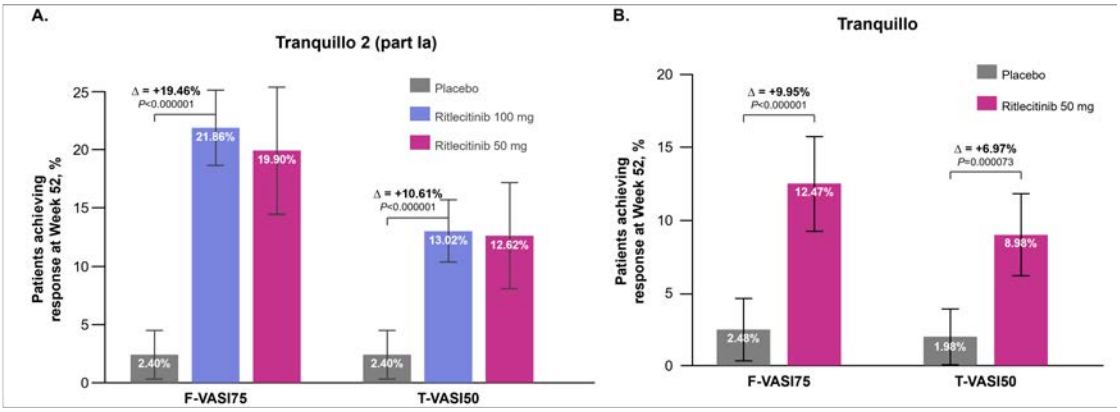


Figure 1. Coprimary endpoints (F-VASI75 & T-VASI50 at Week 52) for the (A) Tranquillo 2 Part Ia and (B) Tranquillo clinical trials. In Tranquillo 2 Part Ia, type I error for the ritlecitinib 100-mg group vs placebo was controlled at 2-sided alpha of 0.05; the comparison between ritlecitinib 50-mg dose vs placebo was not alpha controlled. In Tranquillo, type I error for the ritlecitinib 50-mg group vs placebo was controlled at 2-sided alpha of 0.05. Response rate was calculated as the number of responders / the total number of patients (%). Whiskers show 95% CI. Δ is defined as the difference between either ritlecitinib 100 mg vs placebo (Tranquillo 2 Part Ia) or ritlecitinib 50 mg once-daily vs placebo (Tranquillo). F-VASI75, ≥75% improvement on the Facial Vitiligo Area Scoring Index from baseline; T-VASI50, ≥50% improvement on the Total Vitiligo Area Scoring Index from baseline.

Conclusion

In 2 Phase 3 NSV studies comprising 2174 patients across 271 sites globally, oral ritlecitinib achieved statistically significant and clinically meaningful improvements compared with PBO in facial and total-body repigmentation

across primary and key secondary efficacy endpoints. Improvements were observed by Wk 24 and increased through Wk 52. The safety profile was consistent with those in prior ritlecitinib studies, with no new signals identified.

	Tranquillo 2 Part 1a			Tranquillo		
	Ritlecitinib 100 mg N=622	Placebo N=208	*P* Value	Ritlecitinib 50 mg N=401	Placebo N=202	*P* Value
F-VASI at Week 24, LSM (SE), %CFB	-19.44 (1.34)	-6.16 (2.04)	<0.05	-17.49 (1.50)	-6.83 (1.96)	<0.05
T-VASI at Week 24, LSM (SE), %CFB	-10.16 (0.75)	-4.25 (1.14)	<0.05	-6.51 (1.00)	-1.59 (1.31)	<0.05
F-VASI at Week 36, LSM (SE), %CFB	-27.52 (1.56)	-7.86 (2.39)	<0.05	-23.22 (1.73)	-6.24 (2.26)	<0.05
T-VASI at Week 36, LSM (SE), %CFB	-15.32 (0.92)	-3.46 (1.40)	<0.05	-10.00 (1.26)	0.15 (1.65)	<0.05
F-VASI at Week 52, LSM (SE), %CFB	-34.63 (1.72)	-8.97 (2.63)	<0.05	-29.77 (2.14)	-4.14 (2.79)	<0.05
T-VASI at Week 52, LSM (SE), %CFB	-21.04 (1.13)	-3.67 (1.73)	<0.05	-13.83 (1.53)	1.74 (2.00)	<0.05
F-VASI75 at Week 24, n (%)*	43 (6.91)	1 (0.48)	<0.05	18 (4.49)	1 (0.50)	<0.05
T-VASI50 at Week 24, n (%)*	22 (3.54)	3 (1.44)	>0.05	13 (3.24)	1 (0.50)	<0.05
F-VASI75 at Week 36, n (%)*	80 (12.86)	3 (1.44)	<0.05	33 (8.23)	3 (1.49)	<0.05
T-VASI50 at Week 36, n (%)*	36 (5.79)	2 (0.96)	<0.05	22 (5.49)	2 (0.99)	<0.05
T-VASI75 at Week 52, n (%)*	17 (2.73)	3 (1.44)	>0.05	12 (2.99)	1 (0.50)	<0.05
PGIS−F at Week 52, n (%)†	265 (42.88)	38 (18.27)	<0.05	140 (35.00)	24 (12.18)	<0.05
PGIS−V at Week 52, n (%)†	200 (32.26)	36 (17.31)	<0.05	93 (23.25)	33 (16.58)	<0.05

Table. Key secondary endpoints for the Tranquillo and Tranquillo 2 Part Ia clinical trials. Type I error was controlled at 2-sided alpha of 0.05. In Tranquillo 2 Part Ia, the ritlecitinib 50-mg dose was not part of the prespecified, alpha-controlled statistical testing hierarchy. CFB, change from baseline; F-VASI, Facial Vitiligo Area Scoring Index; F-VASI75, ≥75% improvement on F-VASI from baseline; LSM, least-squares mean; PGIS–F, Patient Global Impression of Severity–Face; PGIS–V, Patient Global Impression of Severity–Vitiligo; SE, standard error; T-VASI, Total Vitiligo Area Scoring Index; T-VASI50, ≥50% improvement in T-VASI from baseline; T-VASI75, ≥75% improvement in T-VASI from baseline. *Proportion of patients achieving F-VASI75, T-VASI50, or T-VASI75. †Proportion of patients achieving a ≥1-point improvement in facial/total body vitiligo in patients with mild, moderate, or severe facial/total body vitiligo at baseline, or ≥2-point improvement in patients with very severe facial/total body vitiligo at baseline.

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Abstract N°: 169

Efficacy and Safety of Zumilokibart (APG777), a Half-Life-Extended Anti-IL-13 Antibody, in Moderate-to-Severe Atopic Dermatitis: Primary Results From the Phase 2 APEX Part B Dose-Regimen-Finding Study

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Introduction
Zumilokibart (APG777) is a novel, half-life-extended, anti-IL-13 antibody that achieves early peak and sustained drug exposures, enabling extended dosing intervals with only 4 dosing days during induction and 2 or 4 dosing days per year during maintenance. In the phase 2 APEX Part A proof-of-concept study in adults with moderate-to-severe atopic dermatitis (AD), treatment with zumilokibart led to rapid improvements in skin signs and itch, with clinical responses maintained through Week 52 with both every-12- and every-24-week dosing. Here, primary 16-week results from the ongoing phase 2 APEX Part B dose-regimen-finding study (NCT06395948) are presented.

Materials and Methods
APEX Part B is a randomized, double-blinded, placebo-controlled, phase 2 study in adults with moderate-to-severe AD (EASI ≥16, vIGA-AD ≥3, and BSA ≥10%). Participants (N=346) were randomized 1:1:1:1 and received a low-, mid-, or high-dose zumilokibart regimen or placebo during the 16-week induction period. The mid-dose regimen was identical to the induction regimen evaluated in APEX Part A. The primary endpoint was the proportion of participants achieving ≥75% reduction from baseline in EASI (EASI-75) at Week 16. Secondary endpoints included percent change from baseline in EASI, vIGA-AD 0/1 with ≥2-point improvement from baseline, EASI-90, EASI-100, and ≥4-point improvement in Itch Numeric Rating Scale (I-NRS4). Missing data were imputed using Markov Chain Monte Carlo multiple imputation, combined with non-responder imputation for rescue medication use or treatment discontinuation due to lack of efficacy.

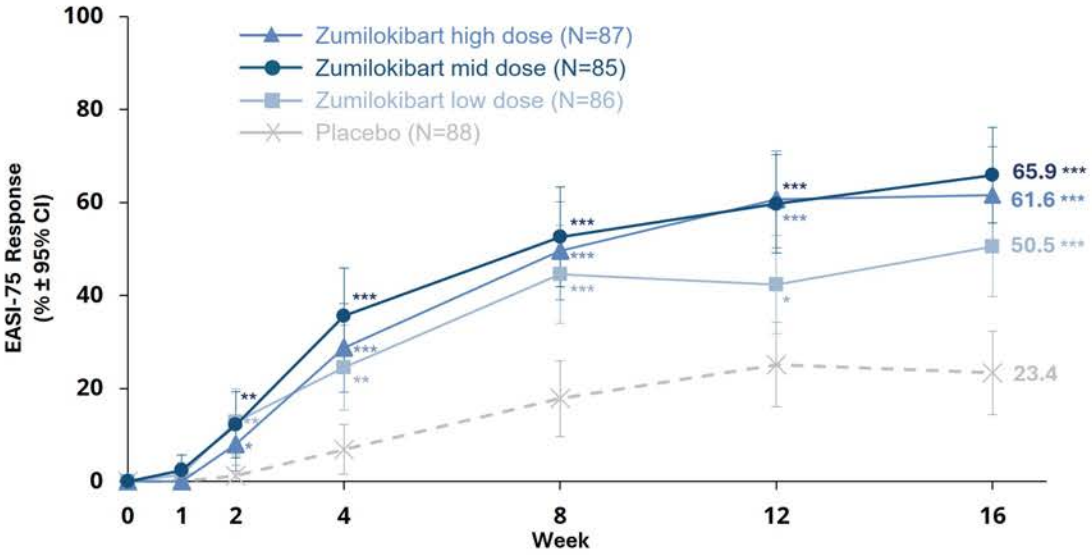
Results
All three zumilokibart dose regimens met the primary endpoint, with significantly greater EASI-75 response rates than placebo at Week 16 (Figure 1; 50.5% [low dose], 65.9% [mid dose], and 61.6% [high dose] vs 23.4% [placebo]; all $p<0.001$). Mid- and high-dose regimens demonstrated similar efficacy, whereas clinical activity was relatively lower with the low-dose regimen. Mid-dose and high-dose zumilokibart demonstrated significantly greater responses than placebo across secondary endpoints (Table 1). Improvements in skin lesions and itch were evident early, with the mid-dose zumilokibart regimen achieving significantly greater percent reductions versus placebo in EASI by Week 1 and I-NRS by Week 2. Overall adverse event rates were balanced across treatment arms through Week 16 (Table 2). Treatment-emergent adverse events (TEAEs) occurred in 67.0%, 75.6%, 60.0%, and 67.8% of patients receiving placebo and low-, mid-, and high-dose zumilokibart, respectively; corresponding rates of

serious TEAEs were 2.3%, 2.3%, 1.2%, and 3.4%. The most common TEAEs (≥5% in any treatment group) were nasopharyngitis, headache, noninfective conjunctivitis, upper respiratory tract infection, dermatitis atopic, and urinary tract infection.

Conclusion

Zumilokibart treatment led to rapid and statistically significant improvements in skin lesions and itch through Week 16, including achievement of complete skin clearance in a subset of patients, with a safety profile generally consistent with approved therapies targeting IL-13 or IL-4/IL-13. These findings support selection of the mid-dose regimen for phase 3 development and further evaluation of every 12- and 24-week maintenance dosing in adults with moderate-to-severe AD.

Figure 1. Primary Endpoint of Proportion of Participants Achieving EASI-75 at Week 16



*p<0.05, **p<0.01, ***p<0.001 (vs placebo). CI = confidence interval. EASI-75 = ≥75% reduction from baseline in Eczema Area and Severity Index. Missing data were imputed using Markov Chain Monte Carlo multiple imputation, combined with non-responder imputation (NRI) for participants who initiated any rescue medication or discontinued study treatment due to lack of efficacy (not for other reasons).

Table 1. Efficacy Outcome Measures at Week 16

Efficacy at Week 16	Placebo (N=88)	Zumilokibart Low Dose (N=86)	Zumilokibart Mid Dose (N=85)	Zumilokibart High Dose (N=87)
Primary endpoint*				
EASI-75, %	23.4	50.5 *p<0.001*	65.9 *p<0.001*	61.6 *p<0.001*
Secondary endpoints				
EASI % change from baseline, LS mean	-34.9	-61.0 *p<0.001*	-70.6 *p<0.001*	-69.3 *p<0.001*
vIGA-AD 0/1, %	10.9	27.6 *p<0.01*	46.0 *p<0.001*	33.4 *p<0.001*
EASI-90, %	9.3	28.2 *p<0.01*	47.4 *p<0.001*	35.8 *p<0.001*
EASI-100†, %	3.4	10.5 *ns*	16.5 *p<0.01*	12.6 *p<0.05*
I-NRS4‡, %	13.9	35.7 *p<0.01*	50.5 *p<0.001*	43.4 *p<0.001*

p values are compared with placebo. *Multiplicity controlled with sequential testing across dose regimens (high dose to low dose).
EASI = Eczema Area and Severity Index. I-NRS4 = ≥4-point improvement in Itch Numeric Rating Scale. ns = not significant. vIGA-AD 0/1 = Validated Investigator Global Assessment for Atopic Dermatitis with ≥2-point improvement from baseline.
For EASI % change from baseline, data collected after the initiation of rescue medication use or study treatment discontinuation were set to missing; missing data were imputed using Markov Chain Monte Carlo multiple imputation (MCMC-MI) for inferential statistics.
For categorical variables, missing data were imputed using MCMC-MI, combined with non-responder imputation (NRI) for participants who initiated any rescue medication or discontinued study treatment due to lack of efficacy (not for other reasons).
†For EASI-100, missing data and data collected after initiation of rescue medication or study treatment discontinuation (including all reasons) were imputed using NRI.
‡For I-NRS4, N's reflect the number of participants with at least 4 points on the I-NRS at baseline (N=84, placebo; N=78, low dose; N=77 mid dose; N=77, high dose).

