Switching from Dupilumab to Upadacitinib in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis and Inadequate Response to Dupilumab: Efficacy and Safety Results from the Phase 3b/4 LEVEL UP Study

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OBJECTIVE

To assess the efficacy and safety of switching patients with moderate-to-severe atopic dermatitis (AD) with an inadequate response to dupilumab (DUPI) to upadacitinib (UPA).

CONCLUSIONS

Treatment of moderate-to-severe AD with upadacitinib (UPA) in patients who received dupilumab (DUPI) for 16 weeks without an adequate response demonstrated improved efficacy in skin (EASI 75, EASI 90 & EASI 100) and itch (WP-NRS 0/1 & ΔWP-NRS≥4) endpoints, as well as simultaneous achievement of both EASI 90 and WP-NRS 0/1 after switching to UPA.

No new safety signals