Abstract N°: LBA-5

Efficacy and Safety of a Selective Oral TYK2/JAK1 Inhibitor, AC-201, in Patients with Plaque Psoriasis: A Phase II, Randomized, Double-blinded, Placebo-Controlled Trial

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Introduction

AC-201 is a novel, oral TYK2/JAK1 Inhibitor under investigation as a potential treatment for plaque psoriasis.

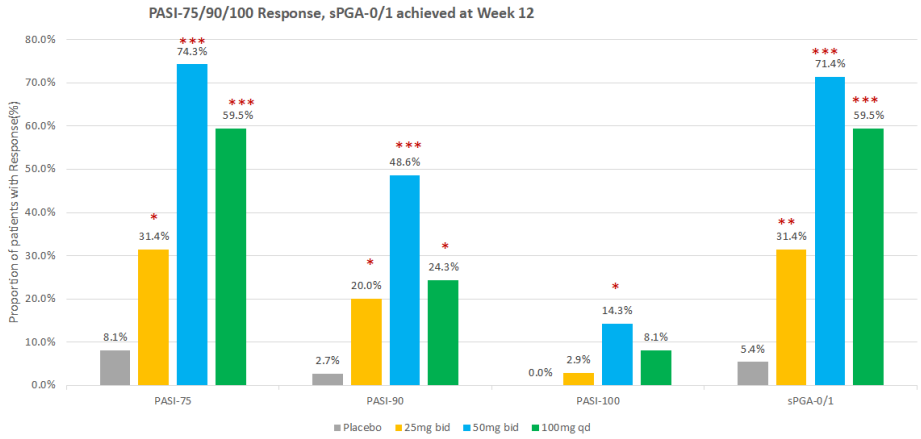
Materials and Methods

This Phase 2 study (AC201-003, NCT06972888) aimed to characterize the efficacy, safety and pharmacokinetic profile of AC-201 vs. placebo in Chinese patients with moderate-to-severe plaque psoriasis.
One hundred and forty-five patients were randomized to receive AC-201 25mg BID, 50mg BID,100mg QD, or placebo over 12 weeks. The primary endpoint was the proportion of patients achieving a ≥ 75%reduction in the Psoriasis Area and Severity Index (PASI-75) score at week 12.

Results

At week 12, PASI-75 response rates were significantly higher for all AC-201 dose groups: 31.4% (25mg BID; P=0.012), 74.3% (50mg BID; P<0.001), and 59.5% (100mg QD; P<0.001), compared with placebo (8.1%). PASI-90 and static Physician's Global Assessment (sPGA)-0/1 (score of 0 ‘clear’ or 1 ‘almost clear’)response rates were also significantly higher for AC-201 vs. placebo. The PASI-90 response rate was 2.7% for placebo, 20% for 25mg BID (P=0.02), 48.6% for 50mg BID (P<0.001), and 24.3% for 100mg QD (P=0.007). The percent of patients achieved sPGA-0/1 were 5.4% for placebo, 71.4% for 50mg BID (P<0.001), 59.5% for100mg QD (P<0.001), and 31.4% for 25mg BID (P=0.004). There was no serious adverse event (SAE) or AE leading to permanent discontinuation reported in the study. The most common Treatment-Emergent Adverse Events (TEAEs) reported were upper respiratory tract infection (8.6% for 25mg BID, 34.3% for 50mg BID,13.5% for 100mg QD and 10.8% for placebo) and hypertriglyceridemia (8.6% for 25mg BID, 17.1% for 50mgBID, 8.1% for 100mg QD and 18.9% for placebo).

PASI-75/90/100 response, sPGA 0/1 at Week 12-FAS population



*p<0.05; **p< 0.005; ***p<0.001 . P-value is comparing proportion in each AC-201 dose group vs placebo using the Cochran-Mantel-Haenszel (CMH) test. NRI (non-responder imputation) was applied for subjects who discontinued study

Conclusion

12-week treatment with oral AC-201 results in significant clinical improvement in patients with moderate-to-severe plaque psoriasis and is generally well tolerated.

Abstract N°: LBA-25

Arginine Undecylenate, a Novel Viral Entry Inhibitor, for the Topical Treatment of Herpes Zoster and Associated Pain: A First-in-Patient, Randomized, Double-Blind, Placebo-Controlled Phase Ib Study

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Introduction

Arginine undecylenate (Arg-UCA) is a novel viral entry inhibitor and represents a new class of antiviral therapy for herpes zoster. Unlike oral antivirals that offer minimal pain relief, Arg-UCA's unique topical delivery and novel mechanism may enable rapid viral inhibition for faster pain relief. This trial represents the first randomized, double-blind, placebo-controlled study with topical Arg-UCA in patients with herpes zoster. The objective of the study was to evaluate safety and preliminary efficacy of Arg-UCA in improving herpes zoster pain and accelerating lesion healing.

Materials and Methods

Thirty herpes zoster patients presenting within 10 days of symptom onset received either topical Arg-UCA (n=20) or placebo (n=10) twice daily for 10 days. Patients received oral antivirals (famciclovir or valaciclovir) as standard of care. Pain was assessed via daily Zoster Brief Pain Inventory (ZBPI) assessments, with worst pain and pain interference scores (0–10 scale) used as key readouts to evaluate changes in pain intensity and its impact on daily function. Digital photographs of lesions taken on Days 1, 5, 11 and 30 enabled blinded assessment of lesion healing using the Local Skin Response scale (total score range: 0–24).

Results

By Day 5, the mean change in ZBPI worst pain scores with Arg-UCA was -24.3% vs +1.5% with placebo, suggesting Arg-UCA treatment relieved pain, while pain slightly worsened in the placebo group. Similarly, the mean change in ZBPI pain interference scores was -25.6% with Arg-UCA vs +21.9% with placebo, suggesting Arg-UCA also improved daily functioning. Clinically meaningful pain relief (≥50% reduction in ZBPI worst pain) by Day 5 was achieved in 45% of Arg-UCA-treated patients vs 22.2% with placebo. Additionally, a ≥50% reduction in ZBPI pain

interference by Day 5 was achieved in 55.6% of Arg-UCA-treated patients vs 0% in the placebo group. Arg-UCA also showed a 20% improvement in lesion healing vs placebo by Day 11, assessed by Local Skin Response scoring. There were no serious treatment-related adverse events.

Conclusion

These early findings suggest topical Arg-UCA is safe and potentially effective at improving herpes zoster pain and lesion healing. As a novel viral entry inhibitor, topical Arg-UCA could address a critical unmet need in the management of herpes zoster.

Abstract N°: LBA-54

Balinatunfib, the first oral selective inhibitor of TNFR1 signalling, in plaque psoriasis: A double-blind, randomized, placebo-controlled Phase 2b study

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Introduction

Balinatunfib is a novel, oral, small molecule selective inhibitor of tumor necrosis factor (TNF) signaling through the TNF receptor 1 (TNFR1) while preserving signalling through the TNF receptor 2 (TNFR2) mediated pathway that plays a role in immune homeostasis, regulatory T-cell function, tissue regeneration, and host defence against pathogens. Excessive production of TNF has been implicated in psoriasis pathogenesis and its inhibition is a clinically validated treatment.

Materials and Methods

This phase 2b, double-blind, placebo-controlled, dose-ranging study evaluated efficacy and safety of balinatunfib vs placebo in adult participants with moderate-to-severe plaque psoriasis and included both patients naïve to and experienced to advanced therapies. Participants were randomized to receive balinatunfib 200 mg twice-daily (BID), 100 mg BID, 200 mg once daily (QD), 100 mg QD, or 50 mg QD or matching placebo orally for 12 weeks. The primary endpoint was the proportion of patients achieving PASI75 at week 12 (W12) in the advanced therapy-naive cohort. A pre-defined hierarchy of testing of primary endpoint followed the order of 200 mg BID->100 mg BID->200 mg QD.

Results

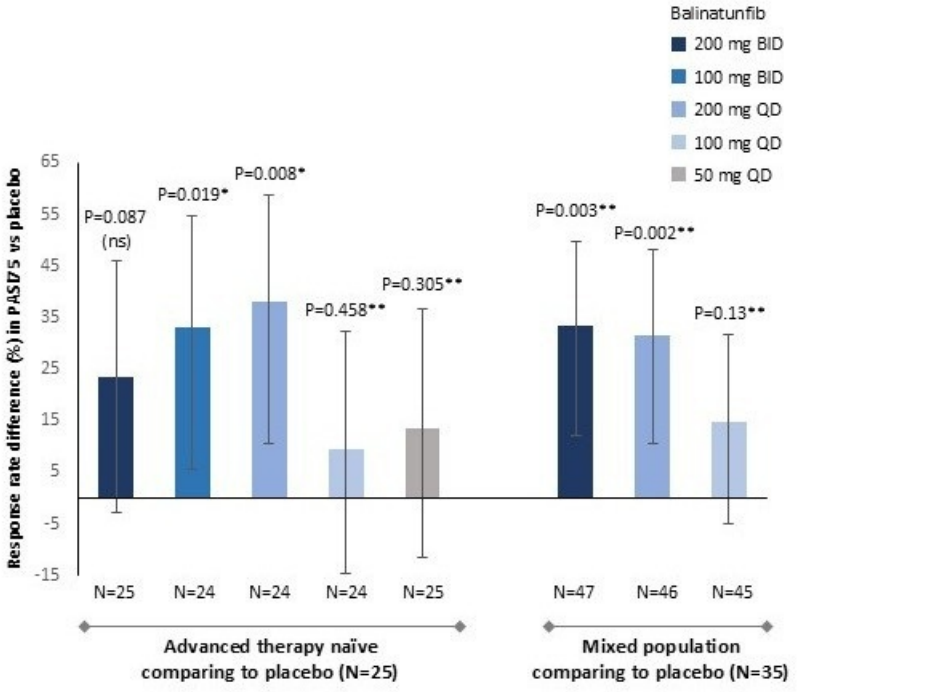
A total of 221 participants with comparable demographic characteristics were randomized to receive balinatunfib

or placebo. An analysis of the primary endpoint showed clinically meaningful efficacy with a numerically higher proportion of patients receiving 200 mg BID balinatunfib in the advanced therapy-naïve population achieving PASI75 vs.placebo at W12 (response rate difference (RRD): 23.43% [95% CI: (-2.74%, 45.98%); P=0.087]). A higher proportion of patients achieved PASI75 with 100 mg BID (RRD: 33.08% [95% CI: 5.71%, 54.83%]; nominal P=0.019), and 200 mg QD, (RRD: 38.02% [10.62%, 58.84%]; nominal P=0.008) in the advanced therapy-naïve patients vs. placebo (Figure). In the mixed study population, comprising both advanced therapy naïve and experienced participants, strong differences were observed in RRD (95% CI) vs. placebo at W12 for PASI75; 33.29% (11.97%, 49.86%) in the 200 mg BID group, 31.62% (10.39%, 48.32%) in the 200 mg QD group (nominal P<0.01 for all) but not in the 100 mg QD group (14.64% [-4.99%, 31.54%]; nominal P=0.13) (Figure). A greater proportion of patients in the mixed population treated with balinatunfib 200 mg QD (41.3%) achieved sPGA 0/1 vs placebo (17.1%) at W12 (nominal P=0.006). Levels of IL-17A, IL-17F, IL-22 and IL-19 were significantly lower in the balinatunfib 200 mg QD group at W4 and W12 vs placebo (nominal P≤0.05). Balinatunfib was generally well tolerated across all tested doses, with no deaths reported and steady-state plasma exposure was maintained until end of treatment. Adverse events were more commonly reported in the 200 mg BID and 200 mg QD groups compared to other doses and placebo. Most frequently reported AEs were nasopharyngitis, dysgeusia and arthralgia.

Conclusion

Balinatunfib, an oral selective inhibitor of TNFR1 signalling, was generally well-tolerated. While the highest balinatunfib dose (200 mg BID) group did not meet statistical significance vs placebo for the primary endpoint (PASI75 at W12) in the naïve population, clinically meaningful and numerically larger (nominal p< 0.05) improvements at W12 were observed with other dose groups vs placebo in both advanced therapy-naïve and experienced patients. Inhibition of TNFR1 signal by balinatunfib was associated with reduction in biomarkers of Th17/Th22-mediated inflammation.

Figure: Response rate difference in PASI75 vs placebo in advanced therapy naïve and mixed population cohorts at Week 12



Error bars represent 95% CI;
*Statistical significance cannot be claimed due to non-significance of 200mg BID dose in the Type-I error multiplicity control plan;
**These comparisons are not under Type-I error multiplicity control, hence p-values are all nominal;
BID, twice daily; CI, confidence interval; ns, non-significant; QD, once daily

Abstract N°: LBA-78

Rocatinlimab With Concomitant Topical Therapy Significantly Improved Clinical Signs and Symptoms of Atopic Dermatitis in Adults: Results From the Phase 3 ROCKET-SHUTTLE Trial

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Introduction

OX40 receptor (OX40R) plays a key role in atopic dermatitis (AD), driving T-cell imbalance and amplifying proinflammatory activity of OX40R+ pathogenic T cells. Rocatinlimab (ROCA; AMG 451/KHK4083) is a T-cell-rebalancing therapy that inhibits and reduces pathogenic T cells by targeting OX40R. The global ROCKET program is evaluating ROCA in adults and adolescents with moderate-to-severe AD.[1] In ROCKET-HORIZON (NCT05651711)[2] and IGNITE (NCT05398445)[3], ROCA Q4W monotherapy significantly improved AD signs and symptoms in adults vs placebo (PBO). From ROCKET- SHUTTLE (NCT05724199), we report results of ROCA with topical corticosteroids and/or topical calcineurin inhibitors (TCS/TCI).

Materials and Methods

746 adults ≥18 years with AD and an inadequate response to TCS (medium-to-high potency)/TCI were randomized (5:4:4) to ROCA 300 mg, ROCA 150 mg or PBO Q4W (plus Wk-2 loading dose) for 24 wks. Concomitant TCS (low-to-medium potency)/TCI were initiated on study Day 1 and tapered based on clinical response. Coprimary endpoints (Wk 24) were ≥75% reduction from baseline in EASI (EASI 75) and a vIGA-AD™ 0 (clear) or 1 (almost clear) with a ≥2-point reduction from baseline. Key secondary endpoints included a ≥90% reduction from baseline in EASI (EASI 90) at Wk 24, EASI 75 and vIGA-AD 0/1 at Wk 16, and a ≥4-point reduction in the weekly average of the daily worst pruritus numeric rating scale at Wk 24. Rescue therapy (RT; high- to super-high–potency TCS or systemics) was permitted from Day 1. Efficacy analyses included all randomized patients, with RT users considered nonresponders and missing data imputed using nonresponder imputation. Safety analyses included all patients receiving ≥1 dose of study drug.

Results

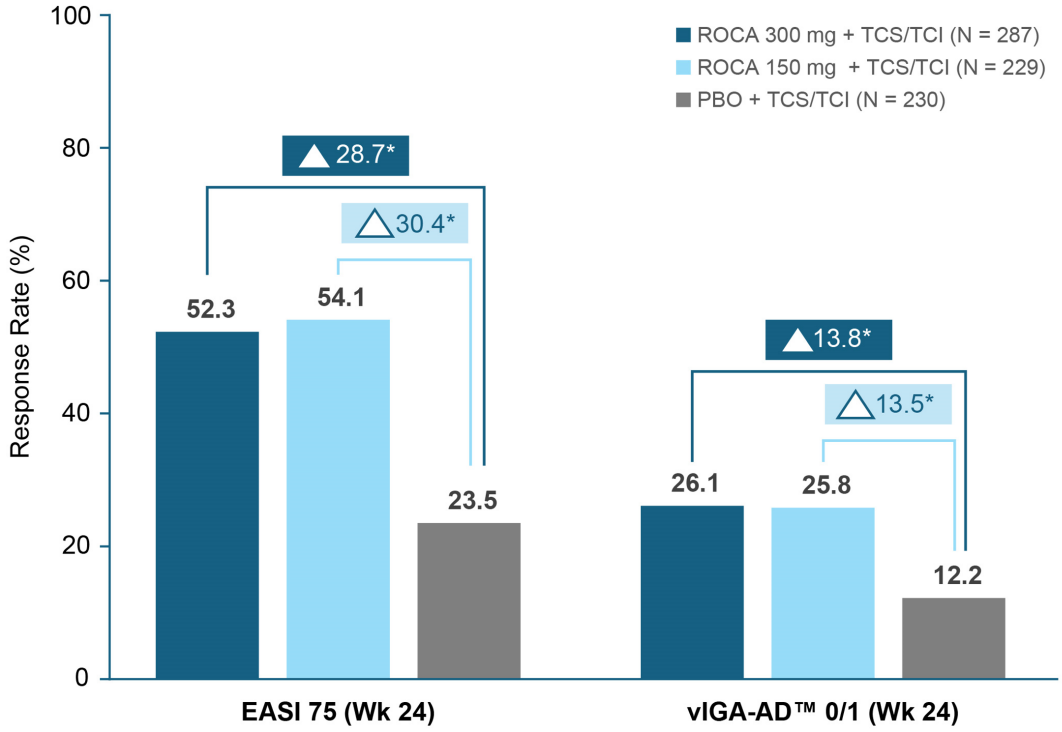
Demographics were well balanced across a diverse global population (Table 1); 59.1% of patients had prior systemic therapy for AD, and 25.3% had prior biologics or systemic JAK inhibitors. Both ROCA arms met the coprimary endpoints (Fig 1; EASI 75 Wk 24, 52.3% [ROCA 300 mg] and 54.1% [ROCA 150 mg] vs 23.5% [PBO]; vIGA-AD 0/1 Wk 24, 26.1% and 25.8% vs 12.2%; all comparisons $P<0.001$) and all key secondary endpoints (data not shown). Progressive efficacy was observed, with no apparent plateau at Wk 24 for the coprimary endpoints (data not shown). TEAEs were balanced across treatment arms (patient incidence of any TEAE, 71.5% [both ROCA arms] vs 67.2% [PBO]; infections, 35.4% [ROCA 300 mg] and 39.9% [ROCA 150 mg] vs 38.0% [PBO]). Incidence of SAEs was higher for ROCA vs PBO (ROCA 300 mg, 3.1%; ROCA 150 mg, 4.4%; PBO, 0.9%); no SAE preferred term was reported by ≥1 patient, and few patients discontinued study drug due to SAEs (ROCA 300 mg, 3/288 [1.0%]; ROCA 150 mg, 4/228 [1.8%]; PBO, 1/229 [0.4%]).

Table 1. ROCKET-SHUTTLE Study Population Demographics and Disease Characteristics

	ROCA 300 mg +TCS/TCI (N=287)	ROCA 150 mg +TCS/TCI (N=229)	PBO +TCS/TCI (N=230)	Total (N=746)
Age, years, mean ± SD	38.8 ± 14.8	38.2 ± 14.3	37.5 ± 14.7	38.2 ± 14.6
Female, n (%)	107 (37.3)	101 (44.1)	95 (41.3)	303 (40.6)
Hispanic/Latino, n (%)	23 (8.0)	17 (7.4)	17 (7.4)	57 (7.6)
Race, n (%)				
White	170 (59.2)	137 (59.8)	132 (57.4)	439 (58.8)
Asian	88 (30.7)	69 (30.1)	78 (33.9)	235 (31.5)
Black or African American	20 (7.0)	16 (7.0)	12 (5.2)	48 (6.4)
Other*	9 (3.1)	7 (3.1)	8 (3.5)	24 (3.2)
Region, n (%)				
Europe	106 (36.9)	90 (39.3)	81 (35.2)	277 (37.1)
North America	97 (33.8)	69 (30.1)	77 (33.5)	243 (32.6)
Asia	68 (23.7)	53 (23.1)	56 (24.3)	177 (23.7)
Other†	16 (5.5)	17 (7.4)	16 (6.9)	49 (6.6)
vIGA-AD™ score,‡ n (%)				
Moderate (score=3)	175 (61.0)	138 (60.3)	137 (59.6)	450 (60.3)
Severe (score=4)	112 (39.0)	91 (39.7)	93 (40.4)	296 (39.7)
EASI total score (0–72),‡ mean ± SD	29.5 ± 11.7	29.1± 10.0	28.9 ±11.2	29.2 ±11.0
Moderate (score ≤21), n (%)	88 (30.6)	54 (23.6)	69 (30.0)	211 (28.3)
Severy/very severe (score >21), n (%)	199 (69.4)	175 (76.4)	161 (70.0)	535 (71.7)
BSA of AD involvement (0%–100%),‡ mean ± SD	45.41 ± 22.57	44.92 ± 21.14	43.60 ± 22.00	44.70 ± 21.95
Prior systemic use, n (%)	164 (57.1)	136 (59.4)	141 (61.3)	441 (59.1)
Prior biologics or systemic JAK inhibitor use, n (%)	66 (23.0)	58 (25.3)	65 (28.3)	189 (25.3)

*Race category of “Other” included American Indian or Alaska native, native Hawaiian or other Pacific Islander, and multiple races. †Region category of “Other” included Australia and Argentina. ‡Baseline vIGA-AD score, EASI score, and BSA were assessed after the first dose of study drug on Day 1.
AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; JAK, Janus kinase; PBO, placebo; ROCA, rocatinlimab; SD, standard deviation; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; vIGA-AD™, validated Investigator Global Assessment for AD.

Figure 1. Significantly higher proportion of patients receiving ROCA vs PBO in combination with TCS/TCI achieved the coprimary endpoints of EASI-75 and vIGA-AD 0/1 at Wk 24



▲ is the risk difference vs PBO; *$P < 0.001$.
EASI 75, a ≥ 75% improvement from baseline Eczema Area and Severity Index (EASI) score; PBO, placebo; ROCA, rocatinlimab; TCS/TCI, topical corticosteroids and/or topical calcineurin inhibitors; vIGA-AD™, validated Investigator Global Assessment for Atopic Dermatitis; vIGA-AD 0/1, vIGA-AD 0 (clear) or 1 (almost clear) at W24 with ≥ 2-point reduction from baseline; Wk, Week.

Conclusion

In a diverse, treatment-experienced AD patient population failing prior topicals, ROCA with concomitant TCS (low-to-medium potency)/TCI demonstrated statistically significant and clinically meaningful improvements vs PBO in AD clinical signs and symptoms with progressive efficacy and no plateau at Wk 24. ROCA combination therapy was well tolerated, and TEAEs were consistent with adult monotherapy studies. With the ROCKET-HORIZON and IGNITE monotherapy studies, ROCKET-SHUTTLE supports the efficacy and safety of ROCA administered with TCS/TCI.

References:

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Abstract N°: LBA-86

Evaluating the Efficacy and Safety of Deucravacitinib in Refractory Lichen Planopilaris: A Single-Center Retrospective Pilot Study

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Introduction

Lichen planopilaris (LPP) is a primary lymphocytic cicatricial alopecia with limited therapeutic options. Although JAK inhibitors have shown promise in refractory cases, partial or non-response persists. This study investigates the efficacy of deucravacitinib—a selective tyrosine kinase 2 (TYK2) inhibitor and a member of the JAK inhibitor family targeting IL-23/Th17 and IFN-I pathways implicated in LPP pathogenesis—based on its established activity in lichen planus.

Materials and Methods

This retrospective study evaluated eight patients with histologically confirmed lichen planopilaris (four with classic LPP, two with FAPD, and two with LPP diffuse pattern) who did not achieve a ≥3-point reduction or had a baseline LPPAI score ≥3 remaining after six months of systemic therapy. All patients received daily 6 mg oral deucravacitinib for at least 12 weeks while concurrently maintaining existing treatments comprising spironolactone (n=3), hydroxychloroquine (n=4), 5% topical minoxidil (n=3), gabapentin (n=2), and topical tacrolimus (n=2). Outcomes were assessed via LPPAI (0-10 scale).

Results

Following a minimum of 12 weeks of treatment, all eight patients exhibited significant reductions in LPPAI scores, with a median pre-treatment score of 3.29 and a post-treatment score of 0.84—an overall 79.6% reduction. All patients experienced relief from pruritus and pain, along with marked improvements in erythema and scaling. One patient even showed partial hair regrowth. One patient discontinued due to hand eczema and herpes simplex.

Conclusion

A 79.6% reduction in LPPAI scores and resolution of symptoms confirm significant clinical efficacy of deucravacitinib in refractory lichen planopilaris, potentially mediated through targeted inhibition of key inflammatory cytokines. Combination therapy demonstrated overall tolerability, though further larger randomized controlled trials are needed to confirm the efficacy and safety of deucravacitinib in LPP.

Abstract N°: LBA-105

Nemolizumab suppressed multiaxial inflammatory pathways and improved barrier protein signatures in skin and blood proteomic analysis of patients with moderate-to-severe AD

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Introduction

Nemolizumab, an anti-IL-31Ra monoclonal antibody, is FDA-approved for the treatment of moderate-to-severe atopic dermatitis (AD) in patients aged ≥12 years. We conducted a biomarker study of blood and cutaneous proteomic profiles using tape strips in a subset of patients with AD enrolled in two phase 3 clinical trials (ARCADIA 1: NCT03985943 and ARCADIA 2: NCT03989349). Patients received nemolizumab 30 mg Q4W with 60 mg loading dose in combination with TCS/TCI or matching placebo in combination with TCS/TCI.

Materials and Methods

Blood samples were collected from 14 nemolizumab-treated and 10 placebo-treated AD patients and tape strips were obtained from lesional and nonlesional skin of 7 nemolizumab- and placebo-treated patients with AD at baseline and after 16 weeks of treatment for OLINK proteomic analysis. Differentially expressed proteins/DEPs were defined by fold change>1.3 and p-value<0.05. Changes in protein expression in nemolizumab-treated patients were correlated with changes in clinical scores: SCORAD, EASI, IGA, and peak pruritus numerical rating scale (PP-NRS).