Table 2. Adverse Events through Week 16

Safety summary through Week 16, n (%)	Placebo (N=88)	Zumilokibart Low Dose (N=86)	Zumilokibart Mid Dose (N=85)	Zumilokibart High Dose (N=87)

≥1 adverse event	59 (67.0)	65 (75.6)	51 (60.0)	59 (67.8)
≥1 serious adverse event	2 (2.3)	2 (2.3)	1 (1.2)	3 (3.4)
Adverse events leading to discontinuation	2 (2.3)	1 (1.2)	2 (2.4)	3 (3.4)
Most common adverse events through Week 16 (≥5% in any treatment group)				
Nasopharyngitis	19 (21.6)	22 (25.6)	12 (14.1)	10 (11.5)
Headache	3 (3.4)	7 (8.1)	6 (7.1)	6 (6.9)
Noninfective conjunctivitis	0 (0.0)	4 (4.7)	5 (5.9)	10 (11.5)
Upper respiratory tract infection	3 (3.4)	5 (5.8)	6 (7.1)	5 (5.7)
Dermatitis atopic	5 (5.7)	7 (8.1)	2 (2.4)	5 (5.7)
Urinary tract infection	1 (1.1)	1 (1.2)	5 (5.9)	0 (0.0)

Treatment-emergent adverse events through week 16. Most common events listed by preferred term.

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Abstract N°: 208

Long-term efficacy and safety of ritlecitinib in patients with alopecia areata and ≥25% scalp hair loss by severity: results from the phase 3 long-term ALLEGRO-LT study through 5 years

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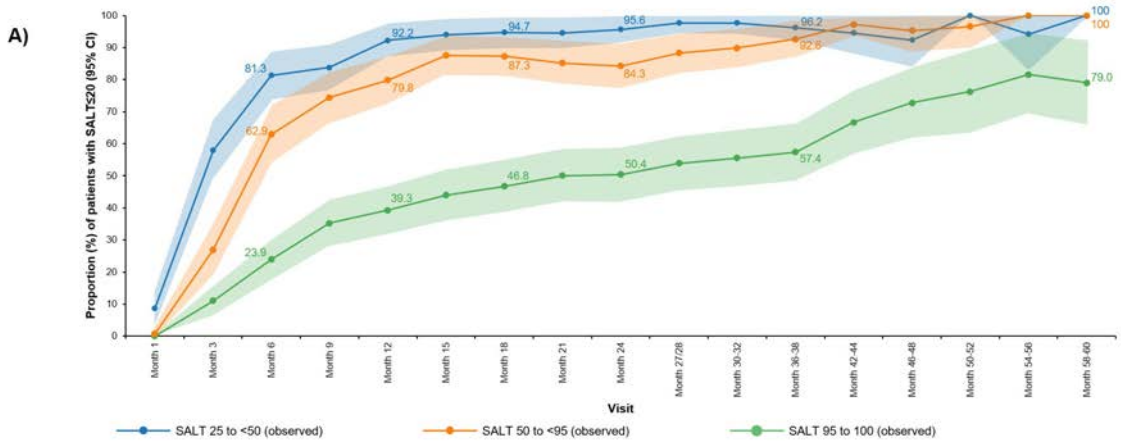
Introduction
The oral JAK3/TEC family kinase inhibitor ritlecitinib demonstrated efficacy and safety in patients aged ≥12 years with alopecia areata (AA) with ≥50% hair loss in the ALLEGRO phase 2b/3 and ALLEGRO-LT studies. ALLEGRO-LT is the only clinical trial among the approved treatments for severe AA to include patients with ≥25% scalp hair loss. This post hoc analysis of de novo patients from ALLEGRO-LT (end of study) evaluated the efficacy and safety of ritlecitinib up to 5 years in patients with AA and ≥25% scalp hair loss at baseline.

Materials and Methods
The open-label, multicenter, long-term ALLEGRO-LT study (NCT04006457) enrolled patients into 2 cohorts. This post hoc analysis only included patients in the de novo cohort who were aged ≥12 years with AA with ≥25% scalp hair loss at baseline and had no previous ritlecitinib treatment. De novo patients received an initial 4-week loading dose of ritlecitinib 200 mg once daily (QD) followed by ritlecitinib 50 mg QD (200/50 mg). Outcomes included the proportions of patients with Severity of Alopecia Tool (SALT) score ≤20 and SALT score ≤10 up to Months 58-60. Patients were stratified by SALT score at baseline: 25 to <50, 50 to <95, and 95 to 100. Observed and last observation carried forward (LOCF) data are reported.

Results
In ALLEGRO-LT, 447 patients received ritlecitinib in the de novo cohort. Of these, 26.4% (n=118), 28.9% (n=129), and 44.7% (n=200) had baseline SALT scores 25 to <50, 50 to <95, and 95 to 100**,** respectively. Patients with baseline SALT score ≥95 generally had longer mean duration of current AA episode (3.5 vs 2.5 years) and disease duration (10.8 vs 8.8 years) than patients with baseline SALT score <50. Observed SALT ≤20 responder rates generally increased and remained stable over time up to Months 36-38, reaching 96.2% in baseline SALT 25 to <50, 92.6% in baseline SALT 50 to <95, and 57.4% in baseline SALT 95-100 (**Figure 1A**). Observed rates fluctuated after Months 36-38, ranging from 92.3%-100.0% in baseline SALT 25 to <50, 95.2%-100.0% in SALT 50-<95, and 66.7%-81.6% in SALT 95-100, reflecting patient discontinuations for various reasons and decreasing patient numbers, which may limit data interpretability at later visits. LOCF response rates increased and remained stable

from Month 18-Months 58-60 in baseline SALT 25 to <50 (84.8%-87.3%) baseline SALT 50-<95 (76.0%-79.1%), and baseline SALT 95-100 (36.0%-39.0%) (**Figure 1B**). SALT≤10 response rates followed a similar trend across severity groups. The most frequently reported treatment-emergent adverse events were SARS-CoV-2 test positive (24.2%), headache (21.7%), and nasopharyngitis (14.1%). Safety events, including adverse events of special interest, were consistent with previously reported data.

Figure 1. Proportion of patients achieving SALT score ≤20 response by AA severity at baseline **A**) as Observed and **B**) LOCF. The de novo cohort of ALLEGRO-LT was treated with an initial 4-week loading dose of ritlecitinib 200 mg QD followed by ritlecitinib 50 mg QD (200/50 mg).



n/N	1	3	6	9	12	15	18	21	24	27/28	30-32	36-38	42-44	46-48	50-52	54-56	58-60
SALT 25 to <50 (observed)	10/116	62/107	87/107	88/105	95/103	93/99	89/94	86/91	87/91	85/87	83/85	76/79	52/55	36/36	22/22	16/17	15/15
SALT 25 to <50 (LOCF)	10/118	62/118	90/118	94/118	102/118	103/118	103/118	102/118	102/118	102/118	102/118	101/118	101/118	100/118	102/118	101/118	101/118
SALT 50 to <95 (observed)	1/129	34/126	78/124	87/117	91/114	98/112	98/110	92/108	91/108	90/102	88/98	88/95	69/71	40/42	28/29	23/23	20/20
SALT 50 to <95 (LOCF)	1/129	34/129	79/129	90/129	94/129	102/129	101/129	90/129	90/129	100/129	100/129	102/129	102/129	102/129	102/129	102/129	102/129
SALT 95 to 100 (observed)	0/193	21/190	45/188	62/176	66/168	69/157	72/154	73/146	69/137	70/130	70/126	70/122	62/93	48/66	32/42	31/38	30/38
SALT 95 to 100 (LOCF)	0/200	21/200	45/200	63/200	68/200	71/200	74/200	75/200	72/200	75/200	76/200	77/200	78/200	77/200	76/200	76/200	75/200

AA, alopecia areata; LOCF, last observation carried forward; QD, once-daily; SALT, Severity of Alopecia Tool.
Shaded areas represent 95% CIs.

Conclusion

Clinically meaningful SALT ≤20 and SALT ≤10 response rates were observed through the end of study in de novo patients receiving ritlecitinib 200/50 mg. Patients with baseline SALT 25-<50 and SALT 50-<95 had higher SALT response rates. The safety profile of ritlecitinib supports its long-term use in adults and adolescents with no new safety risks through 5 years.

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Abstract N°: 209

Efficacy and Safety of Upadacitinib in Adolescents and Adults for Treatment of Non-segmental Vitiligo at Week 76 and in Combination With NB-UVB Therapy

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Introduction

Non-segmental vitiligo (NSV) is a chronic immune-mediated disease characterized by skin depigmentation due to a loss of melanocytes. Upadacitinib (UPA) is an oral, once-daily, selective, and reversible small-molecule JAK inhibitor with demonstrated efficacy and safety in two phase 3 trials (Viti-Up) through 48 weeks (Passeron et al. *Lancet*. 2026:408:636-48). UPA has been approved by the European Medicines Agency and United Arab Emirates for treatment of NSV in adults and adolescents. Narrow-band ultraviolet B (NB-UVB) phototherapy has been shown to be effective in producing clinically meaningful repigmentation for patients with NSV, with greater improvements seen when combined with an adjunctive therapy (Seneschal et al. *JEADV.* 2023;37[11]:2185-95). Here we extend findings from Viti-Up through 76 weeks of treatment and evaluate the efficacy and safety of UPA in combination with whole-body NB-UVB phototherapy for the treatment of adults with NSV.

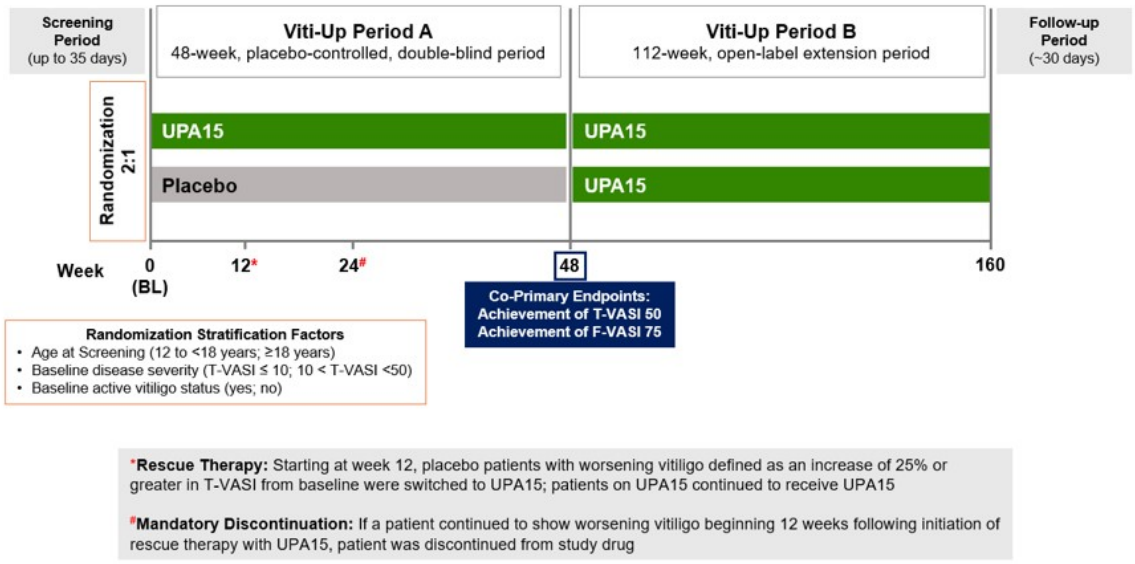
Materials and Methods

Viti-Up is comprised of 2 ongoing randomized, placebo (PBO)-controlled phase 3 studies (Viti-Up-1/Viti-Up-2)

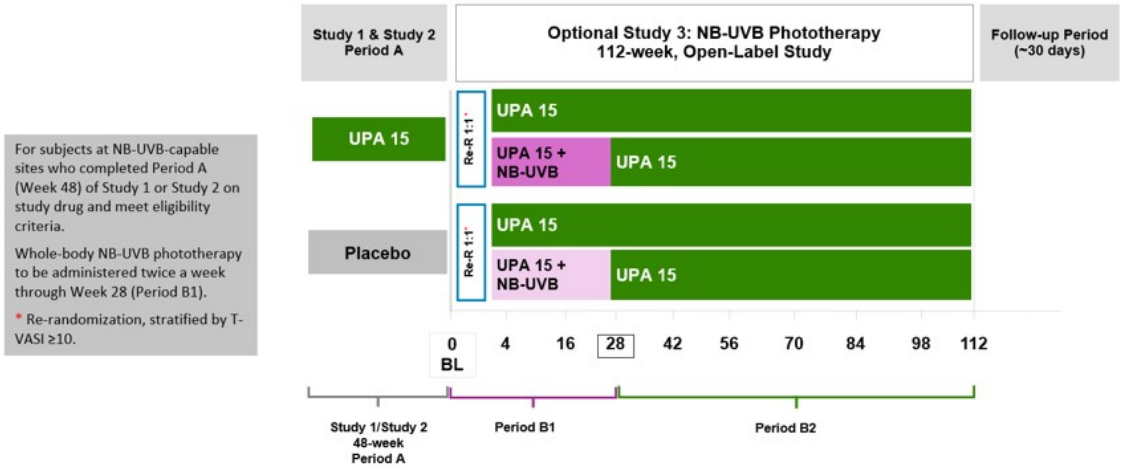
assessing safety and efficacy of UPA (15 mg) administered once-daily. Skin repigmentation was evaluated based on achievement of ≥75% improvement in Facial Vitiligo Area Scoring Index (F-VASI 75) and ≥50% improvement in Total Vitiligo Area Scoring Index (T-VASI 50) at 76 weeks. Following the 48-week PBO-controlled period A in Viti-Up-1/Viti-Up-2, patients either continued UPA or were switched from PBO to UPA for the 112-week open-label extension (OLE) period B. Alternatively, eligible patients from period A at NB-UVB-capable sites continued to Study 3, designed to evaluate combination therapy with UPA and NB-UVB. At week 48, patients receiving UPA or PBO in period A were re-randomized at Study 3 entry to either UPA monotherapy or UPA + whole-body NB-UVB phototherapy administered twice weekly for approximately 28 weeks (period B1). Re-randomization was stratified by baseline disease severity in Study 3 (T-VASI ≤10 vs T-VASI >10). Non-responder imputation was used for analysis for period A and in Study 3; observed cases was used for the OLE.