Results

In skin, nemolizumab significantly downregulated inflammatory proteins including Th1- (IFNGR1, CXCL9/10, CCL4), Th2- (IL13, TSLP, CCL7/11, ST2), and Th17-related proteins (IL6, IL17RA, S100A12) after 16 weeks of treatment with no comparable changes observed in the placebo group. Nemolizumab also downregulated proteins related to innate immunity (LGALS8, RAGE, IL18), Extracellular Matrix (ECM) degradation (MMP1/3/10), and epidermal remodeling (COL1A1, PLAU). Decreases in inflammatory proteins (CRTAM: T-cell marker; CSF2RA: eosinophil marker) were correlated with improvements in EASI, SCORAD, and IGA ($r>0.74$, $p<0.05$ for all). Decreases in several proteins related to pruritus (KLK11, RET) and inflammation (CSF3, PVR, KNYU, MIC A/B) were correlated with improving PP-NRS scores ($r>0.88$, $p<0.05$ for all).

In blood, nemolizumab significantly attenuated T cell activation (ICOS-LG, CD6), innate immunity (IL18, LGALS3), and other inflammatory proteins (IL1R1, CCL16, CXCL16, IL16) after 16 weeks of treatment, which was not observed in the placebo group. Nemolizumab also significantly downregulated proteins related to ECM and barrier degradation (EPCAM, S100A4). Decreases in several inflammatory proteins (CCL15/16, TNFRSF1B, IL2RA,

IGFBP2) were correlated with improving EASI ($r>0.42$, $p<0.05$ for all). Decreases in ADAMTS13, involved in vascular inflammation, were correlated with improving EASI, SCORAD, and IGA ($r>0.49$, $p<0.05$ for all).

Conclusion

Nemolizumab significantly downregulated Th1, Th2, Th17, and innate immunity markers in both skin and blood after 16 weeks of treatment, with changes correlating with clinical improvement. Notably, reductions in ECM remodeling and fibrosis-related proteins suggest nemolizumab may also impact barrier repair in AD.

Abstract N°: LBA-108

Efficacy and Safety of Rezpegaldesleukin, A Selective Regulatory T-Cell-Inducing Interleukin-2 Conjugate, in the Treatment of Atopic Dermatitis: Final Results from the 16-Week Induction of a Randomized Phase 2b Study (REZOLVE AD)

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Introduction

Rezpegaldesleukin (NKTR-358, rezpeg) is an IL-2 receptor (IL-2R) pathway agonist shown to increase the number and function of regulatory T-cells (Tregs), which represents a novel therapeutic strategy for multiple autoimmune and inflammatory diseases. Rezpeg previously demonstrated a differentiated efficacy and safety profile in a Phase 1b trial in adults with moderate-to-severe AD.[1] Here, we present the final 16-week induction efficacy and safety results from an ongoing dose-ranging Phase 2b trial (NCT06136741). The blinded maintenance to Week 52 and follow-up to Week 104 assessments are ongoing.

Materials and Methods

REZOLVE AD is a 104-week, randomized, double-blinded, placebo-controlled Phase 2b monotherapy trial. Adults (18 years or older; n=393) with moderate-to-severe AD were randomized 3:3:3:2 to receive subcutaneous rezpeg 24 µg/kg q2w (n=104), 18 µg/kg q2w (n=106), 24 µg/kg q4w (n=110), or placebo (n=73) during 16-wk induction therapy. The primary endpoint was mean percent change in Eczema Area and Severity Index (EASI) score from baseline at Week 16 and key secondary endpoints included percentage of patients with at least 50%, 75% and 90% reduction from baseline in EASI (EASI-50, -75 and -90, respectively), percentage of patients with Validated Investigator Global Assessment for AD response of 0 (clear) or 1 (almost clear) and a reduction from baseline of ≥2 points (vIGA-AD 0/1), and percentage of patients with a weekly average reduction of Numerical Rating Scale Itch (NRS-Itch) ≥4 points from baseline among those with baseline score ≥4. Exploratory endpoints included additional patient-reported outcome assessments. Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics

Characteristic	Rezpegaldesleukin 24 µg/kg q2w (N=104)	Rezpegaldesleukin 18 µg/kg q2w (N=106)	Rezpegaldesleukin 24 µg/kg q4w (N=110)	Placebo (N=73)
Mean age, years (SD)	38.0 (13.7)	36.3 (15.4)	36.5 (14.3)	37.9 (14.4)
Sex, n (%)				
Male	55 (52.9%)	50 (47.2%)	47 (42.7%)	38 (52.1%)
Race, n (%)				
White	87 (83.7%)	90 (84.9%)	96 (87.3%)	58 (79.5%)
Black or African American	7 (6.7%)	3 (2.8%)	5 (4.5%)	2 (2.7%)
Asian	9 (8.7%)	11 (10.4%)	7 (6.4%)	9 (12.3%)
Region				
North America	27 (26.0%)	29 (27.4%)	31 (28.2%)	21 (28.8%)
Rest of World	77 (74.0%)	77 (72.6%)	79 (71.8%)	52 (71.2%)
EASI				
Mean score (SD)	25.4 (9.14)	27.2 (10.40)	26.1 (10.45)	25.2 (8.57)
≥16 and <21, n(%)	44 (42.3%)	43 (40.6%)	44 (40.0%)	29 (39.7%)
≥21, n (%)	60 (57.7%)	63 (59.4%)	66 (60.0%)	44 (60.3%)
Mean BSA score (SD)	39.3 (18.8)	40.7 (20.9)	39.6 (20.6)	38.2 (19.7)
vIGA-AD score, n (%)				
3 (moderate)	71 (68.3%)	70 (66.0%)	75 (68.2%)	51 (69.9%)
4 (severe)	33 (31.7%)	36 (34.0%)	35 (31.8%)	22 (30.1%)
Itch NRS score				
Mean (SD)	6.8 (2.0)	6.7 (1.9)	7.1 (1.8)	6.3 (2.2)
≥4, n (%)	95 (91.3%)	92 (86.8%)	102 (92.7%)	63 (86.3%)
Pain NRS score				
Mean (SD)	5.9 (2.5)	5.9 (2.5)	6.2 (2.4)	5.4 (2.6)
≥4, n (%)	84 (80.8%)	82 (77.4%)	90 (81.8%)	50 (68.5%)
DLQI score				
Mean (SD)	14.5 (7.2)	13.8 (7.3)	15.9 (7.1)	13.4 (7.1)
≥4, n (%)	100 (96.2%)	102 (96.2%)	107 (97.3%)	65 (89.0%)
ADCT score				
Mean (SD)	15.4 (4.9)	15.5 (5.3)	16.3 (5.0)	14.5 (5.7)
≥5, n (%)	101 (97.1%)	104 (98.1%)	107 (97.3%)	67 (91.8%)
ADSS Q1 score				
Mean (SD)	1.9 (1.1)	2.0 (1.2)	2.1 (1.0)	1.8 (1.2)
≥1.25, n (%)	71 (68.3%)	70 (66.0%)	85 (77.3%)	45 (61.6%)

SD: standard deviation.

Results

Significant improvement over placebo was observed with rezpeg 24 µg/kg q2w in mean percent change in EASI ($p<0.001$), EASI-75 ($p<0.001$), EASI-90 ($p<0.05$), vIGA-AD 0/1 ($p<0.05$), NRS-Itch ($p<0.01$), NRS-pain ($p<0.05$), DLQI-response ($p<0.05$), and ADCT response ($p<0.001$) (Table 2). The other rezpeg arms showed significant dose-dependent improvement in disease severity compared to placebo for the primary endpoint ($p<0.001$) and several key secondary and exploratory endpoints (Table 2). The safety profile (Table 3) was consistent with previously reported safety data based on the integrated safety from 592 exposed subjects[2]. Compared with placebo, there were sustained increases in absolute numbers of circulating total (FoxP3+CD25+) and $CD25^{bright}$ Tregs in the rezpeg groups, as well as dose-dependent reductions of key T helper 2 (Th2) inflammatory markers: IL-19, TARC/CCL17, periostin, and MDC/CCL22.

Table 2. Efficacy assessments at Week 16.

	24 µg/kg q2w	18 µg/kg q2w	24 µg/kg q4w	Placebo
Primary Endpoint	N=104	N=106	N=110	N=73
Mean improvement in EASI score from baseline	61% *p<0.001*	58% *p<0.001*	53% *p<0.001*	31%
Key Secondary Endpoints				
EASI-75	42% *p<0.001*	46% *p<0.001*	34% *p<0.05*	17%
vIGA-AD 0/1	20% *p<0.05*	26% *p<0.01*	19% *ns*	8%
EASI-90	25% *p<0.05*	18% *ns*	17% *ns*	9%
Itch NRS*	42% *p<0.01*	35% *p<0.05*	23% *ns*	16%
Mean improvement in BSA score from baseline	54% *p<0.001*	48% *p<0.001*	43% *p<0.001*	17%
EASI-50	66% *p<0.001*	66% *p<0.001*	55% *p<0.01*	34%
Select Exploratory Endpoints				
DLQI response*	72% p<0.05	64% *ns*	73% p<0.05	54%
ADCT response*	67% p<0.001	61% p<0.01	61% p<0.01	35%
Pain NRS*	45% p<0.05	35% ns	23% ns	22%
ADSS Q1 response*	57% p<0.01	41% ns	46% ns	30%

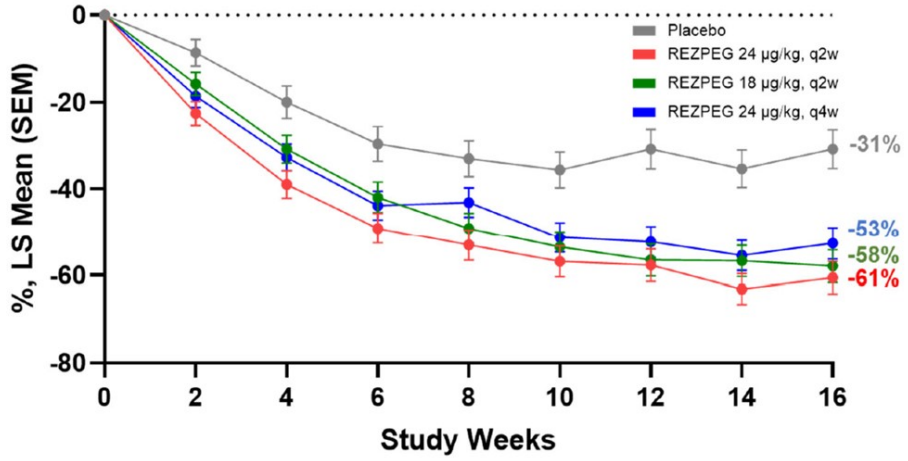
p-values are compared to placebo. ns is not significant. Itch NRS/Pain NRS response is reduction of weekly average score of ≥4 points from baseline; DLQI response is reduction of ≥4 points from baseline; ADCT response is reduction of ≥5 points from baseline; ADSS Q1 response is reduction in weekly average score of ≥1.25. Primary estimand analysis is used where patients who used rescue therapy outside protocol specifications (n=11) or who discontinue treatment due to lack of efficacy (n=2) were considered nonresponders. Data after patients who discontinue due to other reasons are set to missing and all missing data are imputed using the multiple imputation method. Continuous endpoints of %EASI/BSA improvement are analyzed using mixed model for repeated measures (MMRM) while binary endpoints are analyzed using logistic regression

Table 3. Summary of safety and tolerability during the 16 week induction period.

	24 µg/kg q2w	18 µg/kg q2w	24 µg/kg q4w	Pooled rezpeg arms	Placebo
	N=104	N=106	N=110	N=320	N=73
Patients with any TEAE, excluding ISRs	69 (66.3%)	60 (56.6%)	64 (58.2%)	193 (60.3%)	42 (57.5%)
Patients With any Serious AE	1 (1.0%)	4 (3.8%)	0	5 (1.6%)	0
Any Drug-Related Serious AE[1]	0	2 (1.9%)	0	2 (0.6%)	0
Patients with Severe AE	3 (2.9%)	6 (5.7%)	1 (0.9%)	10 (3.1%)	1 (1.4%)
Any Drug-Related Severe AE[2]	3 (2.9%)	3 (2.8%)	0	6 (1.9%)	0
TEAEs leading to study drug discontinuation	8 (7.7%)	5 (4.7%)	5 (4.5%)	18 (5.6%)	0

1. Serious TRAEs: Drug hypersensitivity – severe; Tonsillitis – moderate. Both events resolved.
2. Severe TRAEs (excluding Serious TRAEs): pyrexia (24 µg/kg q2w); two events of injection site reaction (24 µg/kg q2w); ISR, chest pain (18 µg/kg q2w). All five events resolved.

Figure 1: LS mean percent change from baseline in EASI over time during the induction period



Conclusion

In patients with moderate-to-severe AD, treatment with rezpeg showed statistically significant and dose-dependent improvements in physician-assessed and patient-reported assessments over the 16-week induction

period of the phase 2b study. Together with the observed safety profile, these results support further development of rezpeg as a novel biologic AD treatment.

References:

1. Silverberg et al. *Nat Commun.* 2024 15(1):9230.
2. Silverberg et al. American Academy of Dermatology Annual Meeting 2025, Poster ID: 65106.

Abstract N°: LBA-141

DELTA TEEN Phase 3 trial: Efficacy and Safety of Delgocitinib Cream in Adolescents with Moderate to Severe Chronic Hand Eczema

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Introduction

Chronic Hand Eczema (CHE) is a common, multifactorial, inflammatory skin disease associated with itch, pain, and a significant physical and psychosocial burden. Delgocitinib cream 20 mg/g, a topical, non-steroidal, pan-Janus kinase inhibitor, is now approved across Europe and other markets for the treatment of moderate to severe CHE in adults. The DELTA TEEN trial aimed to assess the efficacy and safety of delgocitinib cream in adolescents with moderate to severe CHE.

Materials and Methods

DELTA TEEN (NCT05355818) was a randomised, double-blind, vehicle controlled, multisite, Phase 3 trial. Adolescents (12-17 years) with moderate to severe CHE were randomised 3:1 to twice-daily applications of delgocitinib cream (N=74) or cream vehicle (N=24) for 16 weeks followed by a 2-week safety follow-up period. The primary endpoint was the Investigator's Global Assessment for CHE treatment success (IGA-CHE TS) at Week (W)16, defined as an IGA-CHE score of 0/1 (clear/almost clear) with a ≥2 step improvement from baseline. Key secondary endpoints were ≥90% improvement in the Hand Eczema Severity Index score (HECSI-90) and ≥4-point reductions in Hand Eczema Symptom Diary (HESD) itch, pain, and total scores from baseline to W16 in patients with a baseline score ≥4 points. The primary and key secondary endpoints were analysed using Bayesian

analyses.

Results

Superiority of delgocitinib cream to cream vehicle was demonstrated for the primary endpoint IGA-CHE TS (63.5% vs. 29.2% responders, probability=0.999) and all key secondary endpoints: HECSI-90 (71.6% vs. 37.5% responders) and ≥4-point improvements in HESD itch (64.8% vs. 36.8% responders), pain (63.3% vs. 33.3% responders), and total score (55.6% vs. 31.3% responders).

No serious adverse events (AEs) were reported, and all AEs reported with delgocitinib cream were mild or moderate in severity. The overall proportion and rate of patients reporting AEs were slightly higher for delgocitinib cream (50.0%, 298.88 events per 100 patient years of observation [PYO]) than for cream vehicle (33.3%, 232.33 events per 100 PYO). Few AEs assessed as probably or possibly related to the trial drug and AEs leading to withdrawal from trial or permanent discontinuation were reported, with numerically lower rates for delgocitinib cream (7.76 and 7.76 events per 100 PYO) than cream vehicle (36.68 and 12.23 events per 100 PYO).

Conclusion

Delgocitinib cream 20 mg/g demonstrated superior efficacy compared to cream vehicle and was well tolerated in adolescents with moderate to severe CHE, with no safety concerns identified over 16 weeks of treatment.

Abstract N°: LBA-149

APG777, a Novel, Half-Life Extended Anti-IL-13 Antibody, Demonstrates Safety and Efficacy in Moderate-to-Severe Atopic Dermatitis: 16-Week Results From the Phase 2 APEX Study

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Introduction

APG777 is a first-in-class, half-life extended, humanized, IgG1 monoclonal antibody (mAb) that binds to IL-13 and blocks IL-13-mediated signaling. APG777 was engineered for improved pharmacokinetics (PK) and reduced dosing frequency compared to current therapies. APG777 is the first extended-half-life mAb to be evaluated in moderate-to-severe AD with the goal of reducing the injection burden for patients with this chronic disease. Here, primary efficacy and safety results are reported from the first 16 weeks of Part A of the phase 2 APEX study (NCT06395948).

Materials and Methods

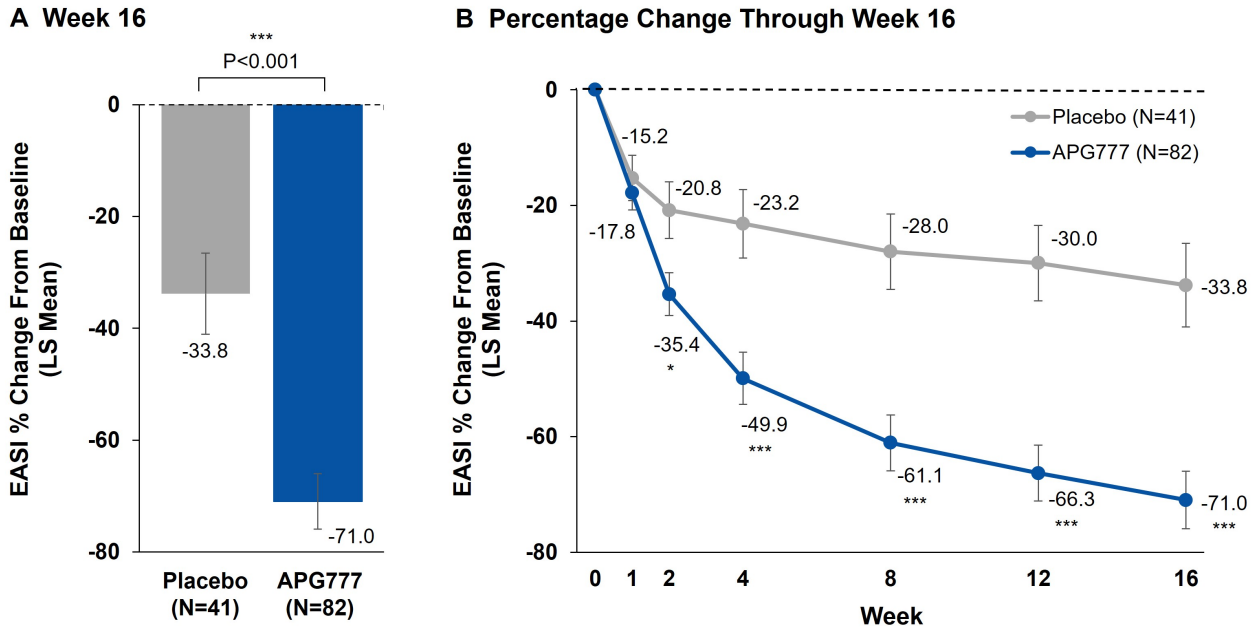
APEX is a 2-part, multicenter, randomized, placebo-controlled phase 2 trial with a proof-of-concept component (Part A) and a dose optimization component (Part B). Part A consists of screening, 16-week induction, and 36-week maintenance periods. Biologic-naïve participants with moderate-to-severe AD (EASI ≥16, vIGA-AD score ≥3, BSA ≥10%) were randomized 2:1 to APG777 (720 mg loading doses at Day 1 and Week 2; 360 mg at Weeks 4 and 12) or matched placebo. The primary endpoint was mean percent change from Baseline in EASI at Week 16. Secondary endpoints included EASI-75, EASI-90, vIGA-AD score of 0/1, and percent change from Baseline in weekly mean I-NRS at Week 16. Post-hoc analyses were conducted to determine the relationship between exposure to APG777 and efficacy.

Results

Treatment with APG777 resulted in a significant 71.0% reduction in EASI from Baseline to Week 16 (vs. 33.8% placebo; $P<0.001$) and was well-tolerated during the 16-week induction period (Figure 1A). Participants receiving APG777 experienced significantly greater percent reductions from Baseline in EASI vs. placebo as early as Week 2 (-35.4% APG777 and -20.8% placebo; $P=0.01$); this effect persisted through Week 16 (Figure 1B). Significantly greater percentages of participants in the APG777 group achieved EASI-75 responses at Week 16 compared with

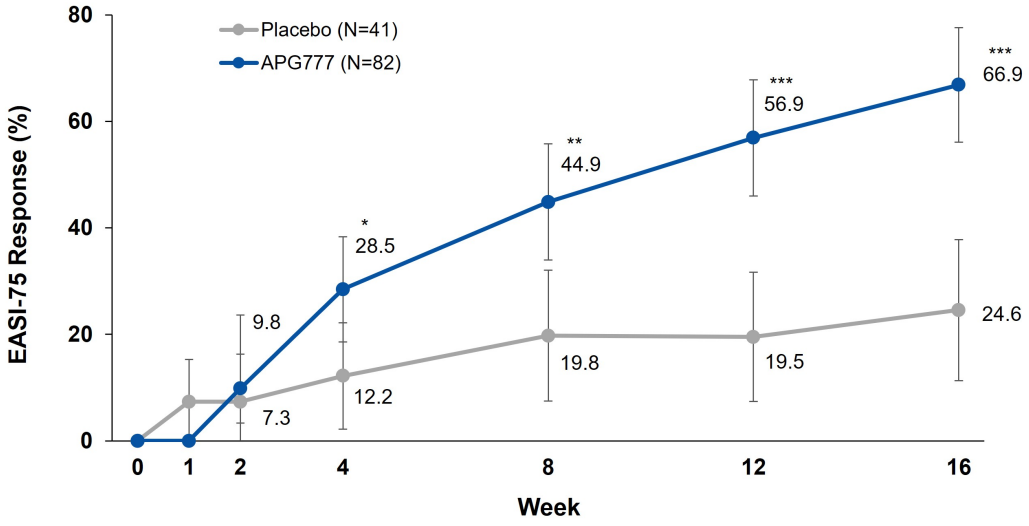
placebo (66.9% vs. 24.6%, P<0.001, Figure 2). Percentages of participants who achieved EASI-90 and vIGA-AD 0/1 responses at Week 16 were also significantly greater with APG777 compared with placebo. In the APG777 group, significant improvement in itch was observed as early as Day 3, as measured by mean percent change in I-NRS from Baseline, and remained significant through Week 16. In post hoc analysis, higher exposures to APG777 led to greater reductions in EASI and higher EASI-75 responses. The most common AEs (occurring in ≥5% of APG777-treated participants) included noninfective conjunctivitis and upper respiratory tract infection, occurring in 14.6% and 8.5% of participants in the APG777 group vs. 2.4% and 12.2% of participants in the placebo group, respectively. Most cases of noninfective conjunctivitis were mild or moderate, transient, and resolved by the end of the induction period.

Figure 1. EASI Percentage Change from Baseline Through Week 16



*p<0.05, week 2; ***p<0.001 vs placebo, weeks 4–16. Error bars represent standard error. Missing data were imputed with Markov Chain Mote Carlo Multiple Imputation (MCMC-MI).

Figure 2 Percentage of Participants Achieving EASI-75 Response Through Week 16



*p<0.05, week 4; **p<0.01, week 8; ***p<0.001 vs placebo, weeks 12, 16.
Error bars represent 95% confidence interval. Missing data were imputed with Markov Chain Mote Carlo Multiple Imputation (MCMC-MI).

Conclusion

Treatment with APG777 over 4 dosing days during the 16-week induction period led to significant improvement in the signs and symptoms of AD and was well-tolerated. Primary results of this phase 2 trial support further evaluation of every 12- or every 24-week dosing in the maintenance portion of APEX Part A, while the demonstration of an exposure-response relationship supports evaluation of higher doses of APG777 in APEX Part B.

Abstract N°: LBA-163

Molecular Design & Characterization of GTX-B001: A Bispecific Antibody targeting c-Kit/CD203c for Selective Mast Cell Silencing

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Introduction

Mast cells (MCs) are a key effector in chronic inflammatory signaling pathways and can be activated via both IgE and non-IgE dependent routes leading to granule release, recruitment of other immune cells and local amplification of immune activation. C-kit represents a cardinal mast cell gene, and phosphorylation of c-Kit triggered by SCF controls mast cell differentiation, migration, adhesion, maturation, survival and activation. It has been shown that c-Kit inhibition, via c-Kit targeting antibodies, can effectively deplete mast cells and ameliorate disease in chronic induced and spontaneous urticaria. However, c-Kit has broad global expression and side effects of c-kit targeting include changes in hair and skin pigmentation, taste disorders and neutropenia. We sought to engineer a bispecific antibody, GTX-B001 (ALY-301), that targets c-Kit selectively in mast cells to maintain efficacy while improving the safety profile to enable chronic dosing for chronic inflammatory disease.

Materials and Methods

Recent advances in single cell proteomics have enabled the characterization of the mast cell proteome and revealed several mast cell selective surface markers. CD203c was of particular interest as expression is upregulated at the surface of activated mast cells while being very much restricted to the granulocyte lineage. GTX-B001 was engineered by combining humanized anti-c-Kit and CD203c heavy chain binding domains with a common light chain using classical knob-in-hole (KiH) mutations in the Fc region to ensure effective heterodimeric pairing. Additional engineering was incorporated into the IgG1 Fc region to ablate FcγR interaction and subsequent engagement with immune effector cells. GTX-B001 was expressed and purified from a stable CHO cell line and characterized for purity, stability, selectivity and potency.

Results

GTX-B001 proved highly productive (>4 g/L) and was purified to >99% homogeneity using a platform purification process combining Protein A and ion-exchange chromatography. Purified GTX-B001 showed excellent stability, retaining >99% purity by SEC and 95% potency as measured by dual binding ELISA after 6 months at 25^0C.

Mast cell selectivity experiments demonstrated a classical co-operative binding mechanism for GTX-B001 with minimal binding being observed on KU812 cells engineered to express only a single target. In contrast, high affinity binding of GTX-B001 was observed to the parental KU812 cells expressing both targets. This differential was also clear when comparing GTX-B001 binding to KU812 cells versus primary melanocytes. When compared with the anti-cKit-specific antibody Barzovolimab, GTX-B001 had an affinity >100x lower on primary melanocytes

while both molecules demonstrated equivalent binding to dual target expressing KU812 cells.

Affinities for each targe ranged from 40-80 nM when measured by SPR, and this was equivalent for the cynomologus monkey orthologs, enabling good translation for in vivo safety studies. GTX-B001 blocked fluorescently labelled SCF from binding to c-Kit expressed on KU812 cells with an IC50 of 0.86 nM and inhibited downstream c-Kit phosphorylation with an IC50 of 5 nM. GTX-B001 bound to primary human skin mast cells isolated from healthy donors in a manner that was dose-dependent, with an affinity that was absolutely driven by CD203c expression level, again confirming the dual target selectivity.

Cell based assays measuring FcγR engagement, including Antibody-Dependent Cell mediated Phagocytosis (ADCP) and Cytotoxicity (ADCC) and Complement Dependent Cytotoxicity (CDC) confirmed that GTX-B001 is not effector function competent.

Conclusion

These studies provide evidence that GTX-B001 is an effective MC-selective agent with demonstrated co-operative binding only to cells that express both c-Kit and CD203c targets. This has the potential for safe and potent mast cell targeting without global c-Kit targeting side effects and enables chronic dosing in chronic inflammatory disease settings.

Abstract N°: LBA-183

Maintenance of Response With Icotrokinra, a Targeted Oral Peptide, for the Treatment of Moderate-to-Severe Plaque Psoriasis: Randomized Treatment Withdrawal in Adults (Weeks 24-52) and Continuous Treatment in Adolescents (Through Week 52) From the Phase 3, ICONIC-LEAD Trial

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Introduction

Icotrokinra (ICO) is a targeted oral peptide that selectively binds the IL-23–receptor and inhibits IL-23 pathway signaling. In the phase 3 ICONIC-LEAD study (NCT06095115), ICO demonstrated significantly higher rates of skin clearance vs placebo (PBO) at Week (W)16, with increasing response rates and no safety signal through W24 in adults and adolescents with moderate-to-severe plaque psoriasis (PsO).[1] Here, we report maintenance of ICO clinical response during the randomized-withdrawal period in adults (ICO vs PBO from W24-52), longer-term ICO effects in adolescents (through W52), and safety in both adults and adolescents through W52 of ICONIC-LEAD.

Materials and Methods

ICONIC-LEAD randomized adults and adolescents (≥12 years) with moderate-to-severe plaque PsO (body surface area ≥10%; Psoriasis Area and Severity Index [PASI] score ≥12; Investigator's Global Assessment [IGA] score ≥3) 2:1 to once-daily (QD) ICO 200 mg through W24 or PBO through W16 followed by ICO 200 mg QD. At W24, ICO-randomized adults who achieved PASI 75 or IGA 0/1 response (W24 ICO responders) were re-randomized 1:1 to either continue ICO or to receive PBO (treatment withdrawal; retreated with ICO 200 mg QD upon loss of ≥50% W24 PASI improvement). Adolescents continued ICO 200 mg QD through W52. Key secondary endpoints (PASI 75/PASI 90 at W52 and time to loss of PASI 75/PASI 90 through W52 among re-randomized adults) for ICO vs PBO were multiplicity-controlled.

Results

Among 412 adults randomized to ICO at baseline, 341 were recorded as PASI 75 or IGA 0/1 responders at W24, with 169 and 172 re-randomized to ICO and PBO, respectively. W24 ICO responders re-randomized to ICO had superior maintenance of PASI response vs PBO at W52 (PASI 75: 89% vs 30%; PASI 90: 84% vs 21% among W24 PASI 75 or PASI 90 responders, respectively; both adjusted $p<0.001$; **Fig 1**). Among W24 ICO PASI 75 or PASI 90 responders, median time to loss of response through W52 was not reached (NR) in those continuing ICO vs 16.9 and 10.1 weeks, respectively, among those re-randomized to PBO (both adjusted $p<0.001$). Among ICO W24 IGA 0/1 responders, higher proportions of ICO vs PBO re-randomized participants (pts) achieved IGA 0/1 at W52 (nominal $p<0.001$; **Fig 1**). Median time to loss of IGA 0/1 response among W24 IGA 0/1 responders was NR in those continuing ICO vs 10.1 weeks among those re-randomized to PBO (nominal $p<0.001$).

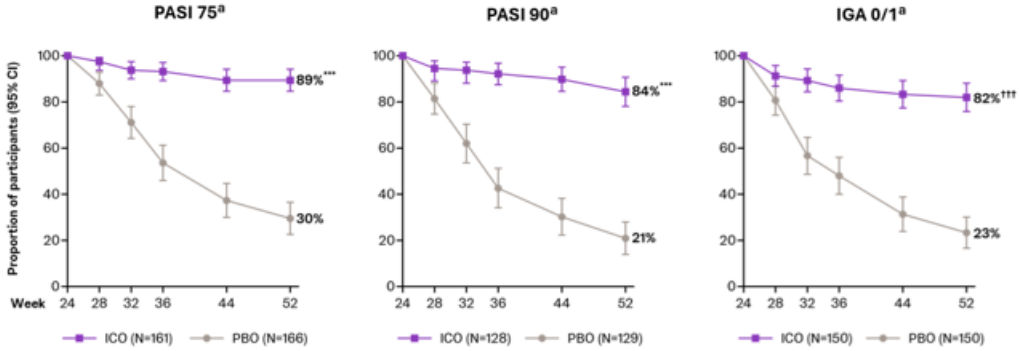
The proportion of ICO adolescent pts who achieved PASI or IGA responses increased over time, with all (100%) achieving PASI 75 by W32 and near maximum response rates achieved for IGA 0/1 (86%) and PASI 90 (89%) by W24. Response rates at W52 were generally stable (IGA 0/1: 82%; PASI 90: 86%; PASI 75: 95%; **Fig 2**). Consistent with overall study population findings through W24,[1] no ICO safety signal was identified through W52.

Conclusion

Among adult W24 ICO responders, pts re-randomized to ICO had superior maintenance of skin response vs those re-randomized to PBO, indicating continued ICO treatment effectively maintained skin response. Adolescents receiving ICO continuously through W52 exhibited robust and durable rates of skin clearance. ICO safety in adults and adolescents with moderate-to-severe plaque PsO through W52 was consistent with that observed through W24.

1. Bissonnette R. AAD Annual Meeting; March 8, 2025; Orlando, FL, USA.

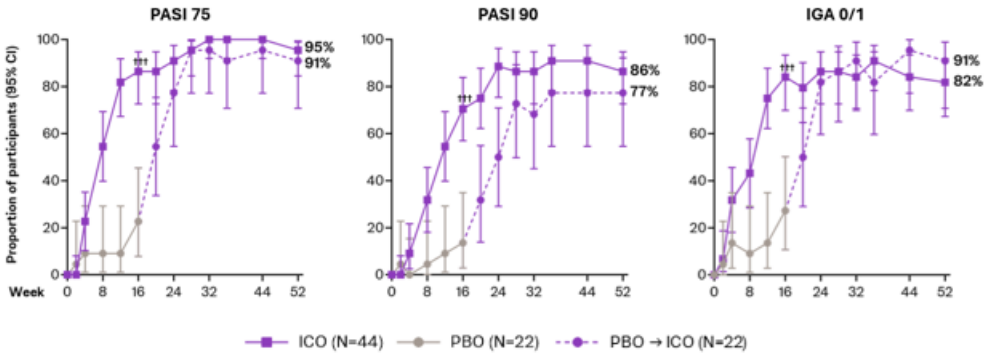
Figure 1: Proportion of Adult W24 ICO Responders Achieving PASI and IGA Responses From W24 Through W52



Adjusted ***p<0.001 vs PBO. Nominal †††p<0.001 vs PBO.

[a]Among W24 ICO PASI 75, PASI 90, or IGA 0/1 responders, respectively. P-values based on Cochran-Mantel-Haenszel chi-square test stratified by geographic region and/or PASI 90 response status at W24. Pts with the following intercurrent events after W24 were considered nonresponders: discontinued study drug due to a lack of efficacy or adverse event (AE) of worsening PsO; initiated a prohibited medication that could impact PsO; or met retreatment criterion during the randomized withdrawal period (for pts randomized to PBO at W24). Observed data were used for pts who discontinued study drug for other reasons. After accounting for these intercurrent events, pts with missing data were considered nonresponders.

Figure 2: Proportion of Adolescent Participants Achieving PASI and IGA Responses Through W52



Nominal †††p<0.001 vs PBO.

P-values based on Cochran-Mantel-Haenszel chi-square test stratified by geographic region. Pts with the following intercurrent events were considered nonresponders: discontinued study drug due to a lack of efficacy or AE of worsening PsO; or initiated a prohibited medication that could impact PsO. Observed data were used for pts who discontinued study drug for other reasons. After accounting for these intercurrent events, pts with missing data were considered nonresponders.

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Abstract N°: LBA-193

Baricitinib in the Treatment of Adults with Pyoderma Gangrenosum: A Phase II Open Label Trial

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Introduction

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis marked by chronic, painful skin ulcerations. While biologics have shown efficacy, none are currently approved for PG by the US Food and Drug Administration or European Medicines Agency. Given its role in autoimmune and inflammatory pathways, the JAK-STAT axis is a promising target. Baricitinib, an oral JAK inhibitor, is approved by the European Medicines Agency (4mg and 2mg) and the Food and Drug Administration (2mg) for rheumatoid arthritis (RA), one of the most common PG comorbidities with several shared inflammatory pathways.

Materials and Methods

This open-label phase II trial evaluated the safety and efficacy of baricitinib in five adult female patients with classic PG (median age 50). Patients received 4mg of baricitinib daily for 24 weeks. A brief course of prednisone (starting at 30 mg daily) was administered for 2-4 weeks prior to baricitinib initiation to stabilize inflammation, then tapered to ≤8 mg by week 7 and discontinued by week 13.

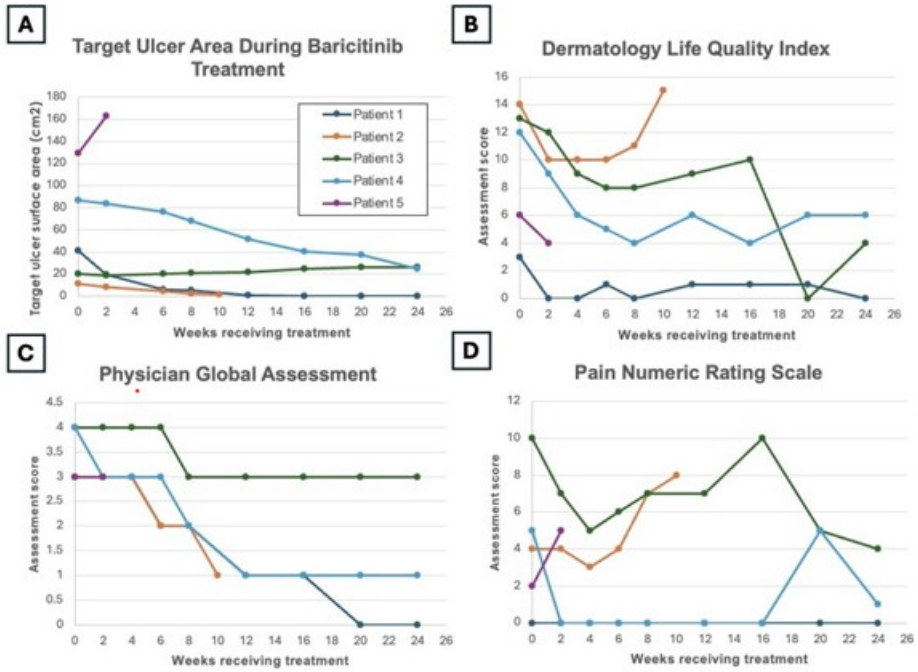
One target ulcer (TU) was followed per patient. The primary outcome was complete TU re-epithelialization. Secondary outcomes included reductions in TU surface area, Physician Global Assessment (PGA) score, Dermatology Life Quality Index (DLQI) score, and Numeric Rating System (NRS) pain score. The DLQI ranges from 0 to 30, the PGA from 0-4, and the NRS from 0 to 10, with higher scores indicating greater impairment, disease activity, and pain respectively. Clinically meaningful thresholds were defined as PGA of 0 or 1 (no to minimal disease activity), ≥4 point reduction in DLQI, and ≥2 point reduction in NRS.

Results

Three of five patients completed the 24-week course. One patient withdrew at week 10 due to lower extremity edema and weight gain. One patient died, likely due a cardiopulmonary event in the setting of multiple risk factors (BMI > 50, hypertension, recent long-haul air travel). This event was deemed possibly related to baricitinib.

Of the five patients, one (20%) achieved complete TU re-epithelialization. Three (60%) reached a PGA of 0 or 1. Three (60%) achieved ≥4-point DLQI reductions. Two (40%) achieved ≥2 point NRS reductions. All four surviving patients successfully discontinued corticosteroids, a common first-line treatment in PG. Adverse events potentially related to baricitinib included peripheral edema, weight gain, and the cardiopulmonary event. No patients developed new ulcers during the study period. Trends in target ulcer area, PGA scores, DLQI and NRS pain scores over 24 weeks are presented in **Figure 1**.

Figure 1. Clinical response over 24 weeks of baricitinib treatment Each line represents an individual patient. Patient 2 withdrew at week 10, and patient 5 died after week 2. A) Target Ulcer Area (cm^2) decreased in 3 of 5 patients, with one patient achieving complete healing. B) DLQI scores decreased for 4 of 5 patients. C) PGA scores decreased for all patients and remained stable in 1 patient. D) NRS scores improved in 3 of 5 patients.



Conclusion

Baricitinib demonstrated signs of clinical benefit in classic PG. Two patients remain healed one year after the trial, and one patient continues to improve after 3 additional months on JAK inhibitor tofacitinib. Only one patient experienced disease recurrence on a location separate from her TU. These findings support further investigation of JAK inhibition in PG, with careful attention to cardiovascular risk stratification.

Abstract N°: LBA-198

Povorcitinib for Moderate to Severe Hidradenitis Suppurativa: Week 24 Interim Phase 3 Results

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Introduction

Hidradenitis suppurativa (HS) is a chronic, recurrent disease marked by periodic flares. Povorcitinib is an oral, next-generation, highly selective Janus kinase 1 inhibitor in clinical development for the treatment of HS. We present the first efficacy and safety data of povorcitinib through Week (Wk) 24 from the registrational phase 3 STOP-HS1/STOP-HS2 studies in patients (pts) with moderate to severe HS.

Materials and Methods

Pts (≥18 y) with HS diagnosis for ≥3 months and prior systemic therapy (oral antibiotic or biologic) were randomized 1:1:1 to once-daily povorcitinib 45 mg, 75 mg, or placebo for 12 wk, followed by a 42-wk extension with povorcitinib 45 or 75 mg. Concomitant use of systemic antibiotics was not allowed, except for rescue. The primary endpoint was the percentage of pts achieving HS Clinical Response (HiSCR50; ≥50% decrease from baseline in abscess and inflammatory nodule (AN) count with no increase in number of abscesses or draining tunnels) at Wk 12. Key secondary endpoints included achievement of HiSCR75 (≥75% decrease), ≥3-point decrease in Skin Pain numerical rating scale (NRS), and percentage of pts experiencing a flare (≥25% increase in AN count [and ≥2 AN increase] from baseline) at Wk 12. Safety and tolerability were also evaluated. Nonresponder imputation was applied through Wk 12, with observed values used thereafter. $P<0.025$ was considered statistically significant.

Results

In STOP-HS1/STOP-HS2, 608/619 pts were randomized (current smokers, 48.8%/45.7%; biologic-experienced, 35.9%/38.6%), and 553/549 entered the extension period .The primary endpoint, HiSCR50 at Wk 12, was achieved by significantly more povorcitinib- vs placebo-treated pts in STOP-HS1/STOP-HS2 (45 mg, 40.2%/42.3%; 75 mg, 40.6%/42.3% vs placebo, 29.7%/28.6%; all P<0.025). Povorcitinib also showed superiority in HiSCR75 (45 mg, 20.6%/25.5%; 75 mg, 24.3%/28.4% vs placebo, 15.8%/13.3%), ≥3-point decrease in Skin Pain NRS (17.2%/29.1%, 22.2%/22.0% vs 11.4%/9.3%), flares (25.0%/21.6%, 26.2%/20.7% vs 33.7%/33.5%), and mean change from baseline in dT (−28.6%/−42.9%, −37.2%/−42.7% vs −10.4%/−15.0%) at Wk 12 (**Table**) .

At Wk 24, HiSCR50 was achieved by nearly 60% of the efficacy-evaluable pts across treatment groups (45 mg, 52.9%/57.1%; 75 mg, 50.0%/58.5%; placebo→45 mg, 64.0%/58.0%; placebo→75 mg, 62.7%/56.3%). Continued improvements were also seen in HiSCR75 (31.0%–40.3%), HiSCR90 (13.8%–27.7%), and HiSCR100 (9.2%–21.3%; **Table**).

Treatment-emergent adverse events (AEs) occurred in 75.1%/73.0% (povorcitinib-randomized) and 53.0%/44.5% (placebo→povorcitinib) of pts through 24 wk; serious AEs in 3.4%/4.6% and 1.1%/3.3%; and AEs of special interest in 4.7%/7.0% and 1.6%/4.4%. Clinically relevant hematological abnormalities occurred in <1.0% of pts treated with povorcitinib for 24 wk.

Table: Summary of STOP-HS1 and STOP-HS2 Endpoints

Endpoints, n (%)	STOP-HS1			STOP-HS2		
Week 12	Placebo (n=202)	Povorcitinib 45 mg (n=204)	Povorcitinib 75 mg (n=202)	Placebo (n=203)	Povorcitinib 45 mg (n=208)	Povorcitinib 75 mg (n=208)
HiSCR50	60 (29.7)	82 (40.2)	82 (40.6)	58 (28.6)	88 (42.3)	88 (42.3)
P value*		0.0240	0.0214		0.0035	0.0033
HiSCR75	32 (15.8)	42 (20.6)	49 (24.3)	27 (13.3)	53 (25.5)	59 (28.4)
P value*		0.1981	0.0309		0.0017	0.0002
≥3-point decrease in Skin Pain NRS	17 (11.4)	27 (17.2)	35 (22.2)	14 (9.3)	48 (29.1)	35 (22.0)
P value*		0.1375	0.0172		<0.0001	0.0015
Flares	68 (33.7)	51 (25.0)	53 (26.2)	68 (33.5)	45 (21.6)	43 (20.7)
P value*		0.0557	0.1053		0.0067	0.0032
Change from baseline in draining tunnels, mean (SD), %	−10.4 (100.4)	−28.6 (88.1)	−37.2 (96.0)	−15.0 (91.6)	−42.9 (58.4)	−42.7 (64.2)
P value (nominal)		0.0865	0.0119		0.0013	0.0014

Endpoints, n (%)	STOP-HS1				STOP-HS2			
Week 24	Placebo →45 mg (n=86)	Placebo→ 75 mg (n=83)	45 mg (n=155)	75 mg (n=158)	Placebo →45 mg (n=81)	Placebo →75 mg (n=87)	45 mg (n=161)	75 mg (n=159)
HiSCR50	55 (64.0)	52 (62.7)	82 (52.9)	79 (50.0)	47 (58.0)	49 (56.3)	92 (57.1)	93 (58.5)
HiSCR75	31 (36.0)	33 (39.8)	58 (37.4)	54 (34.2)	31 (38.3)	27 (31.0)	60 (37.3)	64 (40.3)
HiSCR90	21 (24.4)	23 (27.7)	37 (23.9)	32 (20.3)	18 (22.2)	12 (13.8)	40 (24.8)	41 (25.8)
HiSCR100	17 (19.8)	17 (20.5)	33 (21.3)	23 (14.6)	17 (21.0)	8 (9.2)	32 (19.9)	31 (19.5)

*$P<0.025$ was considered statistically significant.
HiSCR, Hidradenitis Suppurativa Clinical Response; HiSCR50/75/100, ≥50%/≥75%/100% decrease in abscess and inflammatory nodule count from baseline with no increase in the number of abscesses or draining tunnels; NRS, Numerical Rating Scale.

Conclusion

Povorcitinib demonstrated clinically meaningful superiority over placebo in pts with HS within 12 wk, with continued improvements through Wk 24, including in high-threshold, stringent endpoints such as HiSCR90 and HiSCR100. Both doses were well tolerated, with a very low frequency of laboratory abnormalities.

Abstract N°: LBA-213

First-in-Class FASN Inhibitor Denifanstat Achieved All Endpoints in the Treatment of Acne Vulgaris: Results from a Phase III Randomised Placebo Controlled Trial

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Introduction

Denifanstat is a fatty acid synthase (FASN) inhibitor that addresses acne vulgaris by inhibiting *de novo* fatty acid synthesis in human sebocytes. A previous Phase II clinical trial (NCT05104125) showed that denifanstat was safe and well tolerated, leading to a significant improvement in acne lesions. Optimal efficacy was observed at a dose of 50mg. Here we report results from a Phase III clinical trial conducted to further evaluate the efficacy and safety of denifanstat in the treatment of acne vulgaris in a larger cohort of patients.

Materials and Methods

This randomised, double-blind, placebo-controlled, multicentre Phase III clinical trial (NCT06192264) was conducted in China. Patients with moderate to severe acne (Investigator's Global Assessment 3 and 4) were randomly assigned at a 1:1 ratio to receive either 50 mg of oral denifanstat tablets or a matching placebo once daily for 12 weeks.

Results

480 patients with moderate-to-severe facial acne vulgaris were enrolled in the trial. The mean age of participants was 22.6 years, with 68.8% female and 94.8% of Han ethnicity. At baseline, the mean inflammatory and non-inflammatory lesion counts were 42.6 and 59.5, respectively. Approximately 85.8% of subjects had an Investigator's Global Assessment (IGA) score of 3 (moderate).

By week 12, the treatment success rate (defined as a ≥2-point reduction in IGA from baseline and an IGA of 0 or 1) was significantly higher in the 50 mg denifanstat group (33.17%) than in the placebo group (14.58%). The difference between the two groups was 18.59% (95% CI: 15.58%, 21.61%, $P < 0.0001$). The denifanstat group showed a significant 57.38% reduction in total lesion count from baseline, which was markedly superior to the 35.42% reduction observed in the placebo group (an inter-group difference of -21.96%, with a 95% CI of -27.51% to -16.40% and a *P*-value of < 0.0001). Specifically, inflammatory lesions decreased by 63.45% in the denifanstat group compared to 43.21% in the placebo group (difference: -20.24%, 95% CI: -26.21%, -14.27%, $P < 0.0001$). Non-inflammatory lesions decreased by 51.85% compared to 28.94% in the placebo group (difference: -22.91%, 95% CI: -30.02%, -15.80%, $P < 0.0001$). Detailed efficacy outcomes are summarized in Table 1.
During the 12-week treatment period, denifanstat at a dose of 50 mg demonstrated a favourable safety and tolerability profile. The overall incidence of treatment-emergent adverse events (TEAEs) was similar in the denifanstat and placebo groups. The incidence of trial drug-related TEAEs was below 10% in both groups. Dry skin (6.3% vs 2.9%) and dry eye (5.9% vs 3.8%) were the only TEAEs to occur in more than 5% of patients in the treatment group. All drug-related adverse events were mild or moderate (Grade 1-2), with no Grade 3 or higher adverse events or serious adverse events (SAEs) reported, and no deaths.

Table 1 Efficacy Outcomes for Denifanstat vs. Placebo at Week 12 (Intention-To-Treat Analysis)

Efficacy endpoints	50mg Denifanstat (N=240)	Placebo (N=240)	Difference LS Mean(95%CI)	*P*-value
Treatment success，n(%)	75 (33.17%)	33 (14.58%)	18.59 (15.58, 21.61)	<0.0001
PCFB in TL, LS Mean (SE), %	-57.38(1.99)	-35.42 (2.03)	-21.96 (-27.51, -16.40)	<0.0001
PCFB in IL, LS Mean (SE), %	-63.45 (2.14)	-43.21 (2.18)	-20.24 (-26.41, -14.27)	<0.0001
PCFB in NIL, LS Mean (SE), %	-51.85 (2.55)	-28.94 (2.58)	-22.91 (-30.02, -15.80)	<0.0001
ACFB in TL, LS Mean (SE)	-58.25 (2.06)	-36.17 (2.08)	-22.08 (-27.79, -16.37)	<0.0001
ACFB in IL, LS Mean (SE)	-26.56 (0.94)	-18.42 (0.95)	-8.14 (-10.74, -5.54)	<0.0001

Treatment success was defined as a ≥2-point reduction in IGA score from baseline and an absolute score of 0 or 1. PCFB: Percent Change from Baseline; ACFB: Absolute Change from Baseline; TL: Total Lesions; IL: Inflammatory Lesions; NIL: Non-inflammatory Lesions; LS: Least Squares; SE: Standard Error. P-values were calculated using ANCOVA.