Figure 1. Study designs for (A) Viti-Up-1/Viti-Up-2 and (B) Study 3

(A) Viti-Up-1/Viti-Up-2



(B) Study 3



BL, baseline; F-VASI, Facial Vitiligo Area Scoring Index; NB-UVB, narrow-band ultraviolet B; PBO, placebo; Re-R, re-randomized; T-VASI, Total Vitiligo Area Scoring Index; UPA, upadacitinib. T-VASI 50, at least 50% reduction in T-VASI score from baseline; F-VASI 75, at least 75% reduction in F-VASI score from baseline.

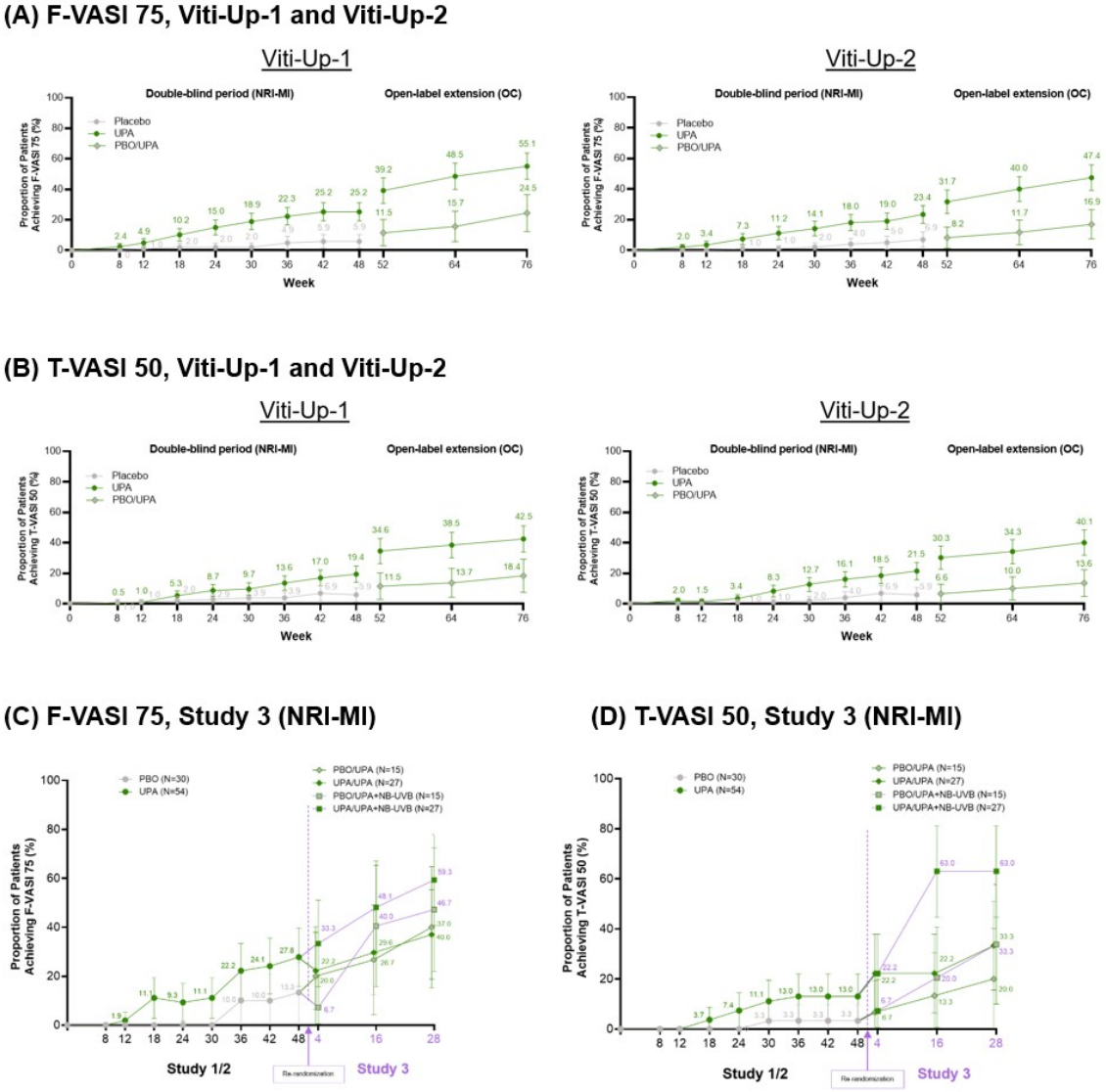
Results

A total of 209 patients continued through week 76 in Viti-Up-1 (PBO/UPA, N=69;UPA/UPA, N=140) and 221 in Viti-Up-2 (PBO/UPA, N=69;UPA/UPA, N=152). At week 76, 24.5% and 16.9% of patients in the PBO/UPA group and 55.1% and 47.4% in the UPA/UPA group in Viti-Up-1 and Viti-Up-2, respectively, achieved F-VASI 75. T-VASI 50 was achieved by 18.4% and 13.6% of patients in the PBO/UPA group and 42.5% and 40.1% of patients in the UPA/UPA group in Viti-Up-1 and Viti-Up-2, respectively at week 76.

Eighty-four adults (56% female/mean age 46.6 years [SD 12.2]) continued to Study 3 and were re-randomized to receive either UPA (PBO/UPA, N=15;UPA/UPA, N=27) or UPA+NB-UVB (PBO/UPA+NB-UVB, N=15;UPA/UPA+NB-UVB, N=27). In Study 3, 40.0% (PBO/UPA) and 37.0% (UPA/UPA) of patients receiving UPA alone and 46.7% (PBO/UPA+NB-UVB) and 59.3% (UPA/UPA+NB-UVB) of patients receiving UPA+NB-UVB achieved F-VASI 75. Similarly, 20.0% (PBO/UPA) and 33.3% (UPA/UPA) of patients receiving UPA alone and 33.3% (PBO/UPA+NB-UVB) and 63.0% (UPA/UPA+NB-UVB) of patients receiving UPA+NB-UVB achieved T-VASI 50.

Compared to baseline, all Study 3 groups receiving UPA had improvements in F-VASI 75 and T-VASI 50. Safety results for Viti-Up-1/Viti-Up-2 week 76 and Study 3 week 28 were consistent with UPA's known safety profile; no new safety signals were reported.

Figure 2. Achievement of F-VASI 75 and T-VASI 50 across time in Viti-Up-1/Viti-Up 2 (A, B) and Study 3 (C, D)



F-VASI, Facial Vitiligo Area Scoring Index; NB-UVB, narrow-band ultraviolet B; NRI-MI, non-responder imputation incorporating multiple imputation; OC, observed cases; PBO, placebo; T-VASI, Total Vitiligo Area Scoring Index; UPA, upadacitinib

Conclusion

Patients with NSV treated with UPA experienced improvements through 76 weeks in Viti-Up, with increasing rates of F-VASI 75 and T-VASI 50 achievement for patients continuing on UPA, and for patients shifting from PBO to UPA after 48 weeks. Combining UPA with NB-UVB therapy in Study 3 further enhanced efficacy of UPA compared to UPA monotherapy regardless of preceding treatment (PBO vs UPA), and efficacy rates continued to increase on the UPA treatment with and without NB-UVB, with no apparent plateau and no new safety signals.

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Abstract N°: 219

Multi-omic profiling identifies early molecular responses to rezpegaldesleukin, a novel regulatory T cell-inducing therapy, in atopic dermatitis

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by T-cell–mediated immune dysregulation highly impacting patients' quality of life. Although current biologics effectively target type 2 inflammation, more than 50% of adults report inadequately controlled disease despite treatment. Rezpegaldesleukin is an IL-2 receptor agonist designed to selectively expand regulatory T cells (Tregs), essential for maintaining immune homeostasis. In the REZOLVE-AD randomized, double-blind, dose-finding, placebo-controlled phase 2b trial (NCT06136741) rezpegaldesleukin 24 µg/kg q2w resulted in statistically significant improvements in the primary and secondary endpoints following the 16-week induction phase (Silverberg et al. The Lancet 2026). In this sub-study, we aim to integrate transcriptomic and proteomic biomarkers with clinical endpoints to characterize the molecular effects and clinical correlations of rezpegaldesleukin in patients with moderate-to-severe AD.

Materials and Methods

100 patients receiving rezpegaldesleukin 24 µg/kg q2w (n=59) or placebo (n=41) were analyzed in this biomarker sub-study. Blood and lesional tape strips were collected at baseline and after 2 and 4 weeks (W). Clinical assessments (EASI, vIGA-AD, Itch Numeric Rating Scale [NRS]) were performed at baseline and at two-week intervals up to W16. Differentially expressed genes/DEGs and proteins/DEPs (fold change/FCH>1.5 and $p<0.05$) were evaluated in tape strips using RNA-seq and the Olink Target 96 multiplex platform as well as in serum using Olink (fold change/FCH>1.3 and $p<0.05$). Clinical severity scores were correlated with changes in biomarker expression using Spearman correlations.

Results

Among the 59 patients in this biomarker sub-study with moderate-to-severe AD treated with rezpegaldesleukin (28 females, 31 males; mean age, 36.6 ± 13.5 years; baseline mean EASI, 26.6 ± 10.2), the mean percentage reduction in EASI from baseline reached 64.3% at W16, with 42.4% of patients achieving EASI75. Significant improvements versus baseline and versus placebo were observed as early as W2 and were significant across all clinical efficacy endpoints, including EASI-50/75/90, IGA 0/1, and≥ 4-point improvement in Itch NRS (all $p<0.05$). RNA-seq revealed that rezpegaldesleukin treatment led to a significant upregulation versus both baseline and placebo of Treg and T-cell activation markers (ICOS, CD3D/E, CTLA4, FOXP3, IL2RA, IL2RB) as early as W2. A significant reduction was conversely observed in markers of T-helper axes, including Th1 (OASL), Th2 (CCL7), Th17 (CXCL17, IL36RN, CXCL2, CXCL3, CAMP/LL-37) and Th22 (S100A12), along with fibrosis-associated markers (POSTN, COL15A1, ELN, COL16A1, COL1A1, LUM; all $p<0.05$). Gene Set Variation Analysis (GSVA) demonstrated significant reduction of Th17 ($p<0.01$) and JAK-STAT signaling ($p<0.05$) by W4. Tape-strip proteomic analyses validated transcriptomic findings, highlighting significant downregulation of markers of T-cell activation, Th17/IL-23-axes, and innate immunity. Serum proteomic analyses complemented tape-strip findings, additionally

demonstrating early, sustained upregulation of regulatory proteins (IL10, CD274, TNFRSF9) starting at W2. Blood analysis also revealed that biomarker changes as early as W2 already correlated significantly with EASI at W16, exclusively in the rezpegaldesleukin arm: IL-10 ($R=-0.621$, $p<0.0001$), CCL17 ($R=0.524$, $p<0.0001$), and TGFB1 ($R=-0.573$, $p<0.0001$). No such correlations were observed in the placebo arm (all $|R|\leq 0.30$, $p\geq 0.06$)

Conclusion

Rezpegaldesleukin induced rapid and sustained clinical improvement accompanied by early modulation of immune pathways consistent with Treg expansion and suppression of pathogenic inflammatory signaling. Early biomarker changes correlated with subsequent clinical response, providing mechanistic support for Treg-directed therapy for AD.

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Abstract N°: 228

Clinical study of RLS-1496 topical cream: targeting senescence and oxidative stress via GPX4 inhibition in patients with actinic keratosis

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Introduction

Actinic keratoses (AKs) are scaling red lesions on chronically sun-exposed skin that could evolve into squamous cell carcinoma (SCC). Accumulation of senescent cells in the epidermis and dermis of photodamaged skin may contribute to the pathogenesis of this age-dependent skin disease. RLS-1496 cream is an investigational, first-in-class, adaptive senotherapeutic drug product that potently inhibits the antioxidant enzyme glutathione peroxidase 4 (GPX4). This induces ferroptosis (non-apoptotic, iron-dependent, regulated cell death) of senescent cells and also leads to an antioxidant reset in stressed, pre-senescent cells through the nuclear factor erythroid 2-related factor 2 (NRF2) pathway, contributing to a pro-repair/regenerative effect.

Materials and Methods

This phase 1b/2a, multi-center, open-label, single-dose, clinical study assessed the safety, tolerability, clinical activity, and pharmacodynamics (PD) of topically applied RLS-1496 1% cream for the treatment of AK lesions on adult male and female patients. Eligible patients with 4-12 clinically typical, discrete AK lesions on each forearm were enrolled and dosed for 28 consecutive days with RLS-1496 1% cream on a predefined 100 cm2 area on the left forearm and followed for an additional 28 days. The right forearm served as an untreated control. Primary endpoints were the frequency and incidence of adverse events (AEs) assessed through Day 57 and the rate of AK lesion clearance following treatment. Changes from baseline in selected PD parameters were assessed from lesional biopsies taken on Days 1 and 29.

Results

Twenty-four (24) patients were enrolled and treated for 28 days. RLS-1496 1% cream was well-tolerated with no application site reactions reported. There was a singular adverse reaction of moderately severe dermatitis (adjacent to the application site) that resolved within one week. All other treatment-emergent AEs (TEAEs) were mild-to-moderate in severity and considered not related to treatment. There were no SAEs and no patient discontinued the study due to an AE. The mean percent change in total AK lesion counts from baseline (Day 1) to Day 29 was -38.3% for the RLS-1496-treated forearm compared to -5.2% for the untreated control forearm. At Day 57, the results were -43.5% and -11.3% for active and untreated control, respectively. A minimum of 75% clearance of AK lesions treated with RLS-1496 1% cream was observed in 25.0% and 34.8% of forearms on Days 29 and 57 and in 0.0% of untreated control forearms at the same timepoints. Analysis of PD biomarkers demonstrated 33% GPX4 target engagement (TE). Spatial transcriptomics and multiplex immunostaining confirmed an AK-specific senescent cell signature and potential treatment-related changes in senescence and disease markers.