Conclusion

Once daily 50 mg denifanstat achieved highly statistically significant and clinically meaningful improvements across all efficacy endpoints. The exceptional efficacy of denifanstat coupled with its favorable safety and

tolerability profile represents a potential major break-through for the treatment of acne vulgaris.

Abstract N°: LBA-221

Remibrutinib decreases specific IgG autoantibody levels in patients with Chronic Spontaneous Urticaria

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Introduction

Chronic spontaneous urticaria (CSU) is a disease characterized by the spontaneous occurrence of itchy wheals and/or angioedema without any definite triggers and lasting for >6 weeks. Elevated serum levels of specific IgG autoantibodies (eg, to thyroid peroxidase [TPO], thyroglobulin [TG] and the high affinity IgE receptor [FcεRI]) are associated with CSU in autoimmune/type IIb CSU patients. Remibrutinib, an oral, highly selective Bruton's tyrosine kinase (BTK) inhibitor, has shown superior efficacy versus placebo and a favorable safety profile in the 52-week pivotal phase 3 studies (REMIX-1 and REMIX-2) when administered as an add-on medication in patients with CSU who remain symptomatic despite treatment with second-generation H_1-antihistamines (Fig. 1). Given the role of BTK in B cell activation and autoantibody production, we examined whether remibrutinib affected autoantibody levels.

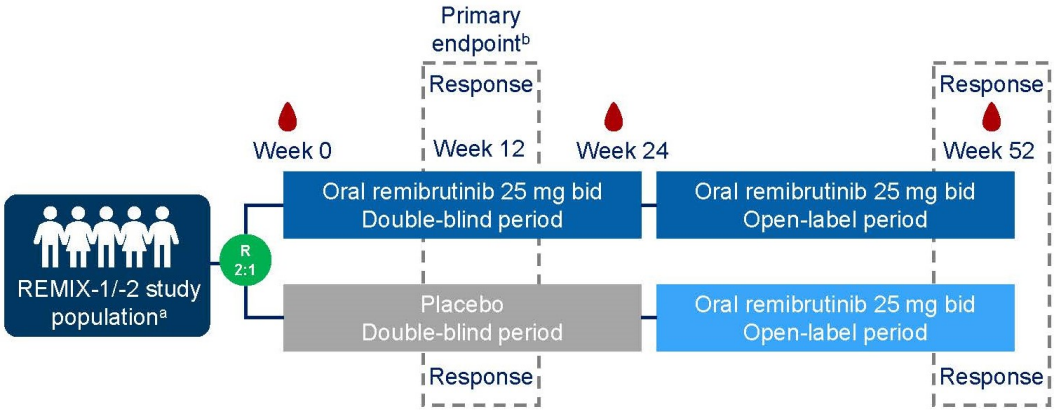

Figure 1: Schematic of the clinical trial design for both REMIX-1 and REMIX-2 studies. Patients were randomized to receive 25mg bid oral remibrutinib or placebo until Week 24 after which all patients received 25mg bid oral remibrutinib until Week 52. Blood samples for autoantibody assessments were taken at Week 0, Week 24 and Week 52. Clinical response to treatment was assessed at Week 12 and Week 52.

[a]Adult patients with a diagnosis of CSU (for ≥6 months) inadequately controlled by second-generation H_1-AH. Patient with presence of itch and hives for ≥ 6 consecutive weeks before screening despite the use of a second-generation H_1-AH; UAS7 ≥ 16, ISS7 ≥ 6 and HSS7 ≥ 6 during the 7 days before randomization (day 1).
[b]The primary endpoint of the analysis is change in UAS7 from baseline to week 12.
bid, twice daily; CSU, chronic spontaneous urticaria. H_1-AH, antihistamine; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score; N, number of patients; R, randomization; UAS7, weekly Urticaria Activity Score.

Materials and Methods

Using a bead-based cytometric assay, we profiled IgG autoantibodies in 1191 samples taken at baseline, Week 24 and Week 52 of 397 CSU patients from the REMIX-1/-2 clinical trials (NCT05030311, NCT05032157; Table 1). Patients were randomized to receive 25mg bid oral remibrutinib or placebo until Week 24 after which all patients received 25mg bid oral remibrutinib until Week 52 (Figure 1). In addition, we quantified levels of soluble CD23/FcεRII, the low affinity IgE receptor, using an immunoassay and measured frequencies of defined B cell subsets using flow cytometry at baseline, Week 4, Week 12, Week 24 and Week 52. We combined biomarkers and available patient data including treatment information, clinical and placebo response and the Chronic Urticaria Index (CUI) test to perform subgroup analysis.

	REMIX-1	REMIX-2
Total number of samples	648	543
Week 0, Week 24, Week 52	216[a]	181[a]
Treatment arm, n (%)		
Oral remibrutinib 25 mg bid	144 (66.7)	119 (65.7)
CUI+	47 (32.6)	40 (33.6)
CUI-	97 (67.4)	79 (66.4)
Placebo	72 (33.3)	62 (34.3)
CUI+	16 (22.2)	18 (29.0)
CUI-	56 (77.8	44 (71.0)
Ethnicity, n (%)		
Non-Asian	189 (87.5)	122 (67.4
Asian	27 (12.5)	59 (32.6)
Sex, n (%)		
Male	74 (34.3)	65 (35.9)
Female	142 (65.7)	116 (64.1)
CU-index, n (%)		
CUI+	63 (29.2)	58 (32.0)
CUI-	153 (70.8)	123 (68.0)
Age, years		
Mean (SD)	46.7 (14.4)	43.8 (14.1)

Table 1: Table highlighting the (i) number of patients and samples that were assessed for autoantibody levels and (ii) patients' treatment allocations, Chronic Urticaria Index (CUI) as well as demographic data
[a]Number of samples at each of the three time points (weeks).
n, number of samples assessed for autoantibody levels.

Results

Baseline levels of specific CSU-associated autoantibodies (e.g. anti-FcεRI, anti-TPO and anti-TG) were significantly higher in CUI positive (CUI+) as compared to CUI negative (CUI-) patients. Subgroup analysis revealed that, following remibrutinib-treatment, only CUI+ patients had a significant drop in FcεRI- and TG-specific IgG autoantibody levels when compared to placebo treated patients at week 24 (Fig. 2A). Patients who switched from placebo to remibrutinib therapy at Week 24 demonstrated a comparable reduction in specific IgG autoantibody levels by Week 52 (Fig. 2A). At baseline, CUI+ patients had significantly higher levels of soluble CD23 (Fig. 2C), a circulating marker of B cell activation. Decreased autoantibody levels in remibrutinib treated patients were associated with reduced numbers of circulating non-switched memory B cell numbers and a significant decrease in soluble CD23 (Fig. 2B, D).

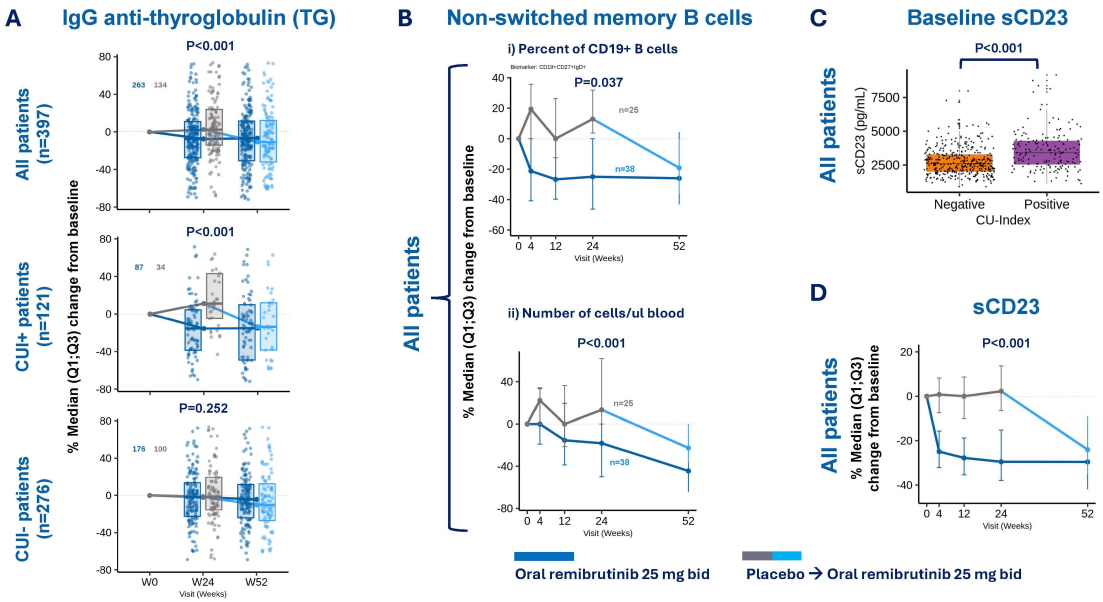

Figure 2: (A) Change from baseline of serum IgG anti-thyroglobulin (TG) levels at Week 24 and Week 52 when calculated off raw data from a multiplex bead-based autoantibody array. Data is either from all patients, Chronic Urticaria Index positive (CUI+) or CUI- patients, where autoantibody data was available at all 3 timepoints, and where spaghetti plot lines indicate the % median change from baseline for Placebo→remibrutinib (grey to light blue) and remibrutinib treated patients (dark blue). Box-Whiskers indicate median, 25th and 75th percentile, each dot represents one patient. **(B)** Flow cytometry-based data showing the change from baseline in the i) percentage and ii) total number of cells of non-switched memory B cells (Defined as CD19+, CD27+, IgD+ cells) at Week 4, 12, 24 and 52. Data is from all patients, where flow cytometry data was available at all timepoints, and where spaghetti plot lines indicate the % median change from baseline for Placebo→remibrutinib (grey to blue) and remibrutinib treated patients (dark blue). **(C)** Baseline data of serum levels of soluble CD23 (sCD23) in CU+ or CU- patients, as measured by an immunoassay. Box-Whiskers indicate median, 25th and 75th percentile, each dot represents one patient. **(D)** Immunoassay-based data showing the change from baseline in serum levels of sCD23 at week 4, 12, 24 and 52. Data is from all patients, where sCD23 data was available at all timepoints, and where spaghetti plot lines indicate the % median change from baseline for Placebo→remibrutinib (grey to light blue) and remibrutinib treated patients (dark blue). Where indicated p-values were calculated using a non-parametric Mann Whitney test.
bid, twice daily.

Conclusion

Our results suggest that remibrutinib reduces aberrantly increased disease-associated IgG autoantibody levels, particularly in CUI+ CSU patients. The association between reduced IgG autoantibody levels, decreased levels of soluble CD23 and decreased numbers of non-switched memory B cells allows for the speculation that remibrutinib leads to a reduction of IgG autoantibodies produced by this B cell subset.

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Abstract N°: LBA-246

Phase 1 clinical data of ORKA-001, a novel half-life extended IL-23p19 monoclonal antibody with potential for once-yearly dosing in plaque psoriasis

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Introduction

ORKA-001 is a novel half-life extended monoclonal antibody targeting IL-23p19 with similar potency and epitope binding to risankizumab. ORKA-001's extended half-life has the potential to enable once-yearly dosing, increased efficacy, and extended off-treatment remission in psoriasis. Here, 24-week results of the First in Human (FIH) Phase 1 study of ORKA-001 in healthy volunteers are presented.

Materials and Methods

This Phase 1, double-blinded, placebo-controlled, randomized FIH study evaluated safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single ascending doses (SAD) of ORKA-001 in 24 healthy adult volunteers.

Participants were randomized 6:2 to receive a single subcutaneous (SC) dose of ORKA-001 or placebo across three ascending dose-level cohorts: 300 mg, 600 mg, and 1200 mg. Participants were admitted to a Clinical Research Unit, where they remained until Day 4 and then returned to the clinic for follow-up safety and PK assessments over one year.

Results

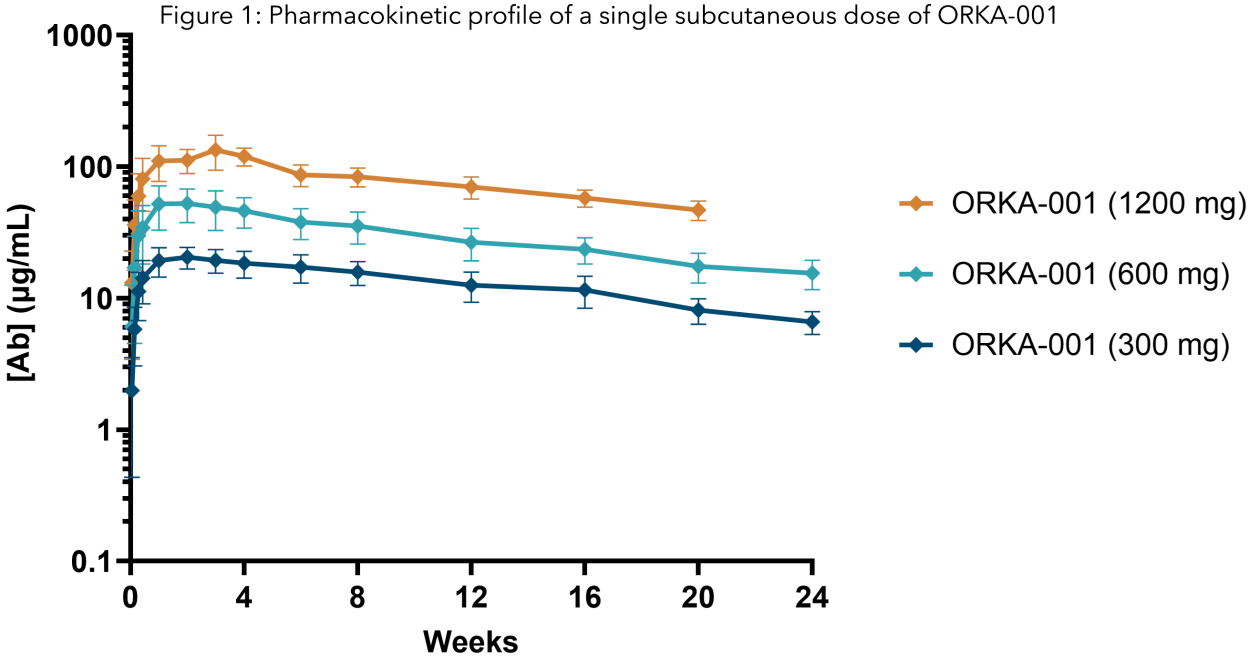
Eight participants were dosed in each of the 3 cohorts: 6 with ORKA-001 and 2 with placebo. Baseline characteristics were typical of a healthy volunteer population.

Half-life of ORKA-001 was approximately 100 days (Figure 1). Individual PK profiles showed no indication of anti-drug antibodies (ADAs).

In an *ex vivo* assay, serum from subjects dosed with ORKA-001 potently inhibited IL-23-mediated STAT3 signaling for 24 weeks (study duration to date).

The study remains blinded; however, no serious or severe adverse events (AEs) were reported and no discontinuations occurred. AEs reported in >2 participants were headache, upper respiratory tract infection, and transient erythema at the injection site. All of these events were mild. No dose-dependent trends in AEs were observed.

Figure 1: Pharmacokinetic profile of a single subcutaneous dose of ORKA-001



Conclusion

PK and PD results in this Phase 1 study of ORKA-001 support the potential for once-yearly dosing while maintaining trough antibody concentrations above approved IL-23 targeting antibodies like risankizumab. In addition, the PK profile supports evaluation of higher antibody exposures that may allow ORKA-001 to achieve higher rates of skin clearance than that of the current standard of care and long-term off-treatment remission in some patients. ORKA-001 was well-tolerated across all dose levels, with a favorable safety profile consistent with the IL-23p19 inhibitor class. These attributes are being further explored in an ongoing Phase 2a study, EVERLAST-A, which is evaluating efficacy and safety of ORKA-001 in adults with moderate-to-severe psoriasis.

Abstract N°: LBA-248

KT-621, an Oral, Once Daily, Targeted STAT6 Degrader: First-in-Human Phase 1a Safety, Pharmacokinetics, Pharmacodynamics and Th2 Biomarker Effects

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Introduction

KT-621 is a potent, first-in-class, once daily, oral small molecule heterobifunctional targeted protein degrader, which selectively degrades signal transducer and activator of transcription 6 (STAT6), an essential transcription factor in the interleukin (IL)-4 and IL-13 pathway. STAT6 plays a central role in the development of atopic and allergic inflammation. It mediates IL-4/13-induced expression of thymus and activation-regulated chemokine (TARC) and eotaxin-3, which are responsible for chemotaxis of Th2 lymphocytes and eosinophils, respectively, to sites of inflammation. KT-621 harnesses the natural cellular homeostatic protein degradation system by engaging an E3 ubiquitin ligase to ubiquitinate STAT6, which then undergoes proteosome-mediated degradation, enabling full pathway blockade similar to upstream injectable biologics like dupilumab targeting IL-4 receptor alpha.

Materials and Methods

The safety, pharmacokinetics (PK) and pharmacodynamics (PD) of KT-621 were assessed in a first-in-human, randomized, double-blind, placebo-controlled Phase 1a trial (NCT06673667). A total of 118 healthy volunteers (HV) received KT-621 or placebo as single ascending doses ranging from 6.25 to 800 mg or multiple ascending doses from 1.5 to 200 mg QD for 14 days. PK and STAT6 degradation in blood were measured in single and multiple dose cohorts, whereas STAT6 degradation in skin and blood levels of TARC and eotaxin-3 were assessed only in multiple dose cohorts.

Results

KT-621 was well tolerated. There were no serious or severe treatment emergent adverse events. Treatment related adverse events (TRAEs) of headache and nausea were reported in one placebo participant each, and asthenia was reported in one participant who received KT-621 in a multiple dose cohort. All TRAEs were mild and none resulted in study discontinuation. No clinically significant changes in vital signs, laboratory values, or electrocardiograms were observed.

KT-621 demonstrated favorable PK with rapid absorption following oral dosing and dose-proportional increase in exposure. Steady-state was achieved by Day 4 of once daily dosing. Single doses of KT-621 resulted in rapid and durable STAT6 degradation in blood, measured by targeted mass spectrometry, with median reduction exceeding 90% across all evaluated doses. With once daily dosing, complete STAT6 degradation, characterized by ≥95% decrease from baseline and/or undetectable levels in most participants, was achieved in both blood and skin at KT-621 doses ≥50 mg at Day 14. KT-621 also demonstrated suppression of Th2 biomarkers with median reductions from baseline of up to 37% in TARC and 63% in eotaxin-3.

Conclusion

These data provide clinical proof of concept for KT-621, the first orally administered STAT6 targeted agent to enter the clinic, demonstrating rapid, potent and sustained STAT6 degradation in blood and skin with a safety profile indistinguishable from placebo. KT-621 resulted in robust decreases in TARC and eotaxin-3 comparable to what has been reported with dupilumab in healthy subjects and asthma patients, respectively, thereby confirming IL-4/13 pathway inhibition. Together, these data demonstrate the potential of KT-621 as a once daily, oral therapy for IL-4/13-mediated diseases such as atopic dermatitis and asthma.

Abstract N°: LBA-260

EVO756, an Oral MRGPRX2 Inhibitor, Demonstrates Robust Treatment Effect in Chronic Inducible Urticaria

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Introduction

EVO756 is a novel, small molecule antagonist of the Mas-related G protein-coupled receptor X2 (MRGPRX2). Ligand binding to MRGPRX2 leads to immunoglobulin E (IgE)-independent degranulation of mast cells and propagates non-histaminergic itch associated with inflammation on peripheral sensory neurons. EVO756 is being developed as an oral treatment for chronic spontaneous urticaria, atopic dermatitis and chronic inducible urticaria (CIndU).

EVO756 has been evaluated in healthy adults at doses up to 240 mg BID and 500 mg QD. EVO756 was well tolerated at all doses tested and potently inhibited agonist-induced skin MC degranulation warranting further study as a potential treatment for patients with MC-mediated diseases.

Materials and Methods

EVO756-CIU001 was a Phase 2a, open-label study designed to evaluate the safety and efficacy of EVO756 in 30 adults with CIndU. Enrolled participants were adults with symptomatic dermographism (SD) for ≥3 months. Positive provocation test results (Total Fric Score (TFS) of ≥2 using the FricTest®) at screening and baseline were required. Subjects were assigned to EVO756, 300mg QD or 50mg BID, based on order of enrollment and treated with EVO756 for 4 weeks.

Safety was assessed via evaluation of treatment emergent adverse events (TEAEs) physical examinations, vital signs, laboratory tests and 12-lead ECGs. Efficacy was assessed using the FricTest, and an 11-point pruritus numeric rating scale (pruritus-NRS) at the provocation site.

The first 11 subjects enrolled were treated with EVO756 300 mg QD and the remaining 19 subjects received EVO756 50 mg BID. Subjects' baseline immunoglobulin E (IgE) levels were collected and those with levels ≥100 IU/mL were limited to approximately 30% of enrollment.

Results

Subjects had a mean age of 36.3 years (range: 21-56 years), 24 (80.0%) were female, and 23 (76.7%) were White (Table 1).

Baseline TFS ranged from 2 (23.3%) to 4 (53.3%). The mean time since CIndU diagnosis was 6.4 years (range 0.3,

25.2). Twenty-three subjects (76.7%) had IgE levels <100 IU/mL.

Decreases in TFS were observed in both treatment groups. Subjects treated with 300mg QD had a mean change from baseline TFS of −1.4, by Week 4. Three subjects (30.0%) had a complete response (TFS=0), and 4 subjects (40.0%) had at least a partial response (decrease of ≥2 points in TFS). In the 50mg BID group, a mean change from baseline TFS of −1.5 points by Week 4 was observed. Five subjects (29.4%) had complete responses, and 7 subjects (41.2%) had at least a partial response. (Table 2)

Decreases in itch intensity (pruritus-NRS scores) were observed following test site provocation in both dose groups. Pruritus-NRS scores showed a mean change of −2.4 points in the 300mg QD group and −2.1 points in the 50mg BID group. Overall, a clinically meaningful improvement (≥4pt improvement in those subjects with at least a pruritus-NRS ≥4 pts at baseline) was observed in 41.2% (Table 4).

Overall, 10 subjects (33.3%) had a TEAE (Table 4). Four events were reported for > 1 subject: alanine aminotransferase (ALT) /aspartate aminotransferase (AST) increased (two in the 300mg QD group), gastroenteritis, and pruritus (one in each group). There were no serious TEAEs, and none led to discontinuation.

Table 1: Demographics (Safety Population)

Characteristic	EVO756		
	300 mg QD (N=11)	50 mg BID (N=19)	Overall (N=30)
Age (years)			
Mean (SD)	38.8 (12.94)	34.8 (9.06)	36.3 (10.60)
Median (Min, Max)	44.0 (21, 56)	33.0 (24, 51)	34.0 (21, 56)
Sex at birth, n (%)			
Male	4 (36.4)	2 (10.5)	6 (20.0)
Female	7 (63.6)	17 (89.5)	24 (80.0)
Ethnicity, n (%)			
Hispanic or Latino	1 (9.1)	5 (26.3)	6 (20.0)
Not Hispanic or Latino	10 (90.9)	14 (73.7)	24 (80.0)
Race, n (%) [a]			
White	7 (63.6)	16 (84.2)	23 (76.7)
Asian	2 (18.2)	2 (10.5)	4 (13.3)
Black or African American	2 (18.2)	3 (15.8)	5 (16.7)
Baseline BMI (kg/m^2)			
Mean (SD)	27.61 (3.801)	26.57 (3.574)	26.95 (3.629)
Median (Min, Max)	28.52 (20.8, 33.7)	26.57 (19.5, 33.7)	27.94 (19.5, 33.7)

BID = twice daily; BMI = body mass index; QD = once daily; SD = standard deviation
Note(s): Age is relative to date of signed informed consent and as collected on the electronic case report form.
Baseline was defined as the last non-missing assessment performed prior to the first dose of study drug.
[a] Subjects who reported more than one race were counted once under each reported race.
Source: Table 14.1.3

Table 2: Summary of FricTest Results (Efficacy Population)

	EVO756 300 mg QD (N=11)	EVO756 50 mg BID (N=18)
FricTest Results		
Baseline		
Mean (SD)	3.5 (0.82)	3.2 (0.86)
Median (Min, Max)	4.0 (2, 4)	3.0 (2, 4)
Week 4		
N (observed)	10	17
Mean (SD)	2.2 (1.69)	1.6 (1.37)

Median (Min, Max)	2.5 (0, 4)	2.0 (0, 4)
Change from Baseline at Week 4		
Mean (95% CI)	−1.4 (−2.53, −0.27)	−1.5 (−2.21, −0.85)
Median (Min, Max)	−1.0 (−4, 0)	−1.0 (−4, 0)
Response at Week 4		
Complete Response[a], n (%)	3 (30.0)	5 (29.4)
At Least a Partial Response[b], n (%)	4 (40.0)	7 (41.2)

BID = twice daily; CI = confidence interval; QD = once daily; SD = standard deviations
[a] A complete response was defined as a total FricTest score of 0.
[b] A partial response was defined as a decrease of at least 2 points in the total FricTest score.
Source: Table 14.2.2.1.1, Table 14.2.2.2.1, Table 14.2.2.2.5

Table 3: Summary of Pruritus-NRS Change from Baseline (Efficacy Population)

	EVO756 300 mg QD (N=11)	EVO756 50 mg BID (N=18)
Change from baseline at Week 4 after provocation		
Mean (95% CI)	−2.4 (−3.95, −0.85)	−2.1 (−3.48, −0.63)
Median (Min, Max)	−2.5 (−5, 1)	−1.0 (−8, 1)

BID = twice daily; CI = confidence interval; NRS = numeric rating scale; QD = once daily; SD = standard deviation
Source: Table 14.2.4.1.1

Table 4: Summary of Pruritus-NRS Clinically Meaningful Improvement (Efficacy Population)

	EVO756 300 mg QD (N=6)	EVO756 50 mg BID (N=11)	Overall (N=17)
Pruritus-NRS Improvement at Week 4			
Clinically meaningful improvement[a], n (%)	3 (50.0)	4 (36.4)	7 (41.2)

BID = twice daily; CI = confidence interval; NRS = numeric rating scale; QD = once daily
[a] A clinically meaningful improvement (or partial response) was defined as a post-provocation change in pruritus-NRS of at least 4 points for subjects who had a post-provocation pruritus-NRS score of ≥4 at Baseline.
Source: Table 14.2.4.2.9

Table 5: Treatment Emergent Adverse Events Reported by >1 Participant by MedDRA Preferred Term (Safety Population)

Preferred Term	EVO756 300 mg QD (N=11) n (%)	EVO756 50 mg BID (N=19) n (%)	Overall (N=30) n (%)
Subjects with at least 1 TEAE	3 (27.3)	7 (36.8)	10 (33.3)
ALT increased	2 (18.2)	0	2 (6.7)
AST increased	2 (18.2)	0	2 (6.7)
Gastroenteritis	1 (9.1)	1 (5.3)	2 (6.7)
Pruritus	1 (9.1)	1 (5.3)	2 (6.7)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; TEAE = treatment emergent adverse event
Note(s): TEAEs are defined as any adverse events (AEs) with onset date on or after the date of the first dose of study drug.
AEs were coded using the MedDRA, version 27.0.
Subjects with multiple AEs with the same preferred term are counted only once with that preferred term.
Source: Table 14.3.1.2

Conclusion

In this 4-week treatment study, EVO756 reduced SD severity, determined via changes in FricTest scores, in both the 300mg QD and 50mg BID groups. Clinically meaningful changes were also observed in post-provocation itch severity scores. As observed with other therapies, longer treatment durations could result in further benefits. All TEAEs were nonserious and none led to discontinuation of treatment. Overall, EVO756 was well tolerated.

Abstract N°: LBA-281

Efficacy and Safety of Ruxolitinib Cream in Patients With Prurigo Nodularis: Pooled Results From the Phase 3 TRuE-PN1 and TRuE-PN2 Randomized, Vehicle-Controlled Studies

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Introduction

Prurigo nodularis (PN) is a chronic inflammatory disease characterized by cutaneous nodules associated with intense itch, driven by Janus kinase (JAK) signaling pathways. Ruxolitinib (RUX) cream is a selective JAK1/JAK2 inhibitor designed for topical administration. Here, we evaluated the efficacy and safety of 1.5% RUX cream up to Week 24 of treatment in patients in the TRuE-PN1 and TRuE-PN2 randomized, double-blind, vehicle-controlled (DBVC) studies (pooled analysis).

Materials and Methods

Adults (aged ≥18 years) with PN for ≥3 months, ≥6 pruriginous lesions on ≥2 body regions, an Investigator's Global Assessment for Stage of Chronic Prurigo (IGA-CPG-S) score ≥2, a Worst-Itch Numerical Rating Scale (WI-NRS) score ≥7, and an affected body surface area (BSA) ≤20% were randomized 1:1 to apply 1.5% RUX cream or vehicle twice daily (BID) for a 12-week DBVC period. Patients then applied 1.5% RUX cream BID as needed during a 40-week open-label extension (OLE) period. The primary endpoint was the proportion of patients with a ≥4-point improvement in WI-NRS (WI-NRS4) at Week 12. Key secondary endpoints included IGA-CPG-S treatment success (TS; IGA-CPG-S score of 0 or 1, with a ≥2-grade improvement from baseline) at Week 12 and overall TS (achievement of both WI-NRS4 and IGA-CPG-S-TS) at Week 12. Patients with missing data were imputed as nonresponders for the primary and key secondary endpoints; in the OLE, data are reported as observed. The proportion of patients who reported very much or much improvement per the Patient Global Impression of Change (PGIC; score of 1 or 2) is reported as observed. Safety and tolerability were also assessed and are reported as observed at the data cutoff (15 May 2025).

Results

A total of 394 patients were randomized, with 197 each in the 1.5% RUX cream and vehicle cohorts. The median (range) age of patients was 62.0 (18–84) years, and most patients were female (59.6%). Mean (SD) baseline WI-NRS was 8.4 (1.0), and 80% of patients had an IGA-CPG-S score of ≥3. At Week 12, significant improvements with RUX cream vs vehicle were observed in WI-NRS4 (42.3% vs 28.1%; P=0.0029), IGA-CPG-S (19.8% vs 7.1%; P=0.0002), and overall TS (12.2% vs 4.6%; P=0.0066). At Week 24, responses were maintained among patients initially randomized to RUX cream. Among patients who crossed over from vehicle at Week 12, responses at Week

24 were substantially improved and similar to those achieved by patients initially randomized to RUX cream (WI-NRS4, 62.8% vs 63.6%; IGA-CPG-S TS, 25.3% vs 32.9%; overall TS, 19.6% vs 21.0%). At Week 12, very much or much improvement (per PGIC) was reported by more patients who applied RUX cream vs vehicle (61.8% vs 41.8%); in the OLE, data were similar between groups at Week 24 (RUX cream, 76.8%; vehicle to RUX cream, 75.9%). Among patients who applied RUX cream in either study period (N=362), application site reactions were infrequent (n=4 [1.1%]). No grade ≥3 treatment-emergent adverse events were considered related to treatment. There was 1 fatal event considered unrelated to study drug.

Conclusion

In this pooled analysis, RUX cream demonstrated statistically significant improvements vs vehicle in the signs and symptoms of PN beginning at early study visits, with improvements maintained through Week 24 (including 12 weeks of as-needed use). These observations continue to support the development of RUX cream as a novel, effective, and well-tolerated topical treatment for PN.

Abstract N°: LBA-286

Initial "Super Response" to Tralokinumab Leads to Stable Long-term Response in Patients with Moderate-to-Severe Atopic Dermatitis: Responder and Predictor Analysis from the ECZTRA 3 & ECZTEND Trials

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Introduction

Unpredictable periods of worsening signs and symptoms are common among patients with atopic dermatitis (AD), making long-term disease control a primary treatment goal. Tralokinumab is a high-affinity monoclonal antibody that specifically neutralizes interleukin-13, a key driver of AD inflammation, and is approved in multiple countries for treatment of moderate-to-severe AD in individuals ≥12 years of age. Here, long-term stability of treatment responses with tralokinumab plus optional TCS was assessed as well as predictors of long-term treatment success.

Materials and Methods

This post hoc analysis included Week 16 responders in the phase 3 ECZTRA 3 trial (NCT03363854) treated with tralokinumab 300 mg once every two weeks (Q2W) plus optional TCS who subsequently enrolled in the open-label extension trial ECZTEND (NCT03587805). Week 16 responder groups included patients who achieved one of the following: ≥75% or 90% improvement from Baseline in Eczema Area and Severity Index (EASI-75 or EASI-90), Dermatology Life Quality Index of 0 or 1 (DLQI 0/1), or a composite EASI-90 with DLQI 0/1 response. Patients who achieved EASI-90 at Week 16 were considered "super responders". Data were evaluated as observed through Week 120 in ECZTEND (up to 3 years total of treatment with tralokinumab). Data were also analysed in a mixed effects model for repeated measures, which allowed for both between-subject and within-subject variability. Absolute EASI at Week 16 was evaluated as a predictor for long-term treatment success (defined as a greater percent EASI improvement from Baseline through Week 120) among subgroups of patients who achieved either EASI-75 or EASI-90 (super responders) at Week 16.

Results

At Week 16 in ECZTRA 3, 56% (n/N, 141/252), 33% (83/252), 25% (62/252), and 15% (39/252) of patients

achieved EASI-75, EASI-90, DLQI 0/1, and EASI-90 with DLQI 0/1, respectively. Among these Week 16 responder groups, 86% (121/141), 92% (76/83), 81% (50/62), and 90% (35/39) entered the ECZTEND trial. In each responder group, ≥60% of patients remained in the ECZTEND trial up to Week 120 and ≤13% of discontinuations were attributed to either lack of efficacy or adverse events. A stable EASI predicted trend line of ≥90% improvement from Baseline was maintained through Week 120 in ECZTEND for both the EASI-75 responders and the super responders. In EASI-75 and super responders, a lower absolute EASI at Week 16 was a strong predictor for improvements in EASI over 120 weeks ($p<0.0001$). The proportion of patients in the EASI-90 with DLQI 0/1 Week 16 responder group (n = 35) who achieved the EASI-90 with DLQI 0/1 response was greater than 48% at each visit in ECZTEND.

Conclusion

Response trends among patients with moderate-to-severe AD who achieved Week 16 endpoints (ie, EASI-75/90, DLQI 0/1, or EASI-90 with DLQI 0/1) with tralokinumab predict stable responses for up to 3 years with continued treatment, regardless of fluctuations in individual response trajectories. These results may help clinicians predict long-term treatment success based on response after 16 weeks of tralokinumab treatment, especially in EASI-90 super responders with low absolute EASI.

Abstract N°: LBA-288

Efficacy and safety of izokibep, a novel interleukin-17A inhibitor, in moderate to severe hidradenitis suppurativa: Week 16 results from a randomised, double-blind, placebo-controlled, multicentre, phase 3 study

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Introduction

Dysregulation of interleukin (IL)-17A plays a key role in hidradenitis suppurativa (HS) pathogenesis. Izokibep is an Affibody® molecule (small protein therapeutic; 18.6 kDa) designed to inhibit IL-17A with high potency through tight and selective binding.[1] In a phase 3 study of patients with moderate to severe HS, izokibep met its primary endpoint of improved HS Clinical Response (HiSCR)-75 vs placebo at week 12. Here, we report week 16 izokibep efficacy and safety results from the phase 3 study.

Materials and Methods

Study 22107 (NCT05905783) included a 16-week, randomised, placebo-controlled treatment period. Eligible patients were 18 years or older with a diagnosis of HS for ≥6 months, lesions present in ≥2 distinct anatomic areas (1 Hurley stage II/III), a total abscess and inflammatory nodule (AN) count ≥5, and an inadequate response, intolerance, or contraindication to oral antibiotics (use of a stable dose of oral antibiotics was allowed in up to 30% of patients). Patients were randomised 1:1 to receive subcutaneous placebo or izokibep 160 mg every week. Efficacy endpoints, including HiSCR75/90/100/50, pain, and quality of life, and safety were assessed at week 16. Response rates were determined using nonresponse imputation or multiple imputation (additional statistical analysis methods are detailed in the **Figure** footnote).

Results

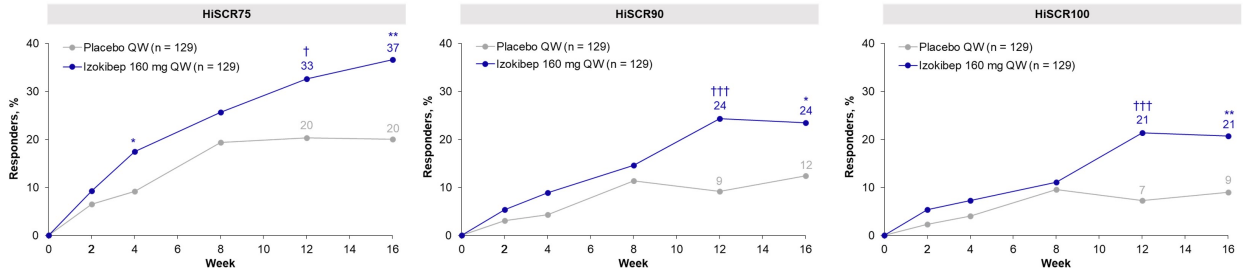
A total of 258 patients were randomised (placebo, n = 129; izokibep, n = 129). Overall, the mean (standard deviation [SD]) age was 37.3 (12.4) years, 69% of patients were female, and the mean (SD) disease duration was 10.2 (8.7) years. At baseline, mean (SD) AN count was 13.5 (13.3) for izokibep and 13.2 (11.5) for placebo. Baseline Hurley stage II/III was 60%/40% and 64%/36%. Other disease characteristics were similar between groups. Efficacy outcomes are shown in **Figure 1A**. At week 16, higher percentages of patients receiving izokibep vs placebo achieved HiSCR75 (37% vs 20%; **Figure 1B**), HiSCR90 (24% vs 12%), HiSCR100 (21% vs 9%), and HiSCR50 (50% vs 32%). Among patients with a baseline pain numeric rating scale (NRS) ≥4 treated with izokibep, 38% achieved a ≥3-point reduction in pain NRS (vs 17% of patients receiving placebo). Greater improvements were seen with izokibep vs placebo in Dermatology Life Quality Index (least squares mean [standard error] change from baseline, −4.4 [0.6] vs −2.9 [0.5]). Izokibep was generally well tolerated. Treatment-emergent adverse events (TEAEs) were reported in 83% and 59% of patients receiving izokibep and placebo, respectively, through week 16. TEAEs occurring in ≥5% of patients treated with izokibep were mostly mild or moderate in severity: injection-site reaction (67%; 1 severe event), headache (11%), nasopharyngitis (9%), diarrhoea (5%), fatigue (5%), and upper respiratory tract infection (5%). Low rates of serious TEAEs were reported (izokibep, 0.8%; placebo, 3.9%). There were no reports of *Candida* infection, inflammatory bowel disease, or suicidal ideation with izokibep.

Figure 1. Efficacy results

A.

	Placebo QW (n = 129)	Izokibep 160 mg QW (n = 129)
HiSCR75, %	20	37**
HiSCR90, %	12	24*
HiSCR100, %	9	21**
HiSCR50, %	32	50**
DLQI, CFB, LSM (SE)[a]	−2.9 (0.5)	−4.4 (0.6)*
AN count of 0, 1, or 2, %[b]	29	46*
≥3-point reduction in pain NRS, %[c]	17	38**
≥1 disease flare, %[d]	34	29

B.



A. Week 16 efficacy results. **B.** HiSCR75, HiSCR90, and HiSCR100 through week 16. Response rates were determined using NRI for patients who received antibiotic therapy that could affect HS and for patients with missing data who discontinued treatment due to an adverse event or lack of efficacy; multiple imputation was used for all other patients with missing data. Statistical significance per the prespecified testing hierarchy: †P<0.05; †††P<0.001 vs placebo. Nominal P-value: *P<0.05; **P<0.01 vs placebo.
[a]LSM using mixed model repeated measures including treatment, baseline DLQI, stratification factors, visit week, and treatment by visit week interaction as covariates. [b]In patients with baseline Hurley stage II (placebo, n = 82; izokibep, n = 78). [c]In patients with baseline pain NRS ≥4 (placebo, n = 79; izokibep, n = 73). Response rates were determined using NRI for patients with missing data who discontinued treatment due to an adverse event or lack of efficacy and patients who received prohibited analgesic therapy for HS within 28 days of the visit; multiple imputation was used for all other patients with missing data. [d]Disease flare was defined as ≥1 flare (a ≥25% increase in AN count with a minimum increase of 2 AN relative to baseline) at any time through week 16.
AN, abscess and inflammatory nodule; CFB, change from baseline; DLQI, Dermatology Life Quality Index; HiSCR50/75/90/100, a ≥50%/≥75%/≥90%/100% improvement in HS Clinical Response (a ≥50%/≥75%/≥90%/100% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count); HS, hidradenitis suppurativa; LSM, least squares mean; NRI, nonresponse imputation; NRS, numeric rating scale; QW, every week; SE, standard error.

Conclusion

Early improvements previously reported with izokibep over placebo were sustained across key HS disease measures at week 16, with over one-third of patients achieving HiSCR75. No new safety signals were observed with izokibep.

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Abstract N°: LBA-300

Safety, Pharmacokinetics, and Pharmacodynamics of LAD191, an IL-1RAP-Targeting Monoclonal Antibody, in Adults with Hidradenitis Suppurativa: Results from Part 3 of a Phase I Study

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Introduction

LAD191 is a monoclonal antibody targeting the interleukin-1 receptor accessory protein (IL-1RAP). Parts 1 and 2 of this first-in-human (FIH) study evaluated single and multiple ascending doses of LAD191, respectively, in healthy volunteers (HV) and have demonstrated a favorable safety and tolerability profile, along with dose-proportional pharmacokinetics (PK). This Part 3 analysis aims to evaluate the safety, tolerability, PK, immunogenicity and pharmacodynamics of LAD191 among patients with hidradenitis suppurativa (HS).

Materials and Methods

This was a Phase I, randomized, 3-part, placebo-controlled study (NCT06488209). Part 3 included adult patients with HS (Hurley stage II or III). Patients were randomized to receive LAD191 or placebo, administered by subcutaneous injection once weekly for up to six doses.

Results

Five patients were randomized, of which three received LAD191 (mean age: 30.0 years; two females; Hurley stage II/III: 2/1 patients) and two received placebo (mean age: 31.0 years; all females; Hurley stage II/III: 2/0 patients). The mean International HS Severity Score (IHS4) at baseline was 30.3 in the LAD191 arm and 13.5 in the placebo arm, with a higher number of severe patients (IHS4 ≥ 11) in the LAD191 arm compared to the placebo arm (3 vs 1 patient). No treatment-emergent adverse events (TEAEs) were reported in the LAD191 arm vs three TEAEs in the placebo arm (two moderate worsenings of HS and a mild acute pharyngitis). No serious TEAEs or TEAEs leading to discontinuation were reported. Transient decreases in neutrophils count were observed in patients receiving LAD191, with spontaneous recovery noted in all cases. A trend toward lower LAD191 exposure (~25%) was observed in HS patients compared to what was previously observed in HV. The half-life of LAD191 in HS patients was 17 days and no anti-drug antibodies were detected. An improvement in HS lesion count was observed following LAD191 treatment, accompanied by reductions in serum inflammatory biomarkers, such as IL-6 and lipocalin-2.

Conclusion

LAD191 was well tolerated and demonstrated a favorable safety and PK profile in patients with HS. Moreover, LAD191 has led to downstream cytokine reduction and early signs of clinical improvement in HS, supporting

further clinical development.

Abstract N°: LBA-302

Molecular Profiling of Inflammatory Palmoplantar Disorders for Diagnosis and Treatment Optimization

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Introduction

Palmoplantar hyperkeratotic dermatitis encompasses a spectrum of inflammatory disorders, including pustular and non-pustular psoriasis, atopic dermatitis (AD), and chronic hand eczema (CHE). Due to overlapping clinical and histopathological features, accurate diagnosis remains challenging, often leading to misclassification and suboptimal treatment.

Materials and Methods

In this study, we applied molecular profiling of seven functional immune modules to lesional biopsies from patients with palmoplantar disorders (n=67).

Results

This approach reproducibly identified four distinct molecular patterns: a combined Th17 and myeloid signature corresponding to pustular psoriasis; a dominant Th17 profile matching non-pustular psoriasis; an exclusive Th2 profile characteristic of atopic dermatitis; and a mixed profile in CHE marked by dominant Th2, subdominant Th1 and macrophagic signatures, and variable expression of Th17. The immune profile observed in CHE overlapped with patterns seen in allergic contact dermatitis, positive patch test reactions, and drug hypersensitivity reactions, suggesting shared pathogenic mechanisms. Molecular clustering improved diagnostic accuracy and revealed a high clinical misclassification rate of approximately 45%, highlighting the limitations of conventional clinical and histological evaluation. Importantly, matching dominant immune profiles to targeted therapies enhanced treatment outcomes: AD and CHE with Th2 dominance responded well to Dupilumab and JAK inhibitors, while Th17-dominant psoriasis and pustular psoriasis responded to anti-IL17 or anti-IL23 agents. All patients whose molecular profiles were mismatched to their treatment target failed to respond, underscoring the clinical utility of molecular stratification.

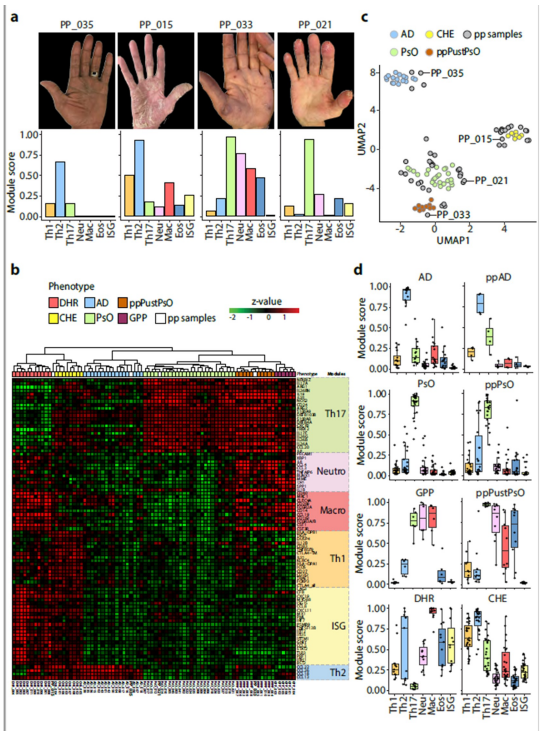

Figure 1. Palmoplantar dermatitis segregate into 4 molecular subgroups based on immune module expression. (**a**) Representative clinical images of four palmoplantar dermatitis (top) with different immune module profiles (bottom). (**b**) Projection of the four palmoplantar dermatitis onto the molecular cartography of sentinel inflammatory skin diseases, using a heatmap representation based on key immune modules: Th1, Th2, Th17, type I interferon, neutrophilic, and macrophage-associated signatures. The color gradient reflects expression levels given as z-scores. Psoriasis (PsO), atopic dermatitis (AD), drug hypersensibility reaction (DHR), chronic hand exczema (CHE), generalized pustular psoriasis (GPP), palmoplantar psutular psoriasis (ppPustPsO), palmoplantar dermatitis (pp samples). (**c**) Module-based UMAP projection of pp samples demonstrating clustering according to disease. The four samples from (a) are highlighted. (**d**) Box plots showing the normalized modules scores in body and palmoplantar samples across all diseases. Each dot represents one sample. AD (n=14), ppAD (n=4), PsO (n=25), ppPsO (n=21), GPP (n=6), ppPustPsO (n=10), DHR (n=11), CHE (n=26).

Conclusion

In conclusion, molecular profiling offers a robust and objective diagnostic tool for inflammatory palmoplantar disorders, guiding personalized therapeutic decisions and improving clinical outcomes by reducing misclassification and mismatched treatments.

Abstract N°: LBA-305

Long-Term Holistic Management in Psoriatic Disease: Tildrakizumab Achieves Sustained Control of Skin Manifestations, Psychological Well-being, and Partner Quality of Life - The POSITIVE Study

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Introduction

At the recent 78th World Health Assembly held in May 2025, Member States adopted a resolution titled "Skin Diseases as a Global Public Health Priority". The resolution calls for a Global Action Plan focused on prevention, early detection, treatment, long-term care, and improved access. The resolution also recognizes the intersection of skin health with mental health, stigma, and social well-being.

Aligned with the global action plan, we assess the long-term (2-years) effectiveness of tildrakizumab on the overall well-being, quality of life (QoL), and skin clearing of patients with moderate-to-severe plaque psoriasis from the POSITIVE study, establishing a new paradigm for value-based dermatological care aligned with the World Health Organisation recommendations.

Materials and Methods

POSITIVE is a 24-month, multinational, phase IV observational study across nine European countries. 785 adult patients with moderate-to-severe plaque psoriasis receiving tildrakizumab were enrolled (table 1). POSITIVE is the first study in dermatology assessing psychological well-being as a primary endpoint (using the WHO-5 score). PASI, DLQI-R, and other innovative outcomes such as the assessment of burden on partners (FamilyPso) were also

included.

Results

In the POSITIVE study, the baseline reported WHO-5 score (mean±SD) was 53.7±21.4, which is significantly below the European population mean (64.9, [p<0.0001].), and comparable to the score of patients with diabetes with distress (51.4) or breast cancer (52.2). The well-being of patients receiving tildrakizumab was restored to the European mean after just 16 weeks, reaching a score of 63.2±20.5. Interestingly, these levels continued improving, surpassing the European population levels after 2-years of tildrakizumab treatment (70.43±20.1).

The PASI decreased from 12.9±8.1 to 2.4±3.3 and 1.7±2.7 at weeks 16 and 28 and maintained over the 2-years (1.5±2.8 and 1.3±2.3 at weeks 52 and 104), with 79.0% of patients maintaining PASI≤ 2 after 2-years. Patients' (DLQI-R) and their partners' (FamilyPsO) QoL improved from 12.0±7.5 and 1.1±0.9 at baseline to 2.1±3.5 and 0.6±0.7 at week 104, respectively. 11.1% of patients had ≥1 treatment-related adverse event (AE).

After 16 weeks, 60.9% reached skin control (PASI≤2) and 57.7% good psychological well-being (WHO-5 ≥64). However, 29.5% of patients suffered from psycholag - delayed psychological recovery despite rapid skin clearance, highlighting the complex relationship between physical and mental health recovery.

Table 1. Demographic and other baseline characteristics of the 785 patients.

Gender, N (%) (female)	277 (35.3%)
Age (years), mean (SD)	46.9 (15.1)
Weight (kg), mean (SD)	84.0 (18.9)
BMI (kg/m^2), mean (SD)	27.9 (5.6)
Smoking habit, N (%)	
Non-smoker	298 (38.0%)
Ex-smoker	159 (20.3%)
Current smoker	289 (36.9%)
Unknown	38 (4.8%)
Years since 1st diagnosis of the disease, mean (SD)	14.9 (12.3)
Location of plaque psoriasis at diagnosis	
Nails	277 (35.4%)
Palms	156 (19.9%)
Soles	106 (13.5%)
Scalp	512 (65.4%)
Genitalia	219 (28.0%)
Flexures	244 (31.2%)
Other	349 (44.6%)
Co-morbidities at inclusion date	383 (48.9%)
High blood pressure	163 (20.8%)
Psoriatic arthritis	83 (10.6%)
Depression	69 (8.8%)
Dyslipidaemia	65 (8.3%)
Diabetes Mellitus	63 (8.0%)
Fatty liver disease	43 (5.5%)
Cardiovascular disease	42 (5.4%)
Metabolic syndrome	25 (3.2%)
Kidney disease	14 (1.8%)
Neoplasm	10 (1.3%)
Inflammatory bowel disease	3 (0.4%)
Psoriasis Drug therapy history	
Topicals	455 (58.0%)
Phototherapy	274 (34.9%)
Systemic non-biologic	430 (54.8%)
Biologic	249 (31.7%)

Conclusion

Aligned with the recent WHO-resolution, the POSITIVE study demonstrates that treatment with tildrakizumab delivers sustained and value-based, long-term health for moderate-to-severe psoriasis over 2 years by consistently improving clinical outcomes, patients' psychological well-being and quality of life with a favourable safety and tolerability profile. However, psycholag was exhibited by some patients, demonstrating that modern dermatological care should assess, not only clinical outcomes, but a deep absence of disease and restoration of well-being when treating patients with psoriasis.

Abstract N°: LBA-306

Dose Reduction of IL-17 and IL-23 Inhibitors in Patients with Plaque Psoriasis is Non-inferior to Usual Care: an International Pragmatic Randomized Controlled Trial – the BeNeBio study

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Introduction

The newest biologics for psoriasis (interleukin (IL)17 and IL23 inhibitors (i)) are highly effective but also expensive. Additionally, it is important to strive for the lowest effective dose to prevent possible overtreatment. Therefore, the aim of this study was to evaluate whether dose reduction (DR) by stepwise interval prolongation of IL17i and IL23i in patients with psoriasis with stable low disease activity was non-inferior to usual care (UC).

Materials and Methods

This pragmatic, open-label, prospective, controlled, non-inferiority randomized clinical trial was carried out in 19 dermatology departments in the Netherlands and Belgium. Patients receiving the standard registered dose of an IL17i (secukinumab, ixekizumab, bimekizumab, brodalumab) or an IL23i (risankizumab, guselkumab, tildrakizumab) with stable low disease activity, were randomized (2:1) to DR or UC (fig.1). In the DR group, intervals were stepwise prolonged: first to 67% of the standard dose, then to 50% in the second step. Disease activity was monitored every 3 months by the Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) during an 18-month follow-up period. In case of disease flare, treatment was adjusted to the previous effective dose. Primary outcome was the difference in cumulative incidence of persistent flares (PASI>5 for ≥3 months) after 18 months between DR and UC, with a non-inferiority margin of 15%. Secondary outcomes included the proportion of patients with successful DR (patients on a reduced dose with PASI≤5), course of PASI and DLQI, serious adverse events, health related quality of life, costs, and pharmacokinetic profile. Results were analyzed in a per protocol (PP) and intention-to-treat (ITT) analysis with missing data imputed by last observation carried forward (LOCF) and also by multiple imputation (MI) in the ITT analysis.

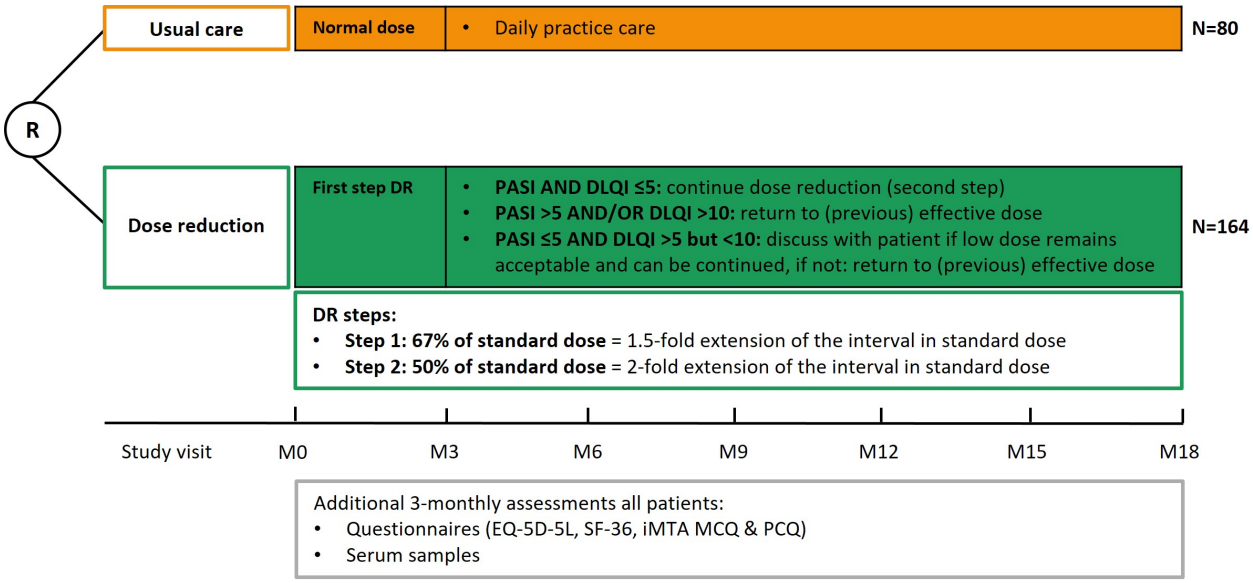

Figure 1: Overview of the dose reduction strategy and study measures according to the study protocol.(1) R = randomization; DR = dose reduction; N = number of patients; PASI = Psoriasis Area and Severity Index; DLQI = Dermatology Life Quality Index; M = month; EQ-5D-5L = European Quality of Life-5 Dimensions-5 Level; SF-36 = Short Form 36; iMTA = institute for Medical Technology Assessment; MCQ = Medical Consumption Questionnaire; PCQ = Productivity Cost Questionnaire.

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Results

Between June 30, 2020 and September 14, 2023, 244 patients were included (mean (±SD) age 51 (±15) years; 67% male). At baseline, median [IQR] PASI and DLQI were 0.0 ([1.1] and [1.0], respectively). The number of patients treated with IL17i or IL23i was equally distributed (46% and 54% respectively), and 47% of patients was biologic naive. After 18 months, the difference in cumulative incidence of persistent flares for DR was non-inferior to UC in all three analyses (PP_LOCF 0.62% (95%CI [-5.84%; 4.64%]); ITT_LOCF 1.16% (95% CI [-5.31%; 5.63%]); ITT_MI 1.91% (95% CI [-2.86%; 6.69%])) (fig.2). The proportion of patients with successful DR after 18 months was 74.5%. The mean PASI and DLQI scores did not significantly differ between DR and UC at 12 and 18 months. No safety signals related to DR were detected.

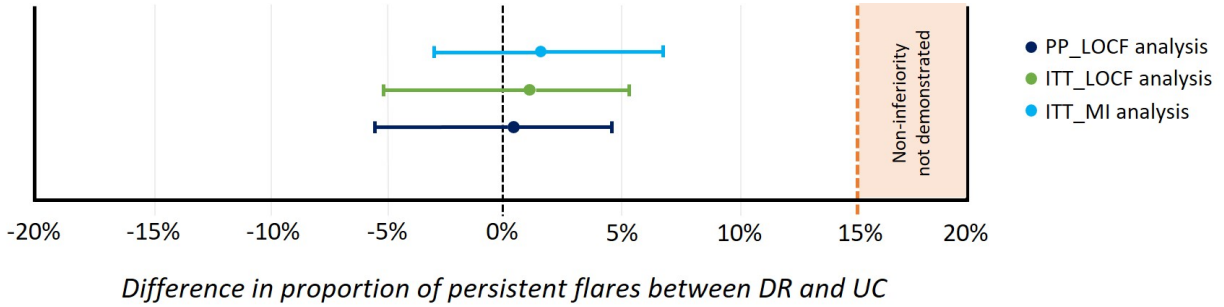

Figure 2: The difference in proportion of persistent flares between dose reduction (DR) and usual care (UC) after 18 months for all three analyses. Error bars indicate 95% confidence intervals. The orange line at 15% shows the non-inferiority margin set at 15%. PP: per-protocol, ITT: intention-to-treat, LOCF: last observation carried forward, MI: multiple imputation.

Conclusion

This study demonstrated that up to 50% dose reduction of IL17i and IL23i for patients with psoriasis with stable low disease activity is non-inferior to usual care. A high proportion of patients (74.5%) in the dose reduction group continued on a reduced dose after 18 months. Both PASI and DLQI scores remained very low in both groups throughout the study. This study provides important evidence for future implementation of dose reduction

of the newest biologics for patients with psoriasis.

Abstract N°: LBA-308

Bimekizumab efficacy and safety through 3 years in patients with hidradenitis suppurativa: Results from the phase 3 BE HEARD I&II trials and their open-label extension BE HEARD EXT

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Introduction

Hidradenitis suppurativa (HS) is a chronic, relapsing skin disease characterised by painful inflammatory nodules, abscesses and draining tunnels that causes disability and reduces patients' health-related quality of life (HRQoL).[1–3] Long-term disease control is essential to prevent irreversible damage and disease progression.[4]

Bimekizumab (BKZ) is a humanised IgG1 monoclonal antibody that selectively inhibits IL-17F in addition to IL-17A and has demonstrated clinically meaningful improvements in patients with HS over 2 years of treatment.[5–7]

Here, the efficacy and safety of BKZ in patients with moderate to severe HS are reported up to 3 years (efficacy: 148 weeks; safety: 144 weeks) of treatment.

Materials and Methods

Data were pooled from BE HEARD I&II (BHI&II; NCT04242446/NCT04242498) and BE HEARD EXTENSION (BHEXT; NCT04901195).

We report HS Clinical Response (HiSCR)50/75/90/100 rates, absolute change from baseline (CfB) in draining tunnel (DT) count and Dermatology Life Quality Index (DLQI) 0/1 achievement at Week 48 and Week 148, plus a safety overview up to 3 years. For efficacy outcomes, we report data for patients who were randomised to BKZ from baseline in BHI&II who entered BHEXT (BKZ Total group; data reported as observed case [OC]). For safety outcomes, we report data for patients who received ≥1 dose of BKZ across BHI&II/BHEXT.

Results

Of 1,014 total patients, 556 patients randomised to BKZ at baseline in BHI&II completed Week 48 and entered BHEXT; of these, 367 completed Week 148.

At Week 48, HiSCR50/75/90/100 responses were 79.9%/64.0%/42.3%/30.2%; responses were maintained to Week 148 at 90.2%/81.2%/64.3%/50.1% (**Figure**). At Week 48, from a baseline mean (standard deviation [SD]) of 3.8 (4.3), the mean absolute CfB (SD) in DTs was −2.4 (3.4); responses were sustained to Week 148 at −3.1 (3.9). The proportion of patients who reported DLQI 0/1 was 27.4% (151/551) at Week 48 and 38.1% (137/360) at Week 148.

Up to 3 years, the exposure-adjusted incidence rate (EAIR) for any treatment-emergent adverse event (TEAE) was 226.8/100 participant-years [PY]) (**Table**). The EAIRs/100 PY for serious TEAEs and TEAEs leading to discontinuation were 7.2 and 6.0, respectively. The most common TEAEs were hidradenitis (20.7/100 PY), coronavirus infection (15.3/100 PY) and oral candidiasis (10.4/100 PY). Serious infection TEAEs occurred in 37 patients (2.0/100 PY). Safety data were consistent with previous observations and with 2-year data from BHI&II/BHEXT.[7]

Conclusion

Efficacy and HRQoL outcomes observed in the bimekizumab HS phase 3 trials were maintained through 3 years of treatment. Bimekizumab was well-tolerated and no new safety signals were identified up to 3 years of treatment.

These data highlight the depth and durability of response to bimekizumab treatment in patients with moderate to severe HS.

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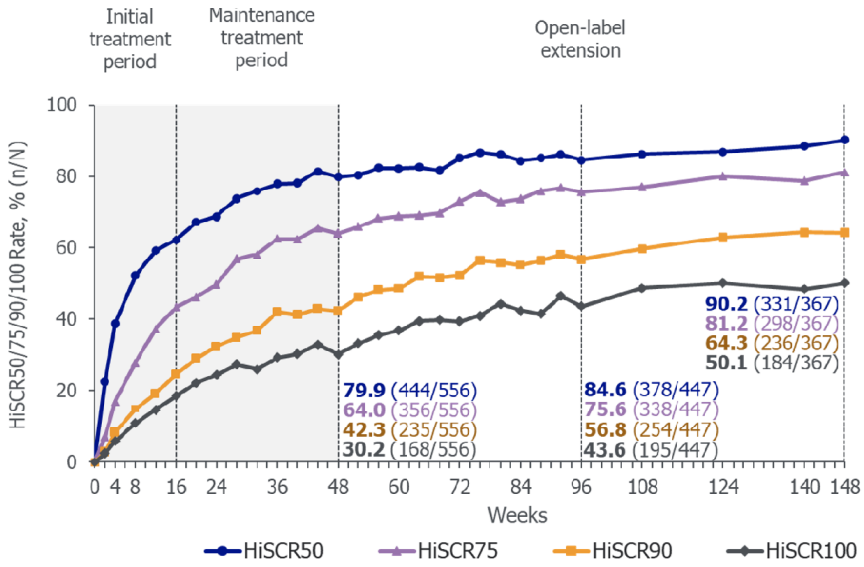
Figure. HiSCR to Week 148 (OC)



OLE set; data reported for the BKZ Total group (N=556) which comprised patients randomised to BKZ from baseline in BE HEARD I&II who entered BE HEARD EXT at Week 48. Only patients who entered the third year are included. OC, n/N: denominator represents number of patients with non-missing lesion count assessment at the given week, and percentages are calculated accordingly. BKZ: bimekizumab; HiSCR: Hidradenitis Suppurativa Clinical Response; HiSCR50/75/90/100: ≥50/75/90/100% reduction from baseline in the total abscess and inflammatory nodule count with no increase from baseline in abscess or draining tunnel count; OC: observed case; OLE: open-label extension.

Table. Incidence of TEAEs per 100 participant-years up to 3 years

	Patients with ≥1 dose of BKZ N=995
	EAIR per 100 PY (95% CI)
Any TEAE	226.8 (212.4, 242.0)
Serious TEAEs	7.2 (6.0, 8.6)
Severe TEAEs	7.7 (6.4, 9.1)
TEAEs leading to discontinuation	6.0 (5.0, 7.3)
Any TEAE leading to death[a]	0.2 (0.0, 0.5)
Most common TEAEs[b]	
Hidradenitis	20.7 (18.5, 23.2)
Coronavirus infection	15.3 (13.4, 17.4)
Oral candidiasis	10.4 (8.9, 12.1)
Serious infections	2.0 (1.4, 2.8)
Fungal infections	24.4 (21.9, 27.1)
Any malignancies	0.7 (0.4, 1.2)
Any hepatic events	4.7 (3.8, 5.9)
Adjudicated suicidal ideation and behaviour[c]	0.7 (0.4, 1.2)
Adjudicated definite or probable IBD[d,e]	0.5 (0.3, 1.0)

Data presented relates to the initial treatment and maintenance periods of BE HEARD I&II, and the open-label extension BE HEARD EXT (total of 3 years). TEAEs were coded using MedDRA v19.0 and reported for up to 3 years of BKZ treatment using EAIRs per 100 participant-years. [a] Up to 3 years, three patients died; one patient with significant cardiovascular history died due to congestive heart failure, one patient died due to possible central nervous system infection in the context of deteriorating HS and one patient with history of gynaecological cancer died of leiomyosarcoma; [b] The three most common TEAEs are presented for the BKZ Total group across the initial, maintenance and OLE treatment periods; [c] There were no events of completed suicide; [d] Evaluated for the overall population with/without a history of IBD; [e] Among the eight patients with a history of IBD, two patients experienced flares up to 3 years. BKZ: bimekizumab; CI: confidence interval; EAIR: exposure-adjusted incidence rate; HS: hidradenitis suppurativa; IBD: inflammatory bowel disease; MedDRA: Medical Dictionary for Regulatory Activities; OLE: open-label extension; PY: participant-years; TEAE: treatment-emergent adverse event.

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Predictive Factors for Early Super Response to Bimekizumab in 341 Patients with Psoriasis -A 24 Week Short Term Multicenter Real Life Experience

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Introduction

The efficacy of bimekizumab has been shown in moderate to severe plaque psoriasis.

Materials and Methods

The aim of this multicenter retrospective study was to investigate the early super responder (ESR) profile (at week 4) of bimekizumab.

Results

A total of 341 adult patients were included. [136 had nail psoriasis (39.9%), 148 had psoriatic arthritis (43.4%), 223 (65.4%) had at least one difficult-to-treat area involvement, 155 (45.5%) were bio-naïve, 110 (32.5%) had ≥ 2 biologics history). At week 4, PASI75 achieved in 144 patients (49.8%), PASI90 achieved in 88 patients (30.4%), PASI100 achieved in 51 patients (17.6%). At week 24, PASI75 achieved in 143 patients (97.3%), PASI90 achieved in 138 patients (93.9%), PASI100 achieved in 110 patients (74.8%). Family history (p = 0.041), palmoplantar involvement (p = 0.008), psoriatic arthritis (p = 0.097) and bio-experienced status (p = 0.060) were associated with lower odds of being an ESR, whereas each 1-point increase in baseline PASI was associated with significantly lower odds of ESR (p<0.001). However, PASI75, PASI90 and PASI100 responses were not affected by bio-naïve status at week 16 and 24. Most common AEs were candidiasis in 47 patients (13.7%). Candida infection was more common in females (p=0.011), patients with family history (p=0.014), bio-experienced patients (p=0.045), patients with ≥ 2 biologic failures (p=0.001), patients with cardiovascular disease (p=0.009), patients who failed to achieve PASI 75, PASI 90, or PASI 100 responses at weeks 4 (p=0.011, p=0.002, p=0.003), 8 (p=0.011, p=0.009, p=0.003), or 12 (p=0.721, p=0.016, p=0.012), patients with longer disease duration (p=0.002), and patients with younger age at disease onset (p=0.044).

Table. Comparison of baseline demographic and clinical characteristics of ESR and Non-ESR

Characteristics	Univariate Analysis			Multivariate Analysis	
	ESR (n=51)	Non-ESR (n=238)	p	OR (95% CI)	p
Male	31 (60.7%)	130 (54.6%)	0.422		
Age (years)	44.6 ± 13,1	44.7 ± 13.3	0.942		
Geriatric patients	3 (5.9%)	22 (9.2%)	0.442		
Disease duration (years)	13.7 ± 10.4	14.7 ± 9.9	0.514		
Age at diagnosis (years)	29.4 ± 15	29.8 ± 14	0,857		
Family history	8 (15.6%)	80 (33.6%)	**0.014**	0.408 (0.173-0.964)	**0.041**
Nail involvement	22 (43.1%)	96 (40.3%)	0.712		
Palmoplantar involvement	7 (13.7%)	65 (27.3%)	0.052	0.289 (0.115-0.724)	**0.008**
≥1 Difficult-to-treat areas	32 (62.7%)	173 (72.6%)	0.158		
Psoriatic arthritis	19 (37.2%)	115 (48.3%)	0.152	0.550 (0.272-1.115)	0.097
Systemic conventional history	48 (94.1%)	226 (95%)	0.806		
Bio-experienced	21 (41.1%)	132 (55.4%)	0.066	0.512 (0.254-1.030)	0.060
≥2 Previous biologics	7 (13.7%)	90 (37.8%)	**0.002**		
Previous anti-TNF	7 (13.7%)	74 (31%)	**0.015**		
Previous anti-IL 12/23	4 (7.8%)	28 (11.7%)	0.421		
Previous anti-IL 17	11 (21.5%)	103 (43.2%)	**0.005**		
Previous anti-IL 23	5 (9.8%)	48 (20.1%)	0.090		
Previous apremilast	1 (1.9%)	10 (4.2%)	0.459		
Any comorbidity	25 (49%)	108 (45.3%)	0.636		
Diabetes	12 (23.5%)	38 (15.9%)	0.298		
Hypertension	9 (17.6%)	48 (20.1%)	0.682		
Hyperlipidemia	7 (13.7%)	25 (10.5%)	0.507		
Cardiovascular disease	1 (1.96%)	13 (5.46%)	0.312		
PASI at baseline	9.9 ± 6.8	16.1 ± 7.6	**0.000**	0.860 (0.812-0.912)	**0.000**

Abbreviations: ESR: Early Super Responder, PASI: Psoriasis Area and Severity Index, OR: Odds Ratio, CI: Confidence Interval.

Conclusion

Bimekizumab is effective treatment in both bio-naïve and bio-experienced patients, however, it may be suggested that bimekizumab may have a more rapid onset of action in bio-naive patients. Further studies are needed on the long-term efficacy and safety data of bimekizumab.

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Comparative Efficacy of an Investigational Oral Minoxidil Extended-Release Tablet Versus Existing Minoxidil Formulations in Androgenetic Alopecia: A Blinded Retrospective IGA Analysis

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Introduction

The use of minoxidil for the treatment of androgenetic alopecia (AGA), both as a topical and as an immediate release (IR) oral tablet, has increased in recent years; however, there are still no oral formulations of minoxidil that are FDA approved for AGA. A recent Phase 2 trial has evaluated an investigational oral minoxidil extended release (ER) tablet (VDPHL01) for the treatment of AGA. To provide a robust comparison of the results of the VDPHL01 Phase 2 trial to existing minoxidil formulations, the authors have conducted a structured, blinded, retrospective Investigator Global Assessment (IGA) study comparing outcomes from the 20 male subjects in VDPHL01 Phase 2 trial with an existing, published, complete trial dataset of 33 males receiving 5 mg oral minoxidil immediate release and 34 males receiving minoxidil 5% solution.

Materials and Methods

The treatments included for IGA analysis were:

(1) VDPHL01 8.5 mg ER oral tablets twice daily (BID) for 4 months;

(2) 1 mL of minoxidil 5% topical solution BID for 6 months; and

(3) Minoxidil 5 mg IR oral tablets daily (QD) for 6 months.

This study was a blinded, retrospective image assessment study using image files containing randomized before-and-after scalp photographs of each treatment. Six total files were created, three for vertex views and three for frontal views, each representing subjects within each treatment group. Each file contained side-by-side image pairs per subject with the order of the before and after images randomly scrambled. U.S. board-certified dermatologists and alopecia experts (n=3) independently reviewed each image set and were asked to identify the baseline image before assigning an IGA score for improvement using a 7-point Likert scale (–3 to +3). After grading, scores were corrected for baseline misidentification by reversing score direction.

Each grader completed assessments for all subjects in the randomized order within each view category (vertex or superior) using identical calibrated monitors. Grading responses were recorded in structured Excel workbooks. A linear model adjusting for grader and accounting for the correlation of scores within an image was used for analysis.

Results

20, 33-34, and 33 subjects were included for frontal and vertex views for treatment groups 1, 2, and 3, respectively. After correction for mis-sequencing, mean IGA improvement scores for the frontal and vertex views, respectively, were: 2.02 ± 0.75 and 2.05 ± 0.79 for VDPHL01, 0.29 ± 1.32 and 0.02 ± 1.03 for topical minoxidil, and 0.59 ± 1.28 and 0.53 ± 1.15 for IR oral minoxidil.

The frequency of correct baseline identification for frontal and vertex views, respectively, were: 97.5% and 96.2% for VDPHL01, 60.3% and 49.6% for topical minoxidil, and 72.9% and 72.3% for IR oral minoxidil.

The proportion of subjects receiving corrected IGA scores ≥ +2 (indicating moderate-to-great improvement) for frontal and vertex views, respectively, was superior for VDPHL01, with 82.8% and 82.1% of subjects meeting this threshold, compared to 19.2% and 14.3% for topical minoxidil and 21.6% and 23.3% for IR oral minoxidil.

Comparative analysis for all metrics demonstrated statistically significant superiority for VDPHL01 compared to both other treatment groups (Tables 1-3).

Table 1

Comparative Analysis of Mean IGA Improvement Scores

View	Comparison	Difference in Means	p-value
Frontal	VDPHL01 BID vs. Topical Minoxidil 5% BID	1.72	<0.0001
	VDPHL01 BID vs. Oral Minoxidil 5 mg QD	1.43	<0.0001
	Oral Minoxidil 5 mg QD vs. Topical Minoxidil 5% BID	0.29	0.3226
Vertex	VDPHL01 BID vs. Topical Minoxidil 5% BID	2.03	<0.0001
	VDPHL01 BID vs. Oral Minoxidil 5 mg	1.52	<0.0001
	Oral Minoxidil 5 mg vs. Topical Minoxidil 5%	0.51	0.0491

Table 2

Comparative Analysis of the Frequency of Correct Baseline Identification

View	Comparison	Difference in %	p-value
Frontal	VDPHL01 BID vs. Topical Minoxidil 5% BID	37.3%	0.0009
	VDPHL01 BID vs. Oral Minoxidil 5 mg QD	24.6%	0.0067
	Oral Minoxidil 5 mg QD vs. Topical Minoxidil 5% BID	12.6%	0.3185
Vertex	VDPHL01 BID vs. Topical Minoxidil 5% BID	46.6%	<0.0001
	VDPHL01 BID vs. Oral Minoxidil 5 mg	23.9%	0.0062
	Oral Minoxidil 5 mg vs. Topical Minoxidil 5%	22.7%	0.0532

Table 3

Comparative Analysis of the Proportion of Subjects Receiving Corrected IGA Scores ≥ +2

View	Comparison	Difference in %	p-value

Frontal	VDPHL01 BID vs. Topical Minoxidil 5% BID	63.6%	<0.0001
	VDPHL01 BID vs. Oral Minoxidil 5 mg QD	61.2%	<0.0001
	Oral Minoxidil 5 mg QD vs. Topical Minoxidil 5% BID	2.4%	0.7753
Vertex	VDPHL01 BID vs. Topical Minoxidil 5% BID	67.8%	<0.0001
	VDPHL01 BID vs. Oral Minoxidil 5 mg	58.7%	<0.0001
	Oral Minoxidil 5 mg vs. Topical Minoxidil 5%	9.0%	0.1955

Conclusion

This study demonstrated that 4 months of treatment with VDPHL01 produced superior efficacy outcomes for AGA compared to 6 months of treatment with topical and IR oral minoxidil. This superiority was demonstrated across both frontal and vertex views in all metrics. Pending further clinical development, these findings suggest VDPHL01 is a potential best-in-class treatment for AGA. Study limitations include potential differences in baseline characteristics of subjects across trials and inherent limitations in retrospective photography-based review methodologies.

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IL-22RA1 antagonism with temtokibart provides significant early and sustained improvements in atopic dermatitis: results from a phase 2b dose-finding trial

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Introduction

Atopic dermatitis (AD) is a chronic, heterogeneous inflammatory skin disease. While inhibition of the interleukin (IL)-4/IL-13 axis is efficacious for many patients with AD, some have inadequate improvement or experience adverse events (AEs), highlighting the need to investigate other pathways. Elevated IL-22 levels are implicated in epidermal thickening and compromised barrier function. Temtokibart is a monoclonal antibody targeting the IL-22 receptor subunit alpha-1 (IL-22RA1), which is predominantly found on epithelial cells, but not on skin-resident immune cells. In a previous phase 2a trial (NCT04922021), temtokibart improved signs and symptoms of AD and was well-tolerated for up to 16 weeks. Here, we evaluate the efficacy and safety of temtokibart in a phase 2b dose-finding trial in AD.

Materials and Methods

In a phase 2b randomized, double-blind trial (NCT05923099), adults with moderate-to-severe AD were randomized 1:1:1:1:1 to subcutaneous temtokibart 600mg, 450mg, 300mg, or 150mg, or placebo (PBO) every two weeks from week 4 (W4) to W14 (**Figure A**). During W0–W3, patients in the 600mg arm received 600mg each week (W0–W3), those in the 450mg arm received 450mg each week (W0–W2), and those in the 300mg and 150mg arms received twice the subsequent dose (600 and 300mg, respectively) at W0 and W2. Previous use of biologics or Janus kinase inhibitors (JAKi) was allowed. The primary endpoint was percentage change in Eczema Area and Severity Index (EASI; EASI % change) from baseline to W16. The secondary endpoint was number of treatment-emergent AEs per patient from baseline to W16.

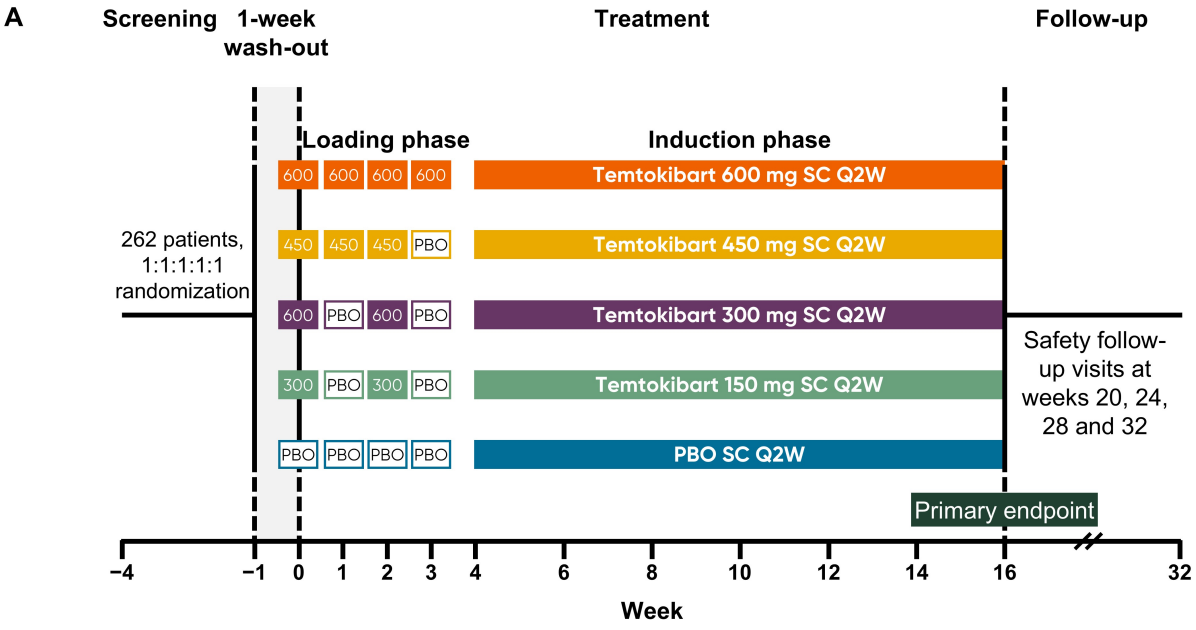
Results

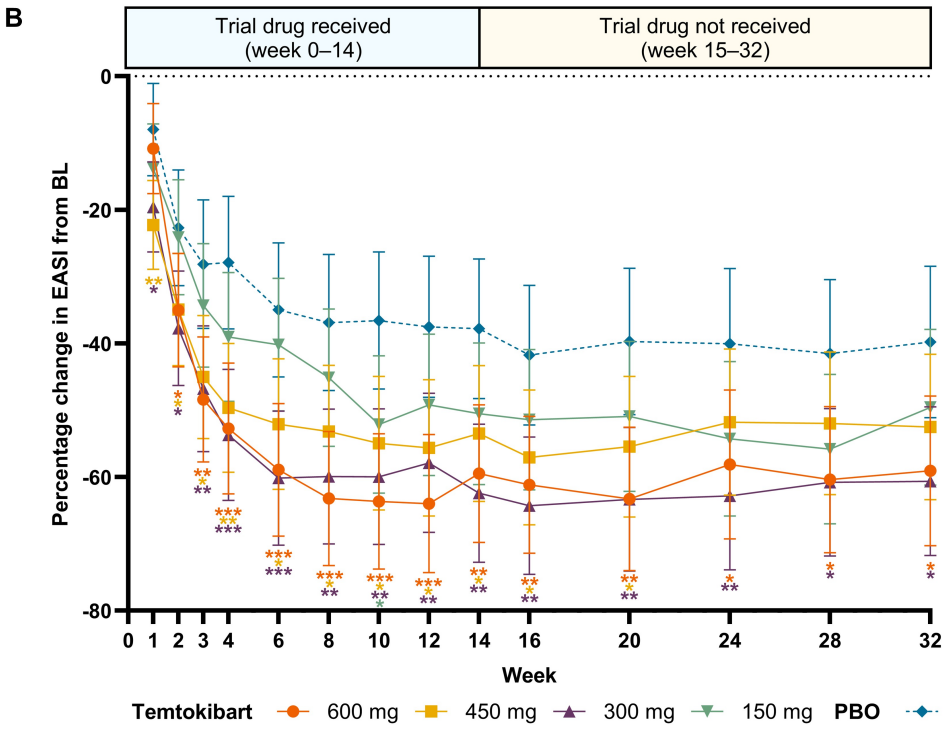
In total, 262 patients were randomized (temtokibart 600mg: n=52, 450mg: n=53, 300mg: n=52, or 150mg: n=53, and PBO: n=52). Baseline and clinical characteristics were similar across treatment arms. Previous use of any systemic biologic or JAKi was reported in 25.0–40.4% of patients across arms. At W16, EASI % change from baseline was −61.2% with temtokibart 600mg (vs PBO: $p<0.01$), −57.1% with 450mg ($p<0.05$), −64.3% with 300mg ($p<0.01$), and −51.4% with 150mg ($p=0.2$), and −41.7% with PBO (**Figure B**). Significantly greater improvements in EASI were reported as early as W1 for temtokibart 450mg (EASI % change: −22.3%; $p<0.01$) and 300mg (−19.6%; $p<0.05$) vs PBO (−8.0%), and as early as W2 for 600mg (−35.0%; $p<0.05$) vs PBO (−22.7%; **Figure B**). Despite no treatment after W14, significant improvements in EASI were maintained up to W32 with temtokibart 600mg (EASI % change: −59.1%; $p<0.05$) and 300mg (−60.6%; $p<0.05$) vs PBO (−39.8%; **Figure B**). From W0–W16, the proportions of patients with AEs were similar across the pooled temtokibart (62.4%) and PBO (59.6%) arms, with no dose-dependent relationship observed. The majority of temtokibart-treated patients had mild (51.7%) vs moderate (32.7%) or severe (5.2%) AEs. Three temtokibart-treated patients (1.4%) had serious AEs, none of which were considered related to temtokibart. There were low incidences of conjunctivitis (temtokibart vs PBO: 2.4% vs 0%) and herpes (temtokibart vs PBO: 3.3% vs 5.7%) AEs. AEs leading to permanent drug discontinuation/withdrawal were reported in 2.4% and 3.8% of patients in the temtokibart and PBO groups, respectively.

Conclusion

Temtokibart demonstrated greater improvements in EASI % change for the three highest doses vs PBO at W16 in adults with moderate-to-severe AD. Significant improvements were observed as early as Week 1 and maintained up to Week 32. Temtokibart was well-tolerated with no dose-dependent AEs, low incidence of conjunctivitis, and no signal for herpes. These findings suggest that IL-22RA1 inhibition with temtokibart could be a valuable treatment option providing patients with a novel way of targeting AD, characterized by early and sustained effects and a favorable safety profile.

Figure. (A) Trial design, and (B) percentage change in EASI from baseline to week 32 across treatment arms (full analysis set)





Patients were randomized 1:1:1:1:1 to subcutaneous temtokibart 600mg, 450mg, 300mg, or 150mg, or PBO every two weeks from week 4 to week 14. From week 0 to week 3, patients in the 600mg arm received 600mg each week (week 0 to week 3), those in the 450mg arm received 450mg each week (week 0 to week 2), those in the 300mg arm received 600mg at week 0 and week 2, and those in the 150mg arm received 300mg at week 0 and week 2. Patients in the PBO arm received PBO each week (week 0 to week 3).

*p<0.05; **p<0.01; ***p<0.001. Differences between treatment arms were evaluated using an ANCOVA model adjusted for treatment, baseline EASI and vIGA-AD, region and prior use of biologics or systemic JAK inhibitors.

Data observed after initiation of rescue treatment or trial drug discontinuation (due to lack of efficacy or an AE related to worsening of AD) were considered missing not at random and imputed using LOCF. Other missing data and data observed after trial drug discontinuation (due to all other reasons) were considered missing at random and imputed from a regression model.

AE, adverse event; AD, atopic dermatitis; BL, baseline; SC, subcutaneous; EASI, Eczema Area and Severity Index; LOCF, last observation carried forward; PBO, placebo; Q2W, every 2 weeks.

Abstract N°: LBA-323

Molecular and Clinical Effects of Oral ATI-2138, an ITK/JAK3 inhibitor, in Moderate-to-Severe Atopic Dermatitis: Sub-study of a Phase 2a Open-Label, Single-Arm Trial

Jessica Beaziz Tordjman[1], Ester Del Duca[1], Jerry Zhou[1], Jacob Fiedler[1], Yeriel Estrada[1], Joel Correa da Rosa[1], Juliana Pulsinelli[1], Digpal Gour[1], Ragasruti Metukuru[1], Joseph Monahan[2], Aparna Kaul[2], Ajay Aggarwal[2], Emma Guttman-Yassky[1]

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder which significantly impairs quality of life despite advancements in Th2-targeted treatments. ATI-2138 is an oral, small-molecule inhibitor of ITK and JAK3 recently evaluated in an open-label, single-arm study (NCT06585202) for patients with moderate-to-severe AD. In this molecular sub-study, we investigated treatment-related changes in molecular biomarkers and correlations with clinical scores.

Materials and Methods

Tape-strips, biopsies and plasma were collected from lesional and non-lesional skin of 9 patients with moderate-to-severe AD from baseline to week 12. Transcriptomic studies were done in tape-strips and biopsies using RNA-Sequencing and RT-PCR while proteomics analysis was performed on 369 analytes in plasma through Olink high-throughput platform. Correlations between biomarkers and clinical scores including EASI, BSA, and PP-NRS were also performed.

Results

BSA decreased by 63.9%, EASI scores dropped by 77.3%, and PP-NRS decreased by 44.8% after 4 weeks of treatment. These changes were statistically significant and sustained through study conclusion (W12). RNA-Seq showed reduction of inflammatory markers including Th1 (CXCL9, IL12RB2, OASL), Th2 (CCL24), and innate immunity (IL6). Fibrosis/hyperplasia-related markers, such as ADAMTS14 and COL1A1 were also suppressed. RT-PCR in biopsies showed additional decreases in IL13, S100A9, DEFB4, CXCL9, MMP12, and CCL13. Downregulation of the ITK pathway was observed, with statistically significant reductions in the expression of multiple ITK-associated T cell proliferation and differentiation markers, including CD4, CD5, IL6R, IL13, and IL4R in biopsy and/or tapestrip data. Systemic inflammation was also attenuated, as measured by Olink analysis in plasma, with significant downregulation of multiple pathways, including Th1 (IL2), Th2 (IL4, IL33), and Th17 (CXCL1, PI3, TGFB1). Reduction in several pro-inflammatory genes (TSLP, CCL21, CXCL12) and fibrosis markers (ELN, SPON1, LUM) were positively correlated with reduced EASI, BSA, and/or PP-NRS scores. Similarly, epidermal barrier genes (KRT77, LPO, KRT23, ELOVL5), demonstrated negative correlations with clinical scores, suggesting a restoration of skin homeostasis with treatment. All p-values < 0.05.

Conclusion

Treatment with ATI-2138 was associated with improvement in clinical measures and reductions in molecular markers of inflammation and fibrosis in skin and plasma. These findings suggest ATI-2138 as a potential new treatment for clinical and molecular reversal of atopic dermatitis.

Abstract N°: LBA-325

Temtokibart, an IL-22RA1 Monoclonal Antibody broadly dampens gene expression markers of activated immune pathways in Atopic Dermatitis: Results from a Phase 2b Trial Subgroup Analysis

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Introduction

Temtokibart is a novel monoclonal antibody targeting interleukin-22 receptor subunit alpha-1 (IL-22RA1), a key mediator of Th22-driven skin inflammation and barrier dysfunction in atopic dermatitis (AD). Its clinical potential has been recently evaluated in a phase 2b randomized, double-blind, placebo-controlled trial (NCT05923099) but the downstream transcriptomic impact of IL-22RA1 blockade in human AD has not been fully elucidated. Our biopsy sub-study evaluates the effect of temtokibart on the cutaneous transcriptomic profile of AD.

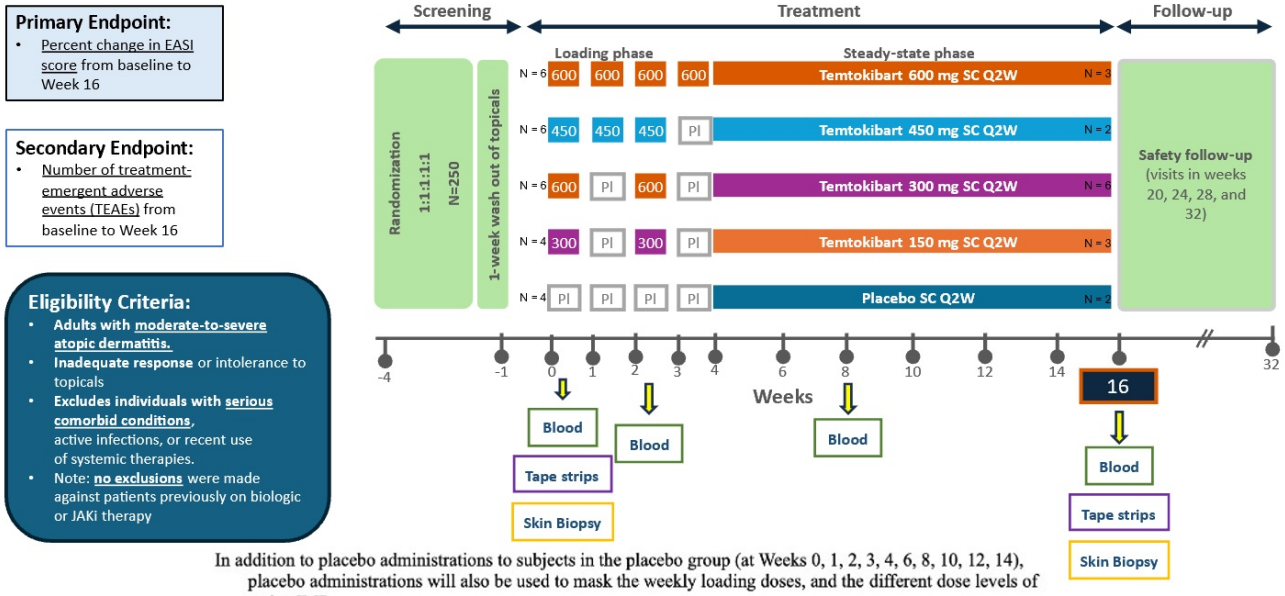
Materials and Methods

26 adults with moderate-to-severe AD were randomized 1:1:1:1:1 to receive placebo or temtokibart at doses of 600 mg, 450 mg, 300 mg, or 150 mg every two weeks after loading doses as depicted in Figure 1A. Biopsies of lesional and non-lesional skin were taken at baseline and Week 16 (W16). Due to lack of statistical power (N=2 at W16), placebo samples were not included in analysis. Due to sample size considerations, active treatment groups were pooled together for transcriptomic analyses, including the minimum effective dose (150mg) group. Whole transcriptome RNA sequencing and targeted RT-PCR were used to assess gene expression changes. Correlation analyses were conducted between changes in gene expression and clinical scores (DLQI, POEM, SCORAD, EASI).

Results

Pooled temtokibart-treated patients (N=22 at baseline, N=14 at W16) demonstrated an overall 97% improvement in immune gene expression by W16. Significant downregulation of key markers was observed across innate immunity (TNF, CXCL8/IL8), Th2 (OX40L, IL13), and Th17/Th22 (S100A7, S100A8, S100A9, CXCL1). Expression of epidermal barrier-related genes including CLDN23, ELOVL3, PPARG was significantly restored by week 16 (Figure 1B). RT-PCR data corroborated these findings, with notable reductions in IL22, S100A8/9/12, IL31, IL17A, PI3, and increases in CLDN8 and CLDN23. Correlation analysis revealed that reductions in EASI and/or SCORAD were significantly associated with reductions in Th2 (CCL24, CCL26) and Th17/22 markers (e.g., IL23A). Similarly, DLQI and/or POEM correlated with reductions of key T-cell, Th2, Th17/Th22 markers (CCL24, CCL13, CXCL12, CCR7, OX40L, IL17BR). All p-values ≤ 0.05.

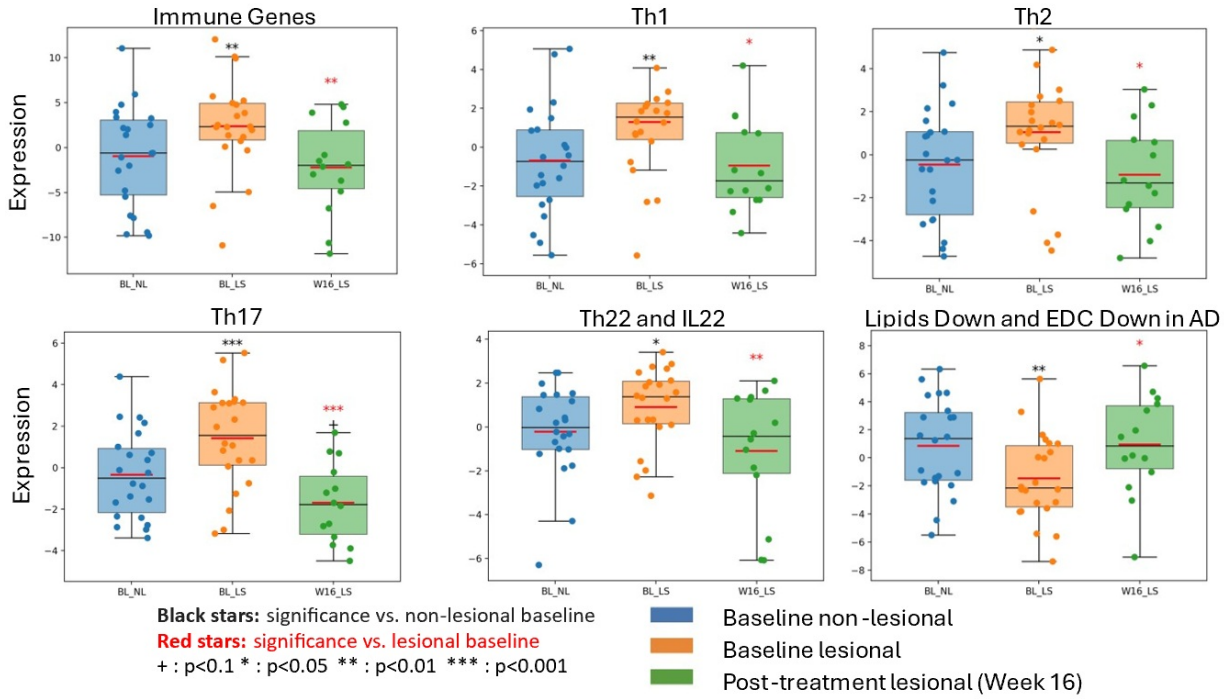
Figure 1A. Phase 2B Study Design and Temtokibart Dose Schedule



In addition to placebo administrations to subjects in the placebo group (at Weeks 0, 1, 2, 3, 4, 6, 8, 10, 12, 14), placebo administrations will also be used to mask the weekly loading doses, and the different dose levels of active IMP.

Abbreviations: AD = atopic dermatitis; N = number of subjects; SC = subcutaneously; Q2W = every 2 weeks; W = Week.

Figure 1B. RNASeq: Expression of Key Pathways



Conclusion

Temtokibart treatment led to broad suppression of inflammatory gene signatures across innate immunity, Th2, Th17, and Th22 axes and promoted recovery of skin barrier function in AD. These transcriptomic improvements were significantly correlated with clinical benefit, underscoring IL-22RA1 as a promising therapeutic target for immune modulation and barrier restoration in moderate-to-severe atopic dermatitis.

Abstract N°: LBA-326

JAK3/TEC Inhibition is Safe and Effective in Cicatricial Alopecias: Evidence from a Prospective Trial

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Introduction

Cicatricial alopecias (CAs) such as frontal fibrosing alopecia (FFA), lichen planopilaris (LPP), and central centrifugal alopecia (CCCA) are chronic, progressive, scarring hair loss conditions impacting quality of life. Th1/JAK3 activation in CAs provides rationale for investigating ritlecitinib, a selective JAK3/TEC kinase inhibitor in CAs (NCT05549934).

Materials and Methods

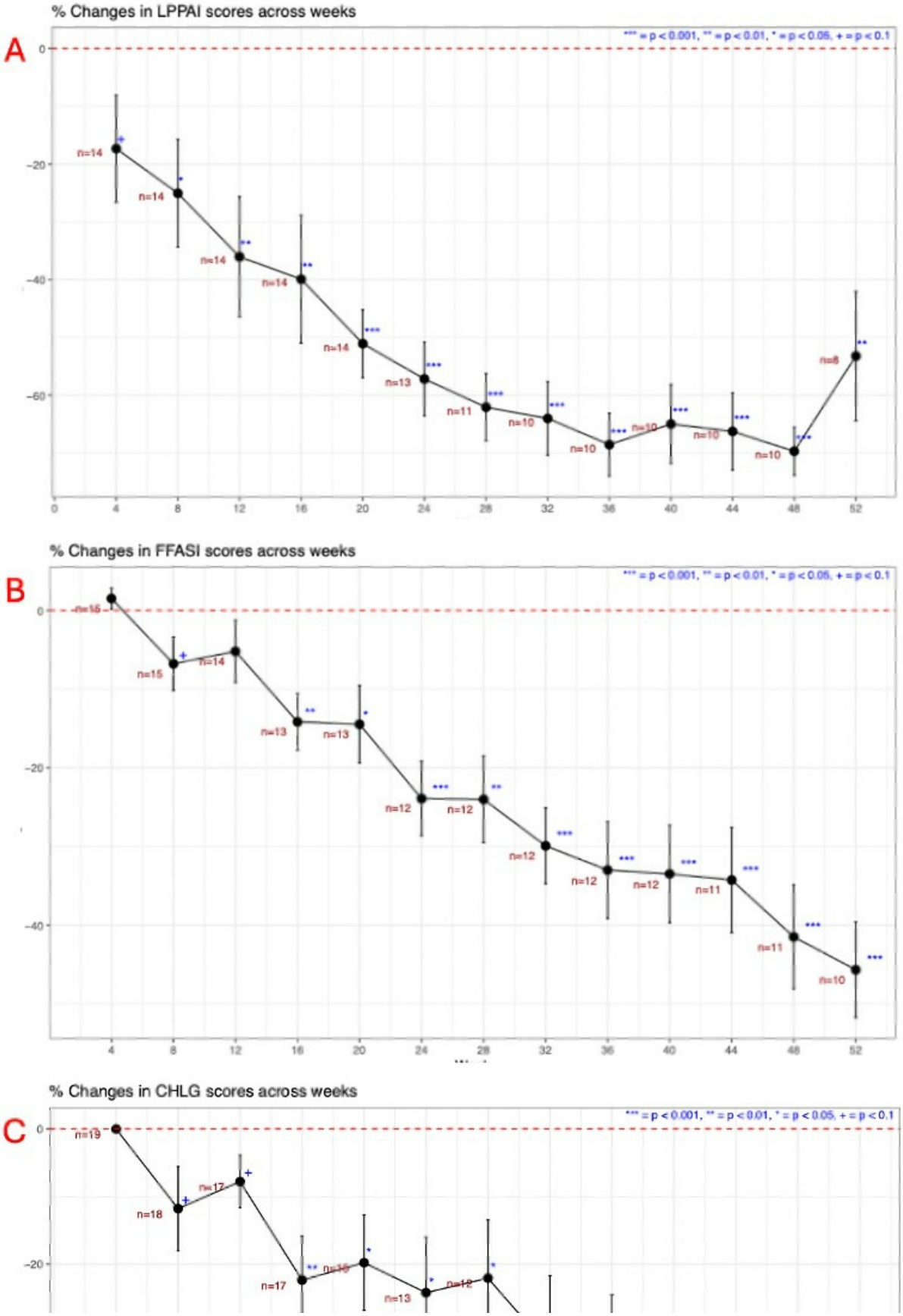
In this single-arm, open-label trial, 50 patients with FFA (N=15), LPP (N=15), and CCCA (N=20) were treated with ritlecitinib for 48 weeks (200 mg daily x 8 weeks, then 100 mg daily). Safety and changes in Th1 biomarkers (CCL5) and fibrosis biomarkers (e.g., TGFB1/2, vimentin) at week 24 were defined as primary endpoints. Secondary endpoints included changes in clinical activity scores (LPP activity/LPPAI, FFA severity index/FFASI, change in hair loss grade/CHLG), Dermatology Life Quality Index (DLQI), and Physician Global Assessment of Improvement (PGA-I). Scalp biopsies were collected from lesional/non-lesional skin at baseline and weeks 8, and 24 and analyzed for molecular changes by RT-PCR.

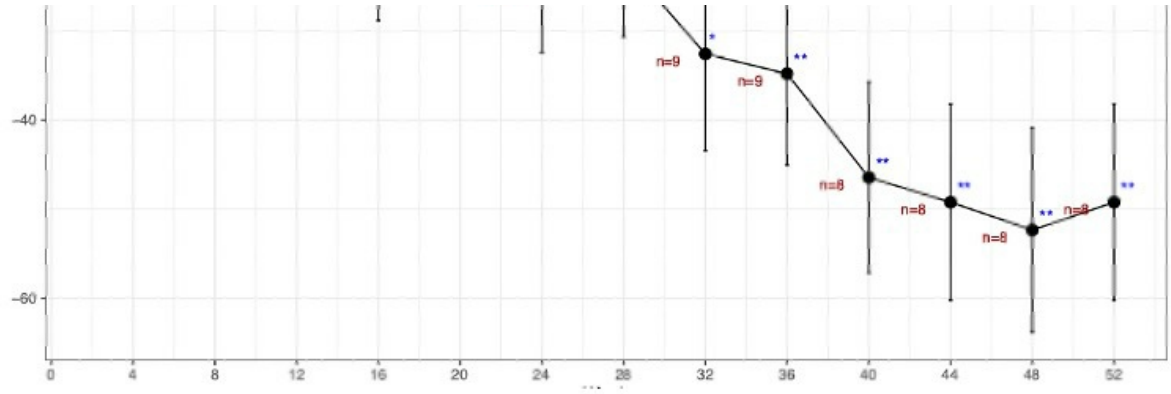
Results

Ritlecitinib (a JAK3/Tec inhibitor) showed improvements from baseline in LPPAI, FFASI, and CHLG scores of 57% ($p<0.001$), 24% ($p<0.01$), and 24% ($p<0.05$) at week 24 (N=38; Figure 1), and 70% ($p<0.001$), 41% ($p<0.001$), and 52% ($p<0.01$) at week 48 (N=29; Figure 1), respectively. No new safety signals were observed over the 48-week period. The majority (92%) of adverse events were mild/moderate with only 9.6% considered likely drug related. Molecular analysis showed significant downregulation of the primary endpoint biomarker CCL5, across all subtypes ($p<0.05$) at Week 24. All groups demonstrated downregulation of key inflammatory genes (already evident at week 8) including significant reductions in markers related to general inflammation (*PDE4B*), Th1 (*CCL5*, *CXCL9*, *CXCL10*), and cytotoxic/NK-T cell markers (*IL2RA*, *GZMB*) in FFA and/or LPP ($p<0.05$). CCCA showed the most significant and robust immune downregulation across multiple axes, including T cell activation (*IL2RA*, *IL2RB*), Th1 (*CCL5, CXCL9, CXCL10, IL12RB1*), Th2 (*CCL13*, *CCL22*), Th17/Th22 signaling (*IL23R*, S100A12), and JAK-STAT and NK/T cell–associated signaling pathways (*IL2RA*, *IL2RB*, *IL15RA*, *IL16*, *JAK1*, *JAK3*, *GZMB*) ($p<0.05$). While COL1A1 showed trends of downregulation across subtypes, no significant downregulation was seen in other fibrosis markers. Upregulation of hair keratins (*KRT85*, *KRT35*, *KRT83*, *KRT75*, *KRT86*, *KRTAP1; p<0.05*) were observed in FFA. While more robust changes were seen during the initial 8-week 200mg treatment, similar

trends were obtained throughout the 24 weeks, with the most pronounced changes seen in CCCA.

Figure 1. Mean (±SE) percentage change from baseline in (A) LPPAI, (B) FFASI, and (C) CHLG scores over 52 weeks of ritlecitinib treatment. Red numbers indicate the number of evaluable patients at each timepoint. Statistical significance versus baseline: ***p<0.001, **p<0.01, *p<0.05, +p<0.1. At week 24, mean improvements were 57%, 24%, and 24% in LPPAI, FFASI, and CHLG scores, respectively (N=38); at week 48, mean improvements were 70%, 41%, and 52%, respectively (N=29).





Conclusion

Ritlecitinib was associated with a favorable safety profile and rapid improvements in clinical scores and molecular biomarkers supporting JAK3/TEC inhibition as a potential therapeutic approach in treatment of CAs.

Abstract N°: LBA-327

Safety of delgocitinib cream in adult patients with Chronic Hand Eczema (CHE): pooled analysis of five phase 2b and phase 3 trials

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Introduction

Chronic Hand Eczema (CHE) is an inflammatory skin disease affecting the hands and wrists that persists for >3 months or recurs at least twice in a year. Delgocitinib cream 20 mg/g, a non-steroidal, topical pan-JAK inhibitor, has been approved in multiple countries for the treatment of moderate to severe CHE in adults for whom topical corticosteroids are inadequate or inappropriate. Here, we assess the pooled short- and long-term safety profiles of delgocitinib cream for the treatment of CHE for up to 52 weeks, integrating data from 5 trials.

Materials and Methods

Safety data were pooled from 1 phase 2b (NCT03683719) and 4 phase 3 (DELTA 1–3 and DELTA FORCE) trials in patients with CHE. Data encompass both the initial treatment period (ITP; delgocitinib cream twice daily [BID] vs cream vehicle BID or alitretinoin once daily for 12-16 weeks) and the subsequent as-needed treatment period (DELTA 3 and DELTA FORCE; delgocitinib cream 20 mg/g BID for up to 52 weeks of total treatment). In the as-needed treatment period, patients with Investigator's Global Assessment for CHE (IGA-CHE) score of ≥2 applied delgocitinib cream until symptoms resolved (i.e., IGA-CHE 0/1 [clear/almost clear]). Adverse events (AEs) that started or worsened after the first study drug dosing were included. The number of AEs, AEs of special interest (AESIs; e.g., eczema herpeticum), and AEs in safety focus areas (e.g., application site reactions) were reported. Event rates (R) were calculated as the number of events per 100 patient-years of observation (PYO).

Results

In the ITP, the rate of AEs with delgocitinib cream (N=944; PYO=291.3; R=302.1) was similar to cream vehicle (N=371; PYO=109.9; R=337.5) and notably lower than alitretinoin (N=247; PYO=53.2; R=830.2) (**Table**). This rate decreased in the as-needed treatment period (N=1040; PYO=581.6; R=224.6). Delgocitinib cream demonstrated a lower rate of AEs leading to withdrawal (n=3; R=1.0) compared with cream vehicle (n=16; R=15.5) and alitretinoin

(n=3; R=13.2) during the ITP, which was similar to the as-needed treatment period (n=9; R=1.7). Throughout the treatment periods, no serious AEs (SAEs) or deaths were found to be probably or possibly related to delgocitinib cream or cream vehicle treatment; 3 SAEs were found related to alitretinoin treatment. Rates of frequent AEs (≥1% of patients; e.g., headache and nasopharyngitis) were similar for delgocitinib cream vs cream vehicle and lower vs alitretinoin in the ITP, remaining consistent in the as-needed treatment period. The only AESI reported was a case of eczema herpeticum (neck and eyelids) during the as-needed treatment period in a patient with a history of atopic dermatitis. Application site reactions occurred in <1% of delgocitinib-treated patients, being less frequent vs cream vehicle (2.4%). No new treatment-emergent safety signals were identified for delgocitinib cream. Overall, rates of AEs in safety focus areas decreased in the as-needed treatment period vs the ITP.

Conclusion

During the ITP, rates of AEs were similar between delgocitinib cream 20 mg/g and cream vehicle and lower than those observed with alitretinoin. The safety profile of delgocitinib cream during the as-needed treatment period remained consistent with the ITP, with AE rates decreasing in frequency over time. These pooled safety data support the robust safety profile of delgocitinib cream 20 mg/g for up to 52 weeks of treatment in adults with CHE.

Table: Overview of AEs

	Initial treatment period (ITP)									As-needed treatment period		
	Delgocitinib cream 20 mg/g (N=944, PYO=291.31)			Cream vehicle (N=371, PYO=109.91)			Alitretinoin (N=247, PYO=53.24)			Delgocitinib cream 20 mg/g (N=1040, PYO=581.56)		
	n (%)	E	R	n (%)	E	R	n (%)	E	R	n (%)	E	R
All events	435 (46.1)	880	302.08	183 (49.3)	371	337.54	170 (68.8)	442	830.20	545 (52.4)	1306	224.57
Severity												
Mild	335 (35.5)	595	204.25	146 (39.4)	255	232.00	130 (52.6)	287	539.07	422 (40.6)	811	139.45
Moderate	181 (19.2)	260	89.25	66 (17.8)	99	90.07	81 (32.8)	139	261.08	267 (25.7)	457	78.58
Severe	19 (2.0)	25	8.58	10 (2.7)	17	15.47	11 (4.5)	16	30.05	28 (2.7)	38	6.53
Serious AEs	16 (1.7)	17	5.84	6 (1.6)	8	7.28	6 (2.4)	6	11.27	27 (2.6)	36	6.19
AEs leading to withdrawal	3 (0.3)	3	1.03	16 (4.3)	17	15.47	3 (1.2)	7	13.15	9 (0.9)	10	1.72
Deaths	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0	3 (0.3)	3	0.52

%, percentage; AE, adverse event; E, number of events; ITP, initial treatment period; n, number of patients with observation; N, number of patients at baseline; PYO, patient-years of observation; R, rate calculated as (E/PYO)*100.

Abstract N°: LBA-332

Whole Genome Sequencing Analysis of Generalized Pustular Psoriasis Samples from a Global Clinical Study

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Introduction

Generalized pustular psoriasis (GPP) is a rare, severe disease characterized by debilitating flares of non-infectious pustular and erythematous skin lesions, with systemic impacts that can be life-threatening. Recurrent flares are common. The pathogenesis of GPP can be mainly attributed to excessive activity of IL-36 pathway. Mutations in the gene encoding the IL-36Ra (*IL36RN*) result in uncontrolled activation of the IL-36 pathway associated with the development of GPP, a rare and life-threatening disease. This study aimed to delineate genetic variants underlying GPP in a multiethnic cohort of patients. Reported here are results from such a large scale WGS analysis of GPP patients.

Materials and Methods

Whole genome sequencing and RNAseq was conducted on baseline samples obtained from GEMINI-1, a randomized, double-blind, placebo (PBO)-controlled, global trial, with GPP. Samples were collected from GPP patients from all over the world providing unique opportunity to study this phenotype globally. Additional ELISA on IL36RN levels was conducted to confirm downstream effects of the identified variants. GPP Physician Global Assessment (GPPPGA) score of clear/almost clear (0/1) collectively across all GPP disease attributes (pustulation, erythema, scaling), a stringent and comprehensive characterization of disease severity was conducted to characterize this cohort of patients.

Results

IL36RN genetic variants constituted the single most enriched cause of the pathophysiology, with pLOFs and missense variants explaining 46% of the studied dataset. Among the core variants were (p.Leu27Pro [rs387906914], p.Asn47Ser [rs28938777], p.Pro76Leu [rs139497891], and p.Ser113Leu [rs144478519]) in *IL36R*N followed by rare splicing variants. Additionally variants in CARD14, AP1S3 and SERPINA3 were identified explaining jointly 60 percent of the cohort. Additioanlly case control analyses pointed to novel loci as well as confirmed well established loci in psoriasis.

We observed a significant improvement in patients with *IL36RN* mutations following treatment with monoclonal antibody that binds the interleukin-36 receptor and antagonizes interleukin-36 signaling with 66.7% of mutant carriers achieving a GPPPGA 0 or 1 score at Week 4 vs 27.3% of non-mutant *IL36RN* carriers. Additionally levels of IL36RN were measured in the serum of the same patients to establish an association between the variants and IL36RN levels in GPP patients. Further characterization of the corresponding RNA is ongoing.

Conclusion

Targeting IL-36 signaling with represents a promising therapeutic option for GPP patients, and other rare skin conditions that lead to aberrant IL36 signalling. Understanding the pathophysiology starting from genetic variants, serum levels of of IL36RN and the cporrespoinding expression levels is at the heart of precision therapeutics that can enable selection of the optimal treatments.

Abstract N°: LBA-335

Long-term efficacy and complete scalp hair regrowth in patients with alopecia areata receiving ritlecitinib 50 mg QD up to 3 years in the ALLEGRO clinical trial program

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[2] Sinclair Dermatology, Melbourne, Victoria, Australia
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[4] Hair Disorders Unit at Ramón y Cajal University Hospital and Pedro Jaén Group Clinic, University of Alcalá, Madrid, Spain
[5] Private Dermatology Practice, Bologna, Italy
[6] Department of Dermatology, Kyorin University Faculty of Medicine, Tokyo, Japan
[7] Huashan Hospital, Fudan University, Shanghai, China
[8] Pfizer Inc, Groton, CT, United States
[9] Pfizer Inc, Collegeville, PA, United States
[10] Pfizer Inc, New York, NY, United States
[11] Pfizer Inc, Paris, France

Introduction

Alopecia areata (AA) is an autoimmune disease characterized by nonscarring hair loss on the scalp, with or without loss of facial and/or body hair. In clinical trials, achievement of Severity of Alopecia Tool (SALT) score ≤20 and ≤10 (≤20% and ≤10% scalp hair loss) are commonly reported, but achievement of SALT score 0, among the most stringent endpoints, is less common. Here, we report efficacy results through Month 36-38, including achievement of SALT score 0, in patients with AA receiving ritlecitinib, an oral, selective JAK3/TEC family kinase inhibitor, in the ALLEGRO phase 2b/3 and ongoing, phase 3, open-label ALLEGRO-LT studies.

Materials and Methods

Patients aged ≥12 years with AA and ≥50% scalp hair loss who received daily ritlecitinib 50 mg in ALLEGRO-2b/3 (NCT03732807) and rolled over to ALLEGRO-LT (NCT04006457; continued to receive 50 mg) were included. Data from patients who received placebo and switched to 50 mg were re-baselined to align time points across groups. Observed and last observation carried forward (LOCF) data are reported to the cutoff date of June 25, 2024 for the proportion of patients with SALT score ≤20, SALT score ≤10, and SALT score 0 at Month 36-38; maintenance of SALT score ≤20 response (patients who had a SALT score ≤20 at Months 12 and 36-38, regardless of SALT score between timepoints); SALT score of 0 at ≥1 time point through Month 36-38; and eyebrow and eyelash assessment (EBA/ELA) response (≥2-grade improvement from baseline or a normal score of 3 at the analysis visit) at Month 36-38.

Results

191 patients were included; 27 (14.1%) were ongoing at the time of data cutoff. At Month 36-38, 65.1% (71/109

observed) and 47.1% (90/191 LOCF) of patients had SALT score ≤20 (**Table 1**). Among patients who achieved SALT score ≤20 at Month 12, 88.3% (53/60 observed) and 89.6% (69/77 LOCF) of patients maintained this response at Month 36-38. At Month 36-38, SALT score ≤10 response rates were 52.3% (57/109 observed) and 36.7% (70/191 LOCF). At Month 36-38, SALT score 0 rates were 31.2% (34/109 observed) and 22.5% (43/191 LOCF).

Complete scalp hair regrowth was defined as a SALT score of 0 at ≥1 time point. Through Month 36-38, 29.8% (57/191) of patients had complete scalp hair regrowth (**Table 1**). Most of these patients (61.4%, 35/57) did not have a subsequent increase in SALT score at later visits (**Figure 1**). Among patients with a subsequent increase in SALT score (38.6%, 22/57), the majority remained at SALT score ≤20. Among patients who achieved a SALT score of 0 at ≥1 visit, most (84.2%, 48/57) remained at SALT score ≤5 at subsequent visits.

Of patients with an abnormal EBA/ELA score at baseline, 63.2% (36/57 observed) and 48.7% (75/154 LOCF) had an EBA response at Month 36-38 and 60.4% (32/53 observed) and 49.6% (69/139 LOCF) had an ELA response (**Table 1**).

Table 1. Observed and LOCF efficacy data

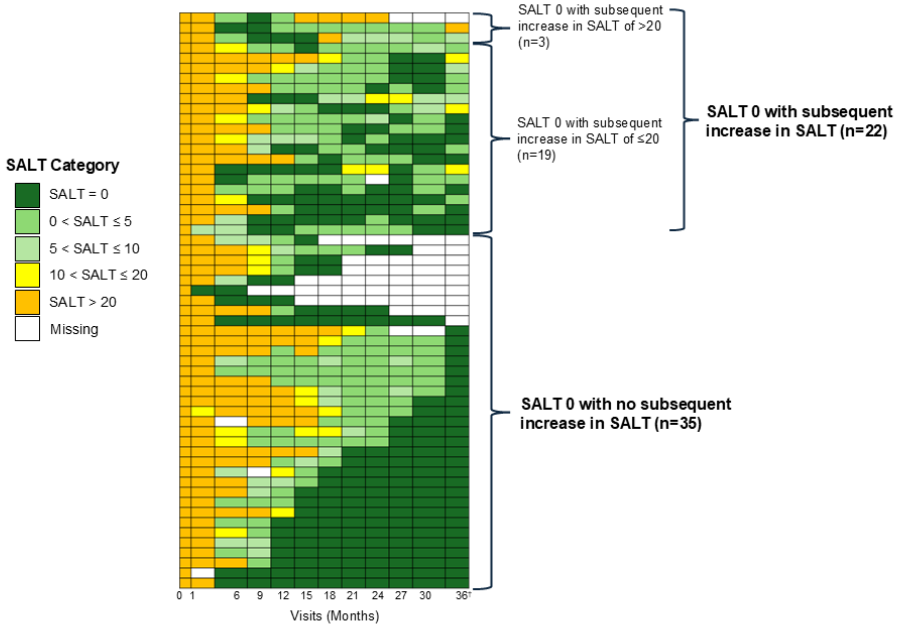
Patients, n/N (%)	Observed	LOCF
At Month 36-38		
SALT score ≤20	71/109 (65.1%)	90/191 (47.1%)
Maintained SALT score ≤20 response*	53/60 (88.3%)	69/77 (89.6%)
SALT score ≤10	57/109 (52.3%)	70/191 (36.7%)
SALT score 0	34/109 (31.2%)	43/191 (22.5%)
EBA response†	36/57 (63.2%)	75/154 (48.7%)
ELA response†	32/53 (60.4%)	69/139 (49.6%)
At ≥1 timepoint through Month 36-38		
Complete scalp responders‡	57/191 (29.8%)	-

EBA, eyebrow assessment; ELA, eyelash assessment; LOCF, last observation carried forward; SALT, Severity of Alopecia Tool.
*Patients who had a SALT score ≤20 at Month 36-38, among patients with a SALT score ≤20 at Month 12.
†≥2-grade improvement from baseline or a normal score assessment score out of patients with an abnormal EBA/ELA score at baseline.
‡Patients who had a SALT score 0 at ≥1 time point.

Conclusion

Ritlecitinib 50 mg demonstrated clinically meaningful clinician-reported efficacy up to Month 36-38, supporting the long-term use of ritlecitinib in patients aged ≥12 years with AA. Almost one-third of patients receiving ritlecitinib 50 mg achieved complete scalp hair regrowth (SALT score of 0) at ≥1 time point, with the majority sustaining that response at later visits or remaining at SALT score ≤5.

Figure 1. Heatmap of complete responders* (as observed) displaying SALT score categories over time.



SALT, Severity of Alopecia Tool.
*Complete responders were defined as patients who achieved a SALT score of 0 at ≥1 time point up to Month 36-38. Each row represents an individual SALT score 0 responder.
†To align timepoints across groups for summarization, visits are calculated as time since the first ritlecitinib dose; the "Month 36" timepoint includes patients in Group C who had 36 months of treatment and patients in Group G who had 38 months of treatment.

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Demonstration of Early Proof-of-Concept for STAR-0310, a Long-Acting OX40 Receptor Antagonist: Initial Safety, PK, and PD Results from a Phase 1a Trial

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Introduction

OX40 (CD134) is a co-stimulatory receptor expressed on activated T cells and implicated in sustaining pathogenic T cell responses in immunologic diseases. Therapeutic blockade of the OX40–OX40L axis has emerged as a promising approach for treating chronic diseases, such as atopic dermatitis, by modulating immune-mediated inflammation and tissue damage. STAR-0310 is a novel, investigational, subcutaneously (SC) administered Fc-engineered monoclonal antibody targeting the OX40 receptor. It incorporates a YTE-modified Fc domain to extend half-life and is designed to reduce antibody-dependent cellular cytotoxicity (ADCC) to minimize adverse immune activation. This is a report of initial results from an ongoing first-in-human, randomized, double-blind, placebo-controlled Phase 1a trial (NCT 06782477) that is evaluating the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of single ascending doses in healthy adult participants.

Materials and Methods

Eligible participants were healthy males and non-pregnant females aged 18–60 years, screened by medical history, physical exam, and laboratory testing. All participants were enrolled at a single clinical site under IRB approval and informed consent. A total of 32 subjects were randomized (3:1) to receive a single SC dose of STAR-0310 or placebo across four dose cohorts: 150, 300, 600, and 1200 mg. Blood samples were collected at predefined time points for STAR-0310 PK and exploratory PD biomarkers.

Results

Initial results show STAR-0310 was well-tolerated at all the dose levels, with no serious treatment-emergent adverse events (TEAEs) or discontinuations. Mild, treatment-related TEAEs were observed in 7/24 (29.2%) participants receiving STAR-0310, with injection site reactions being the most frequently reported (4/24, 16.6%). No fevers or chills were observed, supporting the preclinical observation that STAR-0310 exhibits low ADCC activity. STAR-0310 exhibited dose-proportional increases in serum concentrations, with slow clearance and an extended half-life of up to approximately 68 days (range 60-78 at the 600 mg dose). Receptor occupancy (RO) data showed rapid and sustained peripheral target engagement, with >90% mean RO achieved immediately and maintained through the follow up time points for 300-1200 mg dose levels. Exploratory biomarker data indicated deep (~50-90%) and durable *ex vivo* cytokine inhibition (IL-2, IL-31, IL-4) supporting target modulation and suggesting that STAR-0310 may modulate a broader spectrum of immune

pathways beyond classical Th2-driven responses.

Conclusion

STAR-0310 is a potential best-in-class, T-cell sparing, immunomodulating OX40 antagonist designed to have a long half-life. Based on the initial results from this trial, STAR-0310 was well-tolerated, with no ADCC-related TEAEs. Preliminary PK and PD exhibited sustained target therapeutic effect for at least 3 months following a single dose, demonstrating early proof of concept for a long-acting differentiated OX40 receptor antagonist. These findings support the potential for infrequent maintenance dosing, including the possibility of dosing intervals as long as every 6 months, which may enhance adherence and reduce the treatment burden for patients with chronic inflammatory diseases, including atopic dermatitis and other immune-mediated diseases.