Conclusion

In this phase 1b/2a study, 4 weeks of topical treatment with RLS-1496 1% cream was associated with a favorable safety and tolerability profile and resulted in clinically meaningful clearance of AK lesions compared to untreated control. Analysis of PD biomarkers demonstrated TE in AK lesions and impact on senescence and disease

biomarkers. Further clinical investigation of RLS-1496 cream in AK is warranted.

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Abstract N°: 245

Long-term Durability and Safety of the Targeted Oral Peptide Icotrokinra for High-Impact Site Psoriasis: 2-year Findings From the ICONIC-TOTAL Randomized Controlled Trial

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Introduction

Plaque psoriasis (PsO) involving high-impact sites, including the scalp, genitals, hands/feet, and nails, can substantially impair health-related quality of life and may be particularly challenging to treat. Icotrokinra (ICO) is a targeted oral peptide that precisely blocks the interleukin (IL)-23 receptor and inhibits IL-23 pathway signaling. Across phase 3 trials in participants (pts) with PsO, ICO demonstrated robust efficacy with favorable safety vs placebo (PBO) through Week (W)16, with consistent results through 1 year (Y).[1-4] Long-term data on durability of response and safety will help inform treatment decisions. Reported here are clinical response rates and safety of ICO through 2Y in ICONIC-TOTAL study pts with high-impact site plaque PsO.

Materials and Methods

ICONIC-TOTAL is an ongoing, phase 3, multicenter, randomized, double-blind, PBO-controlled trial in adult and adolescent pts (≥12 years of age) with Investigator's Global Assessment (IGA) score ≥2 and PsO body surface area ≥1%. Eligible pts had at least moderate involvement of ≥1 high-impact site, defined as a score ≥3 for scalp specific-IGA (ss-IGA), static Physician's Global Assessment of Genitalia (sPGA-G), or hand/foot PGA (hf-PGA). Pts

were randomized (2:1) to receive once-daily oral ICO 200 mg or PBO with transition to ICO at W16. Topical therapies were permitted after W52. Rates of achieving clear/almost clear (IGA 0/1 with ≥2-grade IGA improvement from baseline) or completely clear (IGA 0) skin overall and clear/almost clear (ss-IGA 0/1, sPGA-G 0/1, hf-PGA 0/1) or completely clear (ss-IGA 0, sPGA-G 0, hf-PGA 0) PsO at high-impact sites were reported through W112. For binary endpoints, non-responder imputation was applied through W52; after W52 multiple imputation was used for missing data. Nail PsO severity was assessed via percent improvement in modified Nail Psoriasis Severity Index (mNAPSI) through W112. Safety was reported as exposure-adjusted rates of pts with ≥1 adverse event (AE) per 100 patient-years (PY) through W112.

Results

Among 311 randomized pts (208 ICO, 103 PBO), 254 (82%) completed treatment through W112. Among ICO-randomized pts, achievement rates of IGA 0/1 increased from W16 (57%) through W24 (67%) and remained stable through W112 (70%; Fig 1A), with similar trends for IGA 0 (W16: 25%, W24: 45%, W112: 48%; Fig 1B). Rates of achieving clear/almost clear skin at high-impact sites increased through W24 and were maintained through W112 for scalp (ss-IGA 0/1; W16: 66%, W24: 78%, W112: 74%; Fig 1C) and genital PsO (sPGA-G 0/1; W16: 77%, W24: 90%, W112: 89%; Fig 1D). Rates increased through W52 for hand/foot PsO (hf-PGA 0/1; W16: 42%, W24: 54%, W52: 62%) and were maintained through W112 (68%; Fig 1E). At W112, high rates of complete skin clearance (score of 0) were reported for scalp (60%), genital (89%), and hand/foot (63%) PsO among ICO-randomized pts. Nail PsO improved progressively among ICO-randomized pts, with mNAPSI percent improvements increasing from 33% at W16 to 62% at W52 and 71% at W112 (Fig 1F), with comparable improvements among PBO-to-ICO pts. Exposure-adjusted incidence rates (95% confidence interval) of ICO-treated pts with ≥1 AE did not increase between W0-W52 (160 [138, 182]/100PY) and W0-W112 (122 [106, 137]/100PY) time periods, with similar trends for serious AEs (W0-W52: 2.7 [1.1, 5.6]/100PY; W0-W112: 2.7 [1.3, 4.1]/100PY). No deaths were reported.

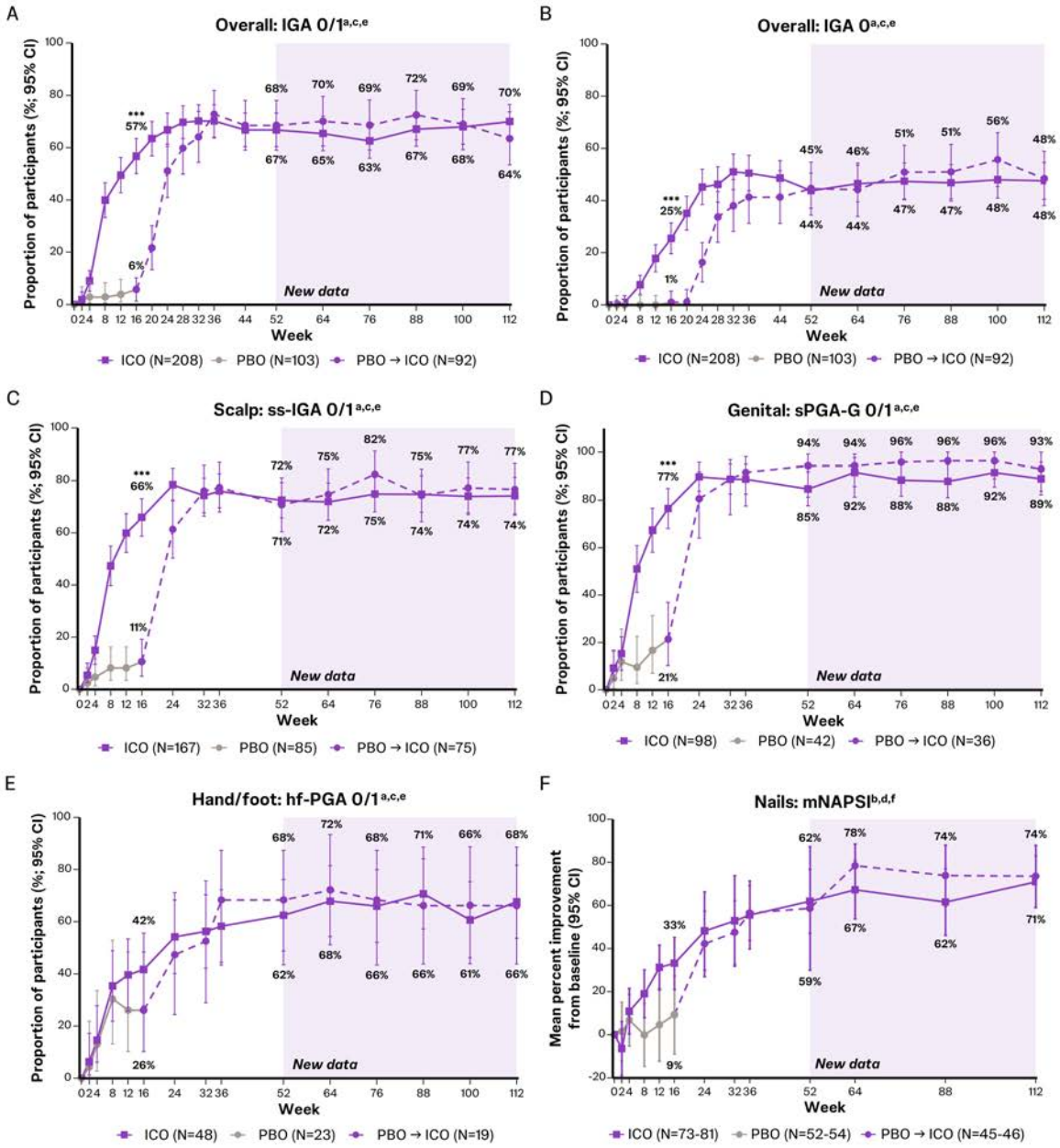
Figure 1. Proportion of pts achieving (A) overall IGA 0/1 with an improvement of ≥2 from baseline, (B) overall IGA 0, (C) ss-IGA 0/1, (D) sPGA-G 0/1, and (E) hf-PGA 0/1; (F) mNAPSI percent improvement through W112.

***Multiplicity-adjusted p <0.001 ICO vs PBO. [d]Through W52 nonresponder imputation / [b]0% improvement from baseline assigned after pts discontinued study drug due to a lack of efficacy or an AE of worsening PsO or initiated prohibited medication that could impact PsO; observed data were used for pts who discontinued study agent for other reasons. [c]After W52 nonresponder imputation / [d]0% improvement from baseline assigned after pts who discontinued study drug due to a lack of efficacy or an AE of worsening PsO. [e]After accounting for these intercurrent events: through W52, pts with missing data were considered nonresponders and, after W52, other missing data were imputed using multiple imputation. [f]The remaining missing data were not imputed. Through W52 CIs were based on the normal approximation or an exact method if the number of responders or number of non-responders was <10. After W52, confidence intervals were derived based on multiple imputations.

ss-IGA evaluated among pts with baseline ss-IGA score ≥3. sPGA-G evaluated among pts with baseline score ≥3. hf-PGA evaluated among pts with baseline score ≥3. mNAPSI evaluated among pts with baseline score >0.

IGA range: 0 (cleared); 1 (minimal); 2 (mild), 3 (moderate); 4 (severe). ss-IGA range: 0 (absent), 1 (very mild), 2 (mild), 3 (moderate), 4 (severe). sPGA-G range: 0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe), 5 (very severe). hf-PGA range: 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), 4 (severe). mNAPSI range: 0-130; higher scores indicate worse severity.

AE: adverse event, CI: confidence interval, hf-PGA: Physician's Global Assessment of the hands and/or feet, ICE: intercurrent event, ICO: icotrokinra, IGA: Investigator's Global Assessment, mNAPSI: modified Nail Psoriasis Severity Index, PBO: placebo, sPGA-G: static Physician's Global Assessment of Genitalia, ss-IGA: scalp specific-Investigator's Global Assessment.



Conclusion

ICO demonstrated high and durable rates of PsO clearance across high-impact sites through 2Y of treatment. Exposure-adjusted rates of pts with AEs and serious AEs remained stable with extended ICO treatment, with no new safety signals identified. The robust efficacy, favorable safety profile, and convenience of once-daily oral dosing support the use of ICO in pts with high-impact site PsO.

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Abstract N°: 253

Tunnel-associated keratinocytes in Hidradenitis suppurativa have a distinct pro-inflammatory program spatially associated with TNFα and OX40L positive cells

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Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease defined by the formation and expansion of epithelial tunnels in the dermis, leading to recurrent painful nodules, abscesses, and suppuration. It typically manifests in intertriginous areas, such as the axillary, groin, genitoanal, and inframammary regions. HS is a complex disorder involving multiple pathogenic processes including epithelial tendril formation, immune response dysregulation, and skin microenvironment remodeling.

While effective therapeutic options remain limited, recent research has elucidated key molecular mechanisms underlying HS, identifying pro-inflammatory mediators such as TNFα, CXCL1, and IL-1β as critical drivers of the innate immune response and pathways which drive adaptive immune responses, including Th17 and OX40/OX40L. A bispecific antibody that targets both arms of the immune response could be very effective; however, selection of appropriate targets requires an understanding of the identity and spatial organization of the cells responsible for inflammatory alterations within HS lesions.

Materials and Methods

In this study, we employed Xenium 5K spatial transcriptomics to profile five HS skin samples from patients with Hurley stage III disease.

Results

The spatial distribution of TNFα- and OX40L-expressing cells, revealed co-localization of both cell populations closer to tunnel-associated keratinocytes than to epidermal keratinocytes. Interestingly, TNFα and OX40L were expressed by distinct cells, with very few cells co-expressing both transcripts, suggesting that these proteins may have unique functions in HS. Consistent with previous reports, keratinocytes showed a distinct inflammatory signature, defined by the upregulation of genes involved in innate immune responses such as DEFB4A, CXCL1, and CTSC. Importantly, we found these inflammatory changes were specifically localized to tunnel-associated keratinocytes, whereas epidermal keratinocytes demonstrated enhanced expression of genes associated with epidermal homeostasis and normal differentiation, including CCL27, EGR3, and KRT2. Tunnel-associated keratinocytes additionally showed increased expression of genes associated with wound healing and inflammatory skin disease, including KRT17, SERPINB4, ANGPTL4, ITGB6, CTSL, KLK6, CD36, and ANXA3. Notably, many of these genes can be regulated by TNFα and genes, such as SERPINB4, have also been reported to be upregulated in other inflammatory skin disorders, most prominently in psoriasis.

Conclusion

Our data places known HS-associated pathomechanisms, TNFα and OX40L, in a spatial context for the first time. This not only highlights the central role of TNFα and OX40L in HS but also reveals a surprising spatial specificity where TNFα-induced inflammatory genes are exclusively observed in tunnel-associated keratinocytes. Collectively, these data suggest that mechanistically a bispecific antibody neutralizing both TNFα and OX40L, such as NAV-240

or NAV-242, could specifically attenuate inflammation at a key disease node providing HS patients with an effective treatment option.

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Abstract N°: 269

Efficacy and safety of abdakibart (ABD), a humanized high affinity and potency IgG4 anti-IL-1β agent for treatment of moderate to severe hidradenitis suppurativa at Week 16; IHS4 subgroup and lesion type ANdT results of the Phase 2 placebo-controlled LOTUS Trial

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Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory disease of the pilosebaceous unit characterized by formation of abscesses (A), nodules (N), and tunnels (dT) in intertriginous areas. Both the Hidradenitis Suppurativa Clinical Response (HiSCR) and International HS Severity Score (IHS4) assess disease severity and are used in clinical trials. Changes from baseline and/or proportions of subjects with significant improvement in IHS4 and ANdT (A+N+dT) are proposed as more inclusive tools due to greater emphasis ontunnel assessment. Anti-cytokine agents (e.g., anti-TNFα, IL17A/F [biologics]) are often prescribed after failed antibiotic therapy, but few demonstrate 40% of subjects achieving 75% improvement from baseline in IHS4 at Week 16. New, novel therapies are still needed. IL-1β is a key upstream inducer for TNFα and IL-17. We present the efficacy and safety results from the LOTUS trial, a double-blind Phase 2, placebo-controlled trial focusing on the changes from baseline in IHS4 scores, achievement of IHS4-55/75/90 and changes in ANdT, A, N, and dT over the 16-week trial period.

Materials and Methods

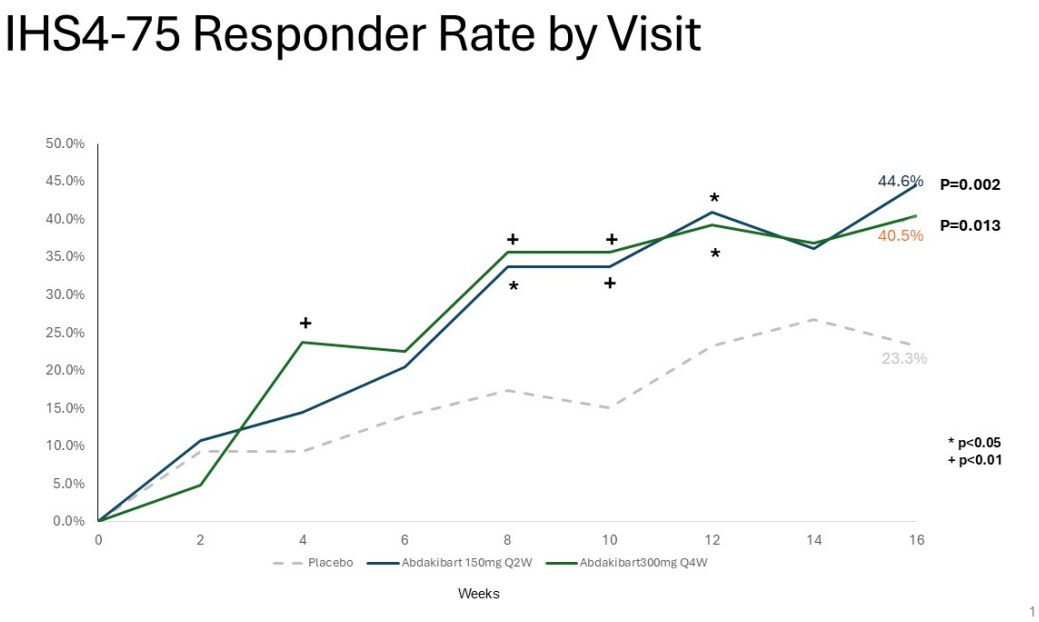
The LOTUS trial compared 2 dosing regimens of ABD (600 mg loading dose, followed by 300 mg every 4 weeks [Q4W], or 300 mg loading dose, followed by 150 mg every 2 weeks [Q2W]) to placebo [PBO] (1:1:1 randomization) in subjects with moderate-severe HS. Eligible subjects: ≥18 years old, symptoms of HS ≥6 months, Hurley Stage II/III, total AN count ≥5, and presence of HS in ≥2 distinct anatomical areas. Subjects with and without biologics experience were eligible. The primary endpoint was the proportion of subjects achieving HiSCR75 at Week 16 (≥ 75% reduction in total AN count; no increase in abscess/dT count relative to baseline). Subjects who received systemic rescue therapy before Week 16, or discontinued study treatment due to adverse events or lack of efficacy were treated as non-responders. Subjects with missing data were imputed as non-responders. Primary endpoint analysis compared both ABD groups to placebo using a closed testing procedure controlling overall Type 1 error at 0.05 significance level (2-sided). Key secondary endpoints included change from baseline in IHS4 and dT. Proportions of IHS4-55/75/90 responders at Week 16 were pre-specified secondary endpoints; changes in A, N, dT and combined ANdT measurements were performed post-hoc with nominal p values provided. Subjects were followed for safety through Week 20.

Results

A total of 253 subjects were enrolled. 86% of subjects completed study treatment. Baseline characteristics were generally balanced, though more subjects in ABD cohorts were female, biologics experienced with baseline dT counts >1 compared to placebo. A greater proportion of subjects in the combined (ABD: 42.5%; placebo: 25.6%; p=0.004; 16.1% vs 6.0%, p= 0.009 at Week 4) and individual ABD groups achieved the primary endpoint of HiSCR75 versus placebo at Week 16. By Week 2, ABD treated subjects demonstrated significantly greater mean change from baseline in IHS4 (PBO: -3.0; Q2W: -5.7; Q4W: -6.9 [p=0.018]) and dT (PBO: 0; Q2W: -0.8 [p=0.018]; Q4W: -0.7 [p=0.025]) and a greater mean change in N for Q4W group by Week 4 (PBO: -2.0; Q4W: -5.4; p=0.0). No significant changes from baseline in A between groups were detected. At Week 16, a significantly higher proportion of ABD treated subjects achieved IHS4-55, IHS4-75 (Figure) and changes in ANdT, with the Q4W cohort significantly separating in IHS4-55/75 from placebo within 4 weeks of treatment (IHS4-55:37.0% vs 20.5%[p=0.025]; IHS4-75:24.7% vs 9.6% [p=0.012]); proportions of IHS4-90 responders trended to significance in the Q2W group. Rates of treatment-emergent adverse events (AE) were similar between ABD and placebo with no unexpected safety findings.

Conclusion

In the LOTUS Trial, rapid (≤2-4 weeks) and significant improvements in IHS-4, IHS4-55/75 and 90, N, dT and ANdT were achieved with ABD compared to placebo with an acceptable safety profile.



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Abstract N°: 309

SPOTLIGHT-204: Primary Results of Intralesional BO-112 in Resectable Basal Cell Carcinoma

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Introduction

Basal cell carcinoma (BCC) is the most common human malignancy with raising global incidence. Mohs micrographic and conventional surgery achieve high cure rates, however, can result in significant scarring and functional compromise, particularly on the head and neck (H&N). Effective non-surgical options remain an unmet clinical need. BO-112 is a dsRNA immunotherapy designed to activate an innate and adaptive immune response and immunogenic tumour-cell death.

Materials and Methods

SPOTLIGHT-204 is a multi-centre, phase 2b, single-arm, two-cohort clinical trial evaluating efficacy, safety and tolerability of intralesional BO-112 injection in 50 patients (40 high-risk [HR] and 10 low-risk [LR], as defined by National Comprehensive Cancer Network [NCCN] criteria) with resectable, histologically confirmed BCC lesions.

Patients received three once-weekly intralesional injections followed by complete surgical excision at week 24. Visual and pathological responses were evaluated by a Central Review Committee. Visual efficacy was Grade: 1) complete (complete lesion disappearance or scar); 2) partial (≥30% reduction in lesion size); 3) no change / smaller than partial; or 4) lesion growth (≥20% increase in lesion size). Pathological response, at the time of surgical excision, was Grade: 1) complete (no residual viable tumour (RVT); 2) major (≤10% RVT); 3) partial (>10% ≤50% RVT); or 4) no response (>50% RVT). We report results in a 46-patient modified intention to treat population with 54 evaluable lesions.

Results

The median age was 75 years (range 34–90), 48% (n=22) were female. Lesions were located on the face (61%,

n=33); scalp (11%, n=6); extremities (15%, n=8); and trunk (13%, n=7). Lesion median longest diameter was 12 mm (range 6–34 mm). Mean BO-112 cumulative exposure was 1.25 mg. The composite primary endpoint was defined as both visual and pathological response of Grade 3 or better in all treated lesions at patient level. This was achieved by 61% (n=28) of patients, with high visual and histological concordance. Response rates were 58% (n=21) in HR patients; and 70% (n=7) in LR patients. Complete and major (Grades 1 and 2) pathological responses were observed in: 56% (n=20) of HR patients; and 50% (n=5) of LR patients. A complete visual and complete pathological response (both Grade 1), was achieved by 56% (n=18) of HR-H&N patients. Of 100 treatment related adverse events (TRAEs (at event level)): 91% (n=91) were Grade 1 (mild); 9% (n=9) were Grade 2 (moderate); none were ≥Grade 3 (severe); none were serious. The most frequent TRAEs were: pyrexia (12%, n=12); injection site pain (20%, n=20); injection site swelling (8%, n=8); and headache (6%, n=6). These events are consistent with BO-112s mechanism of action. No AEs were serious, led to dose reduction, or discontinuation.

Conclusion

Intralesional BO-112 achieved high rates of composite visual and pathological response in both LR and HR patients, with a manageable and predominantly low-grade safety profile. Of note, in HR patients with H&N lesions, high percentages of complete visual and pathological responses were achieved. These results support further development of BO-112 as a non-surgical option for treating BCC.

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Abstract N°: 312

Zasocitinib, a highly selective, once-daily oral TYK2 inhibitor, demonstrates superior skin clearance (PASI 100) versus an approved oral TYK2 inhibitor, deucravacitinib, and a consistent safety profile in moderate-to-severe plaque psoriasis: results from a randomized phase 3 intraclass head-to-head trial (LATITUDE Atlas)

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Introduction
Zasocitinib is an investigational, next-generation, highly selective, once-daily oral tyrosine kinase 2 (TYK2) inhibitor that maintains 24-hour inhibition of interleukin-23 plus other core disease-driving immune pathways. In two pivotal phase 3 placebo- and active- (apremilast) controlled trials in adults with moderate-to-severe plaque psoriasis (LATITUDE-PsO-3001 [NCT06088043] and -3002 [NCT06108544]), zasocitinib demonstrated rapid, durable and reproducible skin clearance with a consistent safety profile. Here, we evaluated the efficacy and safety of zasocitinib vs an approved oral TYK2 inhibitor, deucravacitinib, in adults with moderate-to-severe plaque psoriasis in a phase 3 head-to-head clinical trial (LATITUDE Atlas; NCT06973291).

Materials and Methods
This multicentre, international, randomized, double-blind, active comparator-controlled trial compared zasocitinib 30 mg once daily (QD) with deucravacitinib 6 mg QD. Eligible adults (Psoriasis Area and Severity Index [PASI] ≥12, static Physician's Global Assessment [sPGA] ≥3, body surface area involvement ≥10%) were randomized 1:1 to receive zasocitinib or deucravacitinib. The primary efficacy endpoint was PASI 100 response at Week 16. Key secondary efficacy endpoints were PASI 90, absolute PASI ≤2 and sPGA 0 responses at Week 16. Exploratory efficacy endpoints included the change from baseline (CfB) in Dermatology Life Quality Index (DLQI) and Itch Numerical Rating Scale (NRS) over time. Safety endpoints included the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs) and laboratory parameters.

Results

Overall, 301 and 303 patients were randomized to receive zasocitinib and deucravacitinib. Baseline patient demographics and disease characteristics were generally balanced between groups. Among patients receiving zasocitinib and deucravacitinib, respectively, most were male (64.1% and 69.6%), mean (standard deviation [SD]) age was 46.1 (12.9) and 45.6 (13.8) years, mean (SD) weight was 87.6 (21.9) and 91.1 (24.6) kg, and overall mean (SD) PASI score was 19.7 (7.2) and 19.0 (6.4).

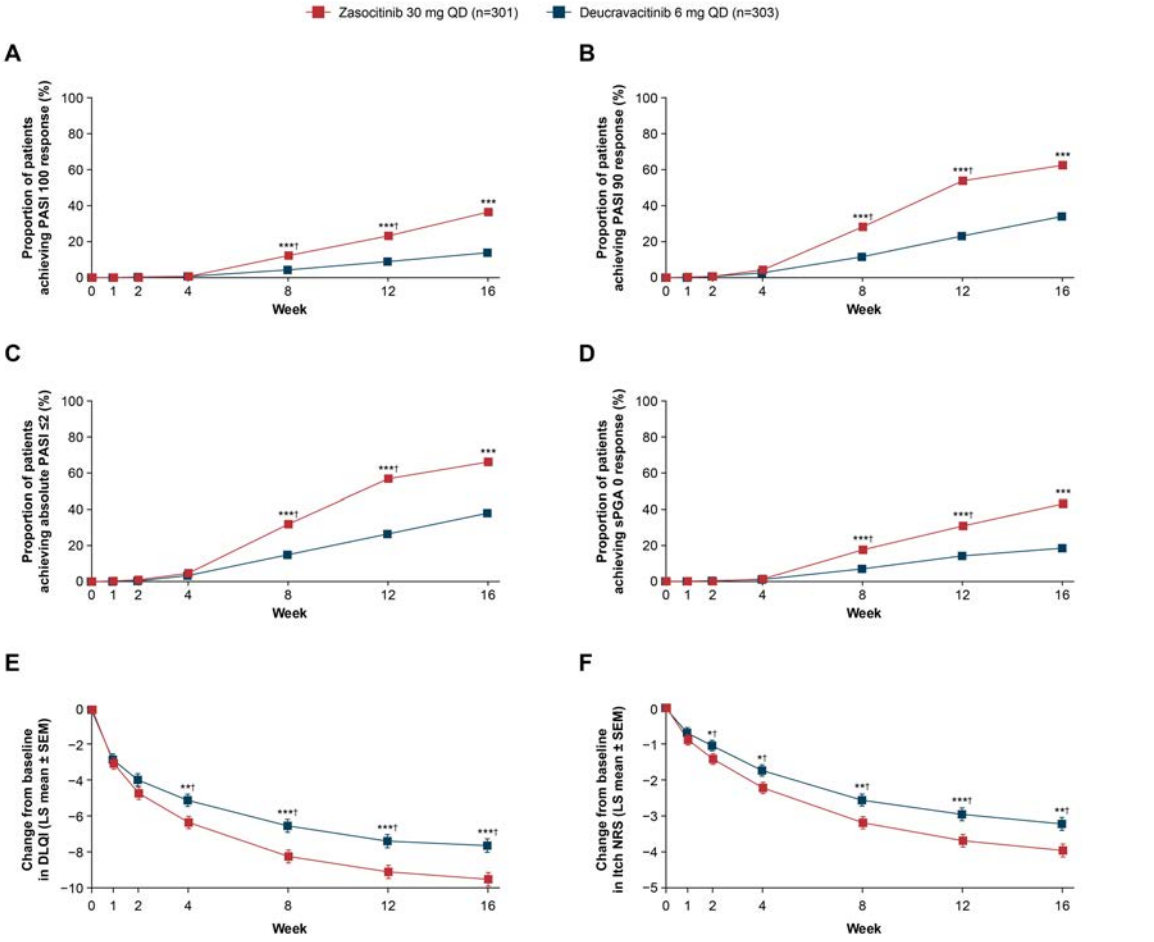
At Week 16, zasocitinib demonstrated a significantly greater PASI 100 response rate vs deucravacitinib (36.5% vs 13.9%; $p<0.001$; **Figure 1A**). Zasocitinib also demonstrated greater PASI 90, absolute PASI ≤2 and sPGA 0 response rates at Week 16 (62.5%, 66.1% and 43.2%, respectively) vs deucravacitinib (34.0%, 38.0% and 18.5%, respectively; all $p<0.001$; **Figure 1B–D**). Higher response rates with zasocitinib than deucravacitinib were observed for all of these outcomes as early as Week 8 (nominal $p<0.001$). In evaluable patients at Week 16, zasocitinib demonstrated a greater least-squares mean (standard error of the mean) CfB versus deucravacitinib in DLQI score (−9.5 [0.4] vs −7.6 [0.4]; nominal $p<0.001$; **Figure 1E**) and Itch NRS score (−4.0 [0.2] vs −3.2 [0.2]; nominal$p=0.001$; **Figure 1F**).

Rates of TEAEs, SAEs and treatment-related AESIs were generally similar between treatment groups. In total, TEAE rates were higher and SAE rates were lower with zasocitinib than deucravacitinib (TEAEs: 65.9% and 58.7%; SAEs: 1.3% and 2.3%; treatment-related AESIs: 2.0% and 2.3%). Consistent with previous trials, the most frequently occurring TEAEs in the zasocitinib group were nasopharyngitis (12.9%), upper respiratory tract infection (11.3%) and acne (7.3%). No treatment-related major adverse cardiovascular or venous thromboembolism events were observed in either group. No clinically meaningful trends in laboratory parameters were observed through Week 16 in either group.

Conclusion

In this phase 3 comparative trial, highly selective TYK2 inhibition with oral zasocitinib 30 mg QD showed superior skin clearance with multiple efficacy endpoints (including PASI 100, PASI 90, absolute PASI ≤2 and sPGA 0) versus the TYK2 inhibitor deucravacitinib at Week 16, with higher response rates from Week 8. The overall safety and tolerability profile of zasocitinib was consistent with previous trials.

Figure 1. Zasocitinib demonstrated significantly greater (A) PASI 100, (B) PASI 90, (C) absolute PASI ≤2 and (D) sPGA 0 response rates versus deucravacitinib as early as Week 8 and through Week 16, and greater changes from baseline in (E) DLQI score[a] as early as Week 4 and (F) Itch NRS score[b] as early as Week 2 versus deucravacitinib through Week 16.



***p<0.001; *†nominal p<0.05; **†nominal p<0.01; ***†nominal p<0.001.
[a]At baseline, n = 295 (zasocitinib) and n = 292 (deucravacitinib).
[b]At baseline, n = 297 (zasocitinib) and n = 293 (deucravacitinib).
For panels A–D, p values for comparison versus deucravacitinib 6 mg QD are based on the Mantel–Haenszel test, with geographic region and prior treatment with biologics as stratification factors. For panels E and F, p values for comparisons versus deucravacitinib 6 mg QD are from a mixed model for repeated measures including treatment, visit and treatment-by-visit interaction as fixed effects and geographic region, prior treatment with biologics and baseline score as covariates.
DLQI, Dermatology Life Quality Index; LS, least-squares; NRS, Numerical Rating Scale; PASI, Psoriasis Area and Severity Index; QD, once daily; SEM, standard error of the mean; sPGA, static Physician's Global Assessment.

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Abstract N°: 313

Lebrikizumab Showed Sustained Efficacy and Safety Through 5 Years in Patients with Moderate-to-Severe Atopic Dermatitis: Results from the ADlong Long-Term Extension Trial

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Introduction

Lebrikizumab, an interleukin-13 inhibitor, is a systemic therapy for moderate-to-severe atopic dermatitis (AD). Longer-term data are key to guide clinical practice.

Materials and Methods

Adults and adolescents (12–17 years, ≥40 kg) from parent trials, regardless of Week (W) 16 response, could enter ADjoin 100W extension study. Upon ADjoin completion, patients in Germany and Poland enrolled in ADlong (NCT05916365; 2-year [108W] extension), receiving open-label lebrikizumab 250 mg every four weeks (Q4W), with permitted Q2W uptitration at investigator's discretion in patients not maintaining clinical benefit. Topical corticosteroids were permitted for AD flares. The primary endpoint was treatment discontinuation due to treatment-emergent adverse events (TEAEs; reported as exposure-adjusted incidence rates [EAIRs] per 100 person years [PY]). Efficacy outcomes were also reported at baseline and W108, including ≥75% improvement in Eczema Area and Severity Index (EASI-75), Investigator's Global Assessment (IGA) 0/1, EASI-90, EASI ≤7, Pruritus Numerical Rating Scale (P-NRS) ≤4 and P-NRS 0/1. Lack of efficacy discontinuations were imputed as non-responders; other discontinuations/missing data were handled using multiple imputation.

Results

174 ADjoin-completers enrolled into ADlong (parent trials: ADvocate1 [n=59]; ADvocate2 [n=36]; ADhere [n=23]; ADore [n=56]). During ADlong, the EAIRs/100PY were 2.0 (n=5) for TEAE-related discontinuations, 70.8 for any TEAE (mild/moderate/severe: 11.2/33.2/2.3) and 2.9 for serious TEAEs. No deaths were reported. At ADlong baseline/W108, 93.1%/92.9% of patients maintained or achieved EASI-75, 70.7%/66.7% IGA 0/1, 79.9%/73.8% EASI-90, 92.5%/89.8% EASI ≤7, 78.3%/78.0% P-NRS ≤4 and 31.6%/31.7% P-NRS 0/1. 39/174 (22.4%) patients underwent ≥1 uptitration to Q2W, of whom 9/39 (23.1%) returned to Q4W.

Conclusion

Long-term lebrikizumab safety profile was consistent with previous studies, with low TEAE-related discontinuations up to 5 years of exposure and no new safety signals. Most ADlong patients (up to 5 years lebrikizumab exposure) showed high rates of skin and itch responses with Q4W dosing through W108.

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Abstract N°: 315

Differential Proteomic Effects of Abrocitinib and Dupilumab in Moderate-to-Severe Atopic Dermatitis: Exploratory Analysis of JADE COMPARE

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Introduction
Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by heterogeneous clinical and molecular phenotypes. Janus kinase (JAK) inhibitors may be effective across the AD spectrum because they modulate signalling from multiple cytokines implicated in AD pathophysiology. Abrocitinib, an oral, once-daily, JAK1-selective inhibitor, and dupilumab, an anti-interleukin-4-receptor α monoclonal antibody, are approved for the treatment of moderate-to-severe AD. The objective of this retrospective exploratory analysis was to characterize the effect of abrocitinib and dupilumab treatment on serum protein biomarkers in patients with moderate-to-severe AD.

Materials and Methods
This study evaluated serum samples stored in Pfizer's Biobank from the Phase 3 JADE COMPARE clinical study (NCT03720470), in which adult patients with moderate-to-severe AD were randomly assigned (2:2:2:1) to receive abrocitinib 200 mg or 100 mg orally once daily, dupilumab 300 mg subcutaneously every other week (after a loading dose of 600 mg), or placebo. Serum expression of 356 proteins was evaluated at baseline and at week 12 through the Olink® Target 96 Multiplex high throughput platform (Olink Proteomics AB, Uppsala, Sweden). Samples were analysed to identify differentially expressed proteins/DEPs; absolute fold changes (FCH) >1.3, *P*-value <0.05. Comparative analyses were conducted to evaluate shared and treatment-specific proteomic changes.

Results
Serum samples were collected from a total of 352 patients; of these, 90, 87, 92 and 83 received abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo, respectively. Abrocitinib 200 mg produced the broadest modulation of the AD serum proteome from baseline to week 12 (8 up- and 27 down-regulated DEPs at W12 vs Baseline), exceeding both dupilumab and abrocitinib 100 mg modulation, while no changes were observed in placebo. Overall, a broad, significant and dose-dependent downregulation of key Th1- (IL12B, CXCL10, CCL3,), and Th17- (TGFB1) related markers was observed in the abrocitinib arms, as well as several T-cell/T-cell activation/migration- (CD4, CD5, CD8A, IL16, CCL19) and innate immunity- (IL1A) related markers; IL-13 was

significantly modulated only with abrocitinib 200mg (P<0.05). Similarly, selected fibrosis- (TNFRSF9, TNF), pruritus- (IL18BP, F2R, CCL3) and cardiovascular- (IGFBP2, MSR1, PGLYRP1) markers were only downregulated by abrocitinib with stronger FCHs observed in the 200mg group (P<0.05). Both abrocitinib and dupilumab also produced a parallel, significant reduction in key AD pathways such as Th2 (CCL17, CCL13), Th17/Th22 (S100A12, PI3, IL-6), fibrosis (IL18, SERPINE1, IL2RA), pruritus (CTSS, TNFRSF1B) and cardiovascular (SELE, IL1RN, PRSS27, HMOX1, PRTN3, TGFA, TNFSF14, RETN, HGF, ULBP2) (all P<0.05).

Conclusion

This study is the largest analysis of therapeutic changes in soluble protein expression levels in moderate-to-severe AD patients to date, identifying treatment-related biomarker changes following both abrocitinib doses and dupilumab therapy. The study findings highlight how JAK inhibition with abrocitinib addresses a broader anti-inflammatory effect that aligns with clinical findings. These findings are consistent with the abrocitinib JADE MOA trial (NCT03915496) and provide results at a much larger scale.[1] Results also align with previous studies describing the effect of dupilumab on protein biomarkers.[2,3] This study provides deeper insight into the mechanism of action of abrocitinib, illustrating how selective, JAK1-inhibition may provide therapeutic benefit to patients with moderate-to-severe AD across multiple domains.

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Abstract N°: 331

A Previously Undrugged Target in Immune Therapeutics: Oral ENV-294 Provides First Clinical and Molecular Proof of Concept for RAC2 Modulation in Atopic Dermatitis

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Introduction

Despite the transformative impact of IL-4/IL-13–targeted biologics, many patients with atopic dermatitis (AD) fail to achieve or sustain adequate disease control, underscoring the need for safe therapies that act more broadly beyond type 2 immunosuppression. ENV-294 is a first-in-class, allosteric, non-degrading molecular glue that selectively binds RAC2 and stabilizes the inactive RAC2:RhoGDI complex. This raises the threshold of immune activation, a novel mechanism with potential to reduce chronic inflammation while preserving protective immune function. Recently, ENV-294 demonstrated promising safety and efficacy in a Phase 1b open-label, single-arm study in moderate-to-severe AD (NCT07336940). In this translational study, weinvestigated the mechanism of action and related treatment-response biomarkers that correlate with clinical scores.

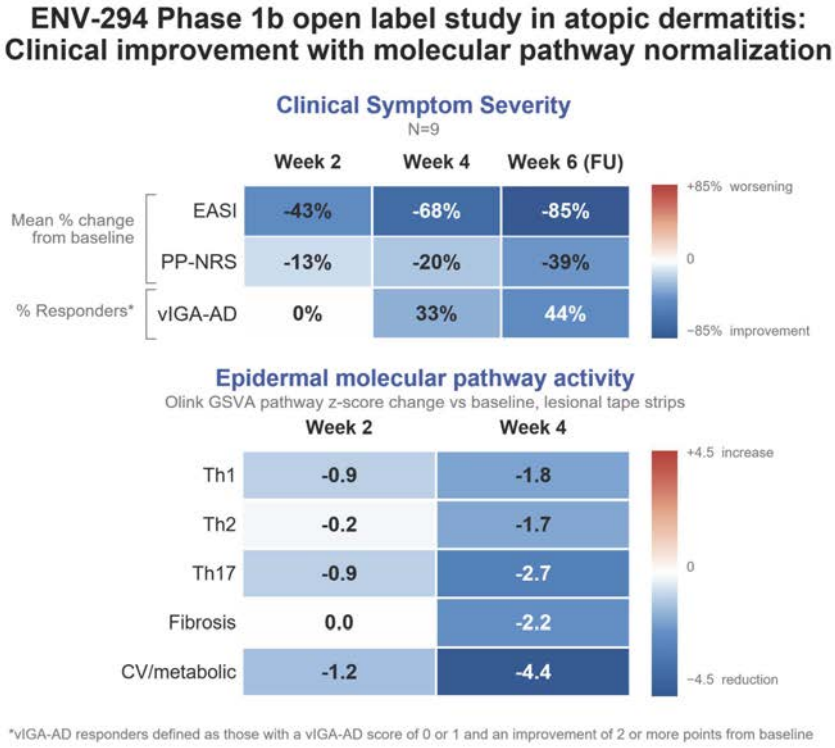
Materials and Methods

Tape-strips and biopsies were collected from lesional and non-lesional skin of adult ADpatients who receivedENV-294 800 mg QD. Tape-strips were collected at baseline, Week 2 (W2) and W4, while biopsies were collected at baseline and W4, from the same lesions at adjacent locations. Proteomic analyses of skin biopsies and tape strips were performed using the Olink Target 96 platform (354 analytes across 4 panels). Given the small, single-arm study design, we employed an exploratory analysis approach where proteins showing a mean |fold change| $\geq$1.3 from baseline or nominal $p<0.05$ were considered modulated by treatment. Coordinated pathway-level responses were assessed by Gene Set Variation Analysis (GSVA) of predefined disease-relevant protein signatures. Modulated proteins and GSVA pathway scores were correlated between compartments and with clinical scores (including EASI, vIGA-AD, BSA, SCORAD and PP-NRS).

Results

Nine patients with moderate-to-severe AD (6F, 3M; mean age 40.7; baseline EASI 21.0) enrolled and completed the study. ENV-294 was well tolerated with no serious or treatment-related adverse events, no discontinuations, and no clinically relevant laboratory changes. At W4, mean EASI score decreased by 68.2% (SD 24.8), with 44.4% of patients achieving EASI-75. Improvements deepened through W6 (2-week off-treatment follow-up); mean EASI reduction reached 84.9%, with 77.8% achieving EASI-75. Olink analysis in tape-strips showed reduction of multiple inflammatory markers at W4. Examples included Th1- (CXCL9, CXCL10, CXCL11), Th2- (CCL17, CCL11, CCL13, IL1RL1), and Th17- (IL17A, IL17RA, IL6, IL6R, CCL20, S100A12) related markers. Hyperplasia/fibrosis-related markers (SERPINE1, MMP1, MMP9, CCL2) were also suppressed. Reductions were also seen in proteins associated

with cardiovascular/metabolic inflammation(e.g., GDF15, SORT1, LDLR, PLAUR, VEGFA, SOD2, ALCAM and CTSL). Proteomic analyses on skin biopsies showed directionally concordant changes to the tape-strip data at the pathway level. Tape-strip and biopsy biomarker changes on treatment were significantly correlated across the proteome (R=0.442, p=0.0002). Reduction in several pro-inflammatory proteins (IL4, IL18, IL17C, IL12B, CCL20) was correlated with reduced EASI, BSA, vIGA-AD, PP-NRS and/or SCORAD scores at W4.



Conclusion

Treatment with ENV-294 was associated with early improvements in clinical measures, accompanied by reductions in cutaneous markers related to inflammation, hyperplasia/fibrosis and cardiovascular/metabolic pathways. Treatment-related biomarkers detected by both non-invasive tape strips and biopsies correlated with improvements in clinical severity scores. These exploratory, hypothesis-generating findings shed light onthe novel

mechanism of action of ENV-294, suggesting broad anti-inflammatory potential without negatively impacting protective immune function, and supporting its continued development as a potential therapy for rapid clinical and molecular improvement in AD and other inflammatory diseases.

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Abstract N°: 339

The integrated 31-gene expression profile (i31-SLNB) identifies patients with a low risk of sentinel lymph node positivity and 31-GEP identifies patients with high 5-year recurrence risk: The largest prospective, multicenter study of GEP for cutaneous melanoma

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Introduction

Patients with cutaneous melanoma (CM) and their treating clinicians face two primary decisions after a CM diagnosis. First, should the patient undergo a sentinel lymph node biopsy (SLNB)? Second, how should the patient be followed with clinic visits and adjunctive surveillance (e.g. imaging, ctDNA) and is treatment with adjuvant/neoadjuvant therapies warranted? The current National Comprehensive Cancer Network (NCCN) guidelines recommend avoiding SLNB in patients with cutaneous melanoma if the risk of a positive SLN is <5% and discussing SLNB if the risk is ≥5%. Further, the NCCN recommends patients with early-stage disease (stage I-IIA) be followed with clinic visits every 6-12 months, with no adjunctive surveillance. In contrast, patients with more advanced disease (stage IIB-IV) should have more frequent follow-up and consider surveillance. However, management of early-stage patients based on these staging groups inadequately addresses individual patient risk, resulting in unnecessary sentinel lymph node biopsies and later detection of recurrences, when disease burden is greater and more difficult to treat. Incorporating the patient's molecular risk information alongside staging augments risk stratification to improve decision-making. In the largest prospective, multicenter study on gene expression profile (GEP) testing in CM to date, we demonstrate the 31-GEP provides significant prognostic information beyond current risk factors used to guide patient care. We also demonstrate that the i31-SLNB predicted risk score (an integrated result that combines the independently validated 31-GEP Class score plus select clinicopathologic factors) identifies patients with <5% risk who can safely avoid SLNB.

Materials and Methods

In this prospective study, patients were enrolled from 2020–2026 at 29 U.S. centers (n=2799). The 31-GEP returns results as low risk (Class 1A), increased risk (Class 1B/2A), and high risk (Class 2B). The i31-SLNB integrates the 31-GEP result with clinicopathologic factors (Breslow thickness, ulceration status, mitotic rate, and age) to provide an individualized percentage risk of a positive SLN. Kaplan-Meier analysis assessed 31-GEP recurrence risk stratification, log-rank test assessed differences between groups, and significant predictors of recurrence were identified by multivariable Cox regression.

Results

Patients with a Class 1A 31-GEP result had significantly higher RFS than those with a Class 1B/2A or 2B result (98.7% vs. 87.8% vs. 76.8%, p<0.0001). Patients with stage I-IIA disease and Class 2B results had RFS rates that were not statistically different than patients with stage IIB disease (85.3% vs. 86.1%, p=0.95). Multivariable Cox modeling demonstrated that Class 1B/2A (HR=3.30, p=0.004), Class 2B (HR=3.49, p=0.008), Breslow depth (HR=1.19, p=0.027), ulceration (HR=1.86, p=0.050), mitotic rate (HR=1.05, p=0.038), and positive SLN (HR=2.95,

p<0.001) were significant predictors of recurrence.

Among patients who underwent SLNB and received an i31-SLNB result (n=676), the i31-SLNB identified 27% (182/676) as low risk (i31-SLNB <5% predicted risk), of whom only 4.4% (8/182) had a positive SLN. By comparison, those with an i31-SLNB-predicted risk >10% (267/676) had a 22.8% (61/267) SLN positivity rate, a 5.2-fold increase over those with <5% i31-SLNB-predicted risk. Among SLNB-eligible patients with <5% i31-SLNB-predicted risk who did not undergo SLNB (n=565), 5-year RFS was 99.6% (95% CI=98.7-100%).

Conclusion

In the largest prospective, multicenter study of GEP in CM, the 31-GEP refined recurrence risk stratification, identifying patients with early-stage disease wherein considering adjunctive surveillance and treatment may be warranted. Importantly, the i31-SLNB accurately identified patients with a true risk of SLN positivity of <5% and those predicted low risk who did not undergo SLNB had 99.6% 5-year RFS, supporting use of the i31-SLNB as a tool to identify patients who can safely avoid SLNB.

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Abstract N°: 349

Lebrikizumab is effective in Patients with Atopic Hand and Foot Dermatitis: 16-Week Results from the Randomized, Double-Blind, Placebo-Controlled ADTouch Trial

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Introduction

Atopic hand and foot dermatitis (AHFD) is a common, recalcitrant, and debilitating manifestation of atopic dermatitis (AD) driven by type 2 inflammation, including overexpression of interleukin-13, with pruritus and pain as primary symptoms. Despite substantial impact on quality of life (QoL) and work productivity, systemic treatment options for AHFD remain limited.

Objective

To evaluate efficacy and safety of lebrikizumab, a selective interleukin-13-inhibitor, as monotherapy in adults and adolescents with moderate-to-severe AHFD.

Materials and Methods

ADTouch (NCT06921759) was a multi-center, randomized, double-blind, placebo-controlled, parallel-group phase 3b trial evaluating lebrikizumab versus placebo in adults (≥18 years) and adolescents (≥12 to <18 years, ≥40kg

total body weight) with moderate-to-severe AHFD.

Eligible patients had AHFD ≥1 year in at least 2 of 4 anatomical areas (left hand/right hand/left foot/right foot) at screening and baseline; a documented history of AD not limited to hands and feet; a Hand Foot Investigator's Global Assessment (HF-IGA) score of moderate (3) or severe (4) at screening and baseline; a HF-Peak Pruritus Numeric Rating Scale (NRS) score ≥4; and inadequate response to topical therapies.

Patients were randomized 1:1 to subcutaneous lebrikizumab (500mg loading doses at baseline and week 2, then 250mg every 2 weeks to week 16) or placebo. The primary endpoint was HF-IGA 0/1 with ≥2-point improvement from baseline at week 16.

Secondary endpoints evaluated safety, pruritus, pain, disease activity, QoL, and Atopic Hand Dermatitis Clearance Satisfaction (AHDCS), a novel single-item patient-reported scale. Results reflect the primary outcome database lock, which included all data through Week 16.

Results

Participants (N=221) were randomized to lebrikizumab (n=110) or placebo (n=111). Baseline disease characteristics were comparable between groups, including HF-IGA (severe: 27.3% vs 27.9%), HF-Peak Pruritus NRS (mean: 7.2 in each arm) and HF-Peak Pain NRS (mean: 6.2 in each arm).

All primary and key secondary endpoints achieved statistical significance. More participants in the lebrikizumab group achieved HF-IGA 0/1 with ≥2-point improvement vs placebo at week 16 (53.3% vs. 27.2%; $p<0.001$). A higher proportion of lebrikizumab vs placebo-treated participants achieved HF-IGA 0/1 with ≥2-point improvement at week 2 (7.8% vs 0.9%; nominal $p<0.05$) and week 4 (16.9% vs 5.6%; $p=0.008$). At weeks 2, 4, and 16, HF-Peak Pruritus NRS ≥4-point improvements were higher with lebrikizumab (15.8%; 27.3%; 57.1%) than with placebo (0.9%; 7.9%; 19.0%; all $p<0.001$). HF-Peak Pain NRS ≥4-point improvements were higher for lebrikizumab vs placebo at week 16 (59.1% vs 18.8%; $p<0.001$).

Among participants who were not satisfied at baseline on AHDCS, more lebrikizumab than placebo-treated participants were "satisfied" or "very satisfied" with hand dermatitis clearance at week 16 (76.7% vs 39.6%; $p<0.001$).

Treatment emergent adverse events (TEAEs) were reported in 41.8% of patients receiving lebrikizumab and 39.6% of patients receiving placebo; no severe TEAEs and no serious AEs were reported, and treatment discontinuations due to AEs were infrequent in lebrikizumab (0.9%) and placebo groups (2.7%).

Conclusion

Lebrikizumab monotherapy achieved clinically meaningful and statistically significant improvements over placebo in atopic hand and foot dermatitis skin clearance, pruritus, pain, and patient satisfaction. Safety findings were consistent with the established lebrikizumab profile.

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Abstract N°: 364

Targeting hair-follicle regulatory mechanisms beyond established approaches: a translational evaluation of MEV-miRNAs/iSFRP1 gel

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Introduction

Advances in hair-follicle biology are opening new avenues beyond conventional approaches by revealing mechanisms that regulate follicular activity and hair-cycle transitions, including miRNA-mediated post-transcriptional regulation and cyclosporine A-like modulation of the SFRP1/Wnt signaling axis. A patented isolation and purification process was developed to obtain standardized milk-derived exosomes (MEV-miRNAs). Characterization of their miRNA cargo identified 25 miRNAs of interest for hair-follicle biology. In parallel, mechanistic studies of cyclosporine A-induced hypertrichosis identified SFRP1 suppression and subsequent Wnt activation as a potential hair-growth mechanism, leading to the development of the non-drug SFRP1 inhibitor iSFRP1. An integrated program evaluated the combination of MEV-miRNAs and iSFRP1 from *in vitro* and *ex vivo* models to controlled and exploratory clinical studies.

Materials and Methods

The objective was to characterize the complementary effects of MEV-miRNAs and iSFRP1 on hair-follicle biology and to assess the efficacy and tolerability of their combination in a once-weekly topical gel vs placebo and as an adjunct to topical minoxidil. MEV-miRNAs were evaluated in human hair-follicle dermal papilla (HFDP) cells for effects on viability, and in organ-cultured human hair follicles for hair-shaft elongation and Wnt-pathway gene expression. iSFRP1 was evaluated in organ-cultured human scalp follicles for effects on hair-cycle staging and Wnt activity. Clinically, 39 adults with androgenetic alopecia (AGA) and/or chronic telogen effluvium were randomized in a multicenter, double-blind study to once-weekly MEV-miRNAs/iSFRP1 gel or placebo for 12 weeks. Anagen hair percentage, anagen/telogen (A/T) ratio and hair-shaft diameter were assessed. An exploratory proof-of-concept series evaluated patients with AGA receiving topical minoxidil (5%, twice daily) at baseline and Month 3. Patients either added MEV-miRNAs/iSFRP1 gel once weekly or continued topical minoxidil alone. Hair density and terminal/vellus hair proportions were assessed in frontal, vertex and occipital regions.

Results

MEV-miRNAs significantly increased HFDP cell viability and upregulated key Wnt-pathway components vs untreated controls. Hair-shaft elongation in human hair follicles cultured in MEV-miRNA-enriched medium showed a trend toward growth promotion. *Ex vivo*, iSFRP1 significantly increased transcription of the Wnt target gene LEF1 and inhibited catagen development, with more follicles remaining in anagen VI than with vehicle. In the randomized clinical study, relative changes with MEV-miRNAs/iSFRP1 gel vs placebo were +23% vs +4% at Week

8 and +36% vs +3% at Week 12 for anagen hair percentage; +80% vs +6% and +173% vs +11% for A/T ratio; and +50% vs +3% and +62% vs +7% for hair-shaft diameter. All three parameters improved significantly from baseline in the MEV-miRNAs group, with significant differences vs placebo, at both time points (all $p \leq 0.001$). In the exploratory series, mean Month-3 increases in hair density with adjunctive gel vs minoxidil alone were +16.1% vs +7.5% frontally, +18.3% vs +8.8% at the vertex and +9.6% vs +4.3% occipitally. Absolute increases in terminal hair proportion were +13.3 vs +6.0, +14.3 vs +6.7 and +9.7 vs +4.3 percentage points, respectively. No product-related clinical signs, discomfort, or adverse events were reported in either study.

Conclusion

MEV-miRNAs and iSFRP1 demonstrated convergent biological effects relevant to follicular activity, Wnt signaling and hair-cycle transitions. Their combination in a once-weekly topical gel significantly improved key trichoscopic outcomes versus placebo, while preliminary adjunctive observations suggested numerically greater improvements than topical minoxidil alone. These findings provide translational support for further controlled evaluation of this dual-component, non-drug approach alongside established hair-loss management.

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The Interferon Signaling Pathway Plays a Key Role in Hailey-Hailey Disease and is Effectively Targeted by Ruxolitinib

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Introduction

The objectives of the study were to better understand the pathophysiology of Hailey-Hailey disease (HHD) and identify therapeutic targets. HHD, also known as familial benign chonic pemphigus, is a rare genetic skin disease caused by pathogenic variants in *ATP2C1* leading to loss of cell-to-cell adhesion of the epidermis (acantholysis). People with HHD develop recurrent vesicular lesions resulting in painful erosions with fissures which predominate in intertriginous areas. The lesions often become infected and progress in flare-ups leading to marked impairment in quality of life. There is no specific treatment and potent topical corticosteroids remain the classical treatment.

Materials and Methods

We conducted a multiomics study to define the molecular and cellular landscape of HHD.Bulk transcriptomic and proteomic analyses of skin biopsies were performed from a cohort of 29 subjects with HHD. Single-cell and spatial transcriptomic analyses (Visium and Xenium) were conducted on 5 patients. The results of integrated multiomics analysis were used for *in silico* candidate drug repurposing and led to targeted therapy in 10 patients.

Results

Integrated bulk transcriptomic and proteomic pathway analysis revealed a striking type I and type II interferon (IFN) signature in HHD skin lesions compared to non-lesional and healthy skin. Spatial transcriptomics (Visium HD) showed significantly increased IFN signaling pathway activity scores in lesional skin, with preferential localization in the epidermal layers. Single cell and high-resolution spatial transcriptomics (Xenium) identified inflammatory niches composed of keratinocytes, immune cells, vascular and stromal cells. These cells create an IFN-driven signaling network through multiple intercellular communications that sustain a self-amplifying loop. Immune module profiles generated from the bulk transcriptomic dataset confirmed the IFN signature to be the predominant axis and were used to identify candidate repurposed drugs through the Open Targets Platform. Ruxolitinib was identified as the best candidate based on its potent inhibition of IFN signaling and other JAK1 or JAK2-dependent pathways along with its suitability for topical delivery. Remarkably, in nine out of ten subjects with refractory HHD, topical treatment with the JAK1/2

inhibitor ruxolitinib led to rapid and sustained skin healing (over 10 months) with drastic reduction in pain, itching, weeping and skin inflammation; resulting in a significant improvement of quality of life (DLQI, Skindex16, NRS for pain and itch). One patient developed a bacterial infection and another a herpes infection in the treated areas, both of which resolved following specific local treatment. Post-treatment histological and immunostaining demonstrated reduced immune cell infiltration and rescued epidermal architecture. This clinical outcome falls in line with recent single case reports.

Conclusion

Collectively, our results identify IFN signaling as a key pathogenic driver in HHD and support JAK inhibition as an effective mechanism-based therapy for HHD.

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Bempikibart, a novel IL-7Rα antibody, produces hair regrowth that persists off treatment in severe and very severe alopecia areata: efficacy and biomarker results from the Phase 2a SIGNAL-AA Part B trial

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Introduction
Alopecia areata (AA) is a T-cell-mediated disease of hair loss. Approved oral JAK inhibitors require continuous administration, with relapse commonly observed after discontinuation. Bempikibart is an antibody against IL-7Rα that potently blocks IL-7 and TSLP signaling, targeting the pathogenic T- cells and type 2 inflammation. SIGNAL-AA Part B evaluated a pharmacokinetically optimized regimen of bempikibart to further characterize safety, efficacy and remittive potential among patients with severe AA.

Materials and Methods
In this ongoing open-label Phase 2a study, 33 patients with severe (SALT score 50-94) or very severe (SALT score 95-100) AA and current-episode duration ≤4 years received bempikibart 200 mg subcutaneously extended through 36 weeks (4 weekly loading doses followed by Q2W doses), followed by 16 weeks off treatment. Baseline mean SALT score was 75.6 (24% SALT score ≥ 95) with a mean current episode duration of 2.07 years. 73% of patients were female; 36% were oral JAKi-experienced. At a 2 September 2026 cutoff, Week 36 analysis datasets were complete, and 10 patients had completed Week 52; missing SALT score values were imputed by LOCF. The pre-specified mITT population (n=25) excluded 8 patients per pre-specified SAP rules. Off-treatment durability was assessed in 12 mITT responder patients with a ≥10 point SALT score improvement by Week 36 who entered follow-up.

Results
Pharmacokinetics: The loading regimen produced a 3-fold higher mean trough of 28.8 µg/mL at Day 22 and reached steady state ~10 weeks earlier than dosing without loading (Week 3 vs Weeks 12-14).

Pharmacodynamics: Peripheral CD3+ T cells showed a median 44% reduction from baseline (n=21), with on-mechanism reductions in four T-effector cytokines assessed at baseline and Weeks 24 and 36 (biomarker-evaluable, n=25). Patients in the upper baseline tier (n=10) showed median reductions up to 46% for IFNγ, 46% for IL-17, 41% for IL-6 and 28% for TNFα. CXCL10, a downstream marker of IFNγ signaling, decreased by a median 32% at Week 36 in responders (biomarker evaluable, ≥$SALT_{30}$, n=8) versus 3% in non-responders (n=12). Th2 biomarkers downstream of TSLP signaling, TARC, IgE (baseline >200 IU/mL) and eosinophils, showed median reductions up to 39%, 29% and 52%. Twelve biopsies were immunostained and post-treatment biopsies showed reduced CD3+/CD4+/CD8+ infiltrates around hair follicles with increased Treg/CD8+ ratios concordant with increased hair growth.

Efficacy: At Week 36, SALT≤20 (≥80% scalp hair coverage) was achieved by 40.0% (10/25) of mITT and 30.3% (10/33) of ITT patients; SALT≤10 by 8.0% and 6.1%; ≥$SALT_{30}$ by 44.0% and 33.3%; ≥ $SALT_{50}$ by 44.0% and 33.3%.

Mean SALT score improvement from baseline was 35.3% (mITT). SALT≤20 responses occurred in severe and very severe disease and in IgE-high and IgE-low patients.

Off-Treatment Durability: Twelve of 25 mITT patients with at least a 10-point SALT score improvement by Week 36 entered follow-up; all 12 (100%) maintained response and 6 (50%) deepened at 8 weeks post (Table 1), one reaching SALT 0 and two additional patients SALT≤10 during off treatment period. Maintenance among Week 36 responders who entered off-treatment period was 10/10 (100%) for ≥$SALT_{30}$. Additionally, six non-responders entered follow-up and one converted to ≥$SALT_{30}$ off treatment.

Safety: All drug-related adverse events were mild or moderate. Injection-site reactions occurred with 4% of administrations, all mild. Asymptomatic reduction in absolute lymphocyte count flattened at Weeks 24-28 with no relationship to infection events.

Table 1. Off-Treatment Durability in Week 36 Responders Who Entered Follow-Up Period (n=12 of 25 mITT)

	Final on-treatment visit (Week 36)	Through 8 weeks post final dose (LOCF, n=12)	Through 16 weeks post final dose (Completers, n=7)
n	12	12	7
Mean Absolute SALT Score	22.5	22.9	23.9
Maintained Response[1], n (%)	—	12 (100%)	7 (100%)
Deepening of Response[2], n (%)	—	6 (50%)	3 (43%)

[1]Maintained Response defined as <20-point SALT score worsening as defined in King et al. JAMA Dermatol. 2024. Deepening of Response defined as any improvement in SALT score. Note one patient who was a non-responder converted to a $SALT_{30}$ by 8 weeks post final dose. LOCF, last observation carried forward. Completers—results only from the specified visit.

Conclusion

An optimized bempikibart regimen led to hair regrowth in severe and very severe AA, including JAK-experienced patients, with concordant biomarker and histologic evidence of dual IL-7/TSLP blockade and a favorable safety profile. Regrowth was maintained in all patients and deepened among a subset after the final dose. This combination of efficacy, safety and durability supports advancement of bempikibart to registrational studies.

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Real-world effectiveness and safety of avelumab in an older, clinically heterogeneous population with advanced Merkel cell carcinoma: a nationwide Austrian multicentre study

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Introduction

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer with a high risk of early metastasis and poor prognosis. Avelumab is an established treatment for advanced MCC, but evidence from routine clinical practice remains limited, particularly in older, comorbid, immunocompromised, and otherwise less-selected patients who are underrepresented in prospective trials.

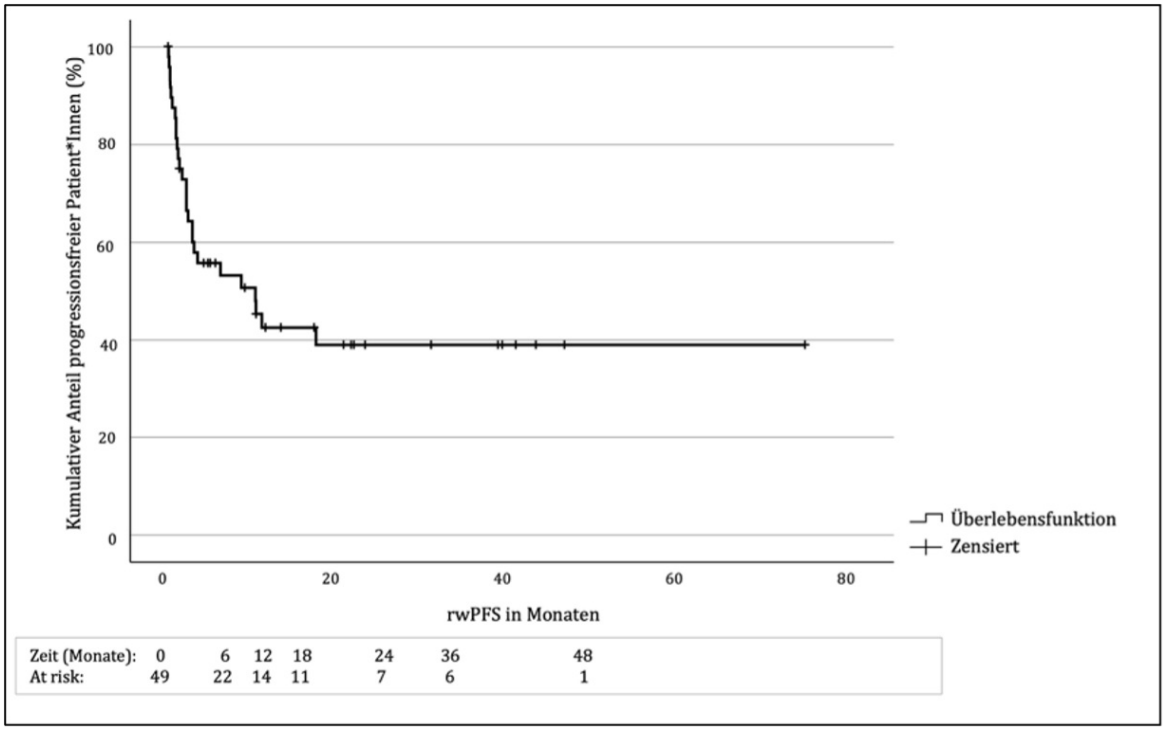
Materials and Methods

We conducted a nationwide Austrian multicentre retrospective chart review of patients with histologically confirmed inoperable locally advanced or metastatic MCC who received at least one cycle of avelumab between September 2017 and December 2023. The primary endpoint was real-world progression-free survival (rwPFS). Secondary endpoints included real-world overall survival (rwOS), objective response rate (rwORR), duration of response (rwDOR), time to response (rwTTR), and safety. Exploratory analyses included real-world time to treatment discontinuation (rwTTD), univariable subgroup analyses, and post hoc multivariable Cox regression models.

Results

Forty-nine patients were included. Median age at avelumab initiation was 81 years (range 62–96), 59.2% were male, 77.6% had ECOG performance status ≤1, and 16.3% were immunocompromised or immunosuppressed. Median age-adjusted Charlson Comorbidity Index was 5.0 (range 2–11). At treatment initiation, 42.9% had stage IIIB and 57.1% stage IV disease. Only 16.3% met the retrospectively assessable eligibility criteria corresponding to the first-line JAVELIN Merkel 200 Part B setting, underscoring the less-selected nature of this real-world population. Avelumab was administered as first-line monotherapy in 77.6%, while 22.4% received additional

treatment modalities, most commonly radiotherapy. Median follow-up was 8.9 months (range 0–73.1). Median rwPFS was 10.1 months (95% CI 1.8–18.4) and median rwOS was 22.9 months (95% CI 5.0–40.8). rwORR was 47.9% (95% CI 34.5–61.7), median rwTTR was 3.9 months (range 1.4–12.7), and median rwDOR among responders was 19.2 months (95% CI 8.9–29.5). Despite limited cross-study comparability, rwPFS and rwOS were in a similar range to those reported in JAVELIN Merkel 200, whereas rwORR was lower. Median rwTTD was 3.9 months (95% CI 2.3–5.5). Adverse events (AEs) were documented in 71.4% of patients. Immune- and/or treatment-related AEs occurred in 53.1%, including grade ≥3 events in 24.5% of the overall cohort. AEs led to treatment interruption or discontinuation in 28.6%, including permanent discontinuation in 12.2%. In post hoc complete-case multivariable models (n=33) including ECOG status, LDH, and CCI, ECOG ≤1 was associated with lower hazards for rwPFS (HR 0.257, 95% CI 0.100–0.658; p=0.005) and rwOS (HR 0.157, 95% CI 0.047–0.521; p=0.002). LDH <240 U/L showed similar associations with rwPFS (HR 0.293, 95% CI 0.105–0.816; p=0.019) and rwOS (HR 0.134, 95% CI 0.028–0.651; p=0.013). CCI showed a counterintuitive association with rwPFS and no association with rwOS and was therefore not interpreted as a prognostic signal. These analyses were exploratory and hypothesis-generating.



Conclusion

In this nationwide real-world cohort of predominantly older and clinically heterogeneous patients with advanced MCC, avelumab achieved clinically relevant response and survival outcomes despite advanced age, immunocompromising conditions, and treatment heterogeneity. AEs frequently prompted treatment interruption or discontinuation. These data support the effectiveness of avelumab in routine clinical practice, while ECOG status and LDH emerged as hypothesis-generating prognostic signals warranting prospective validation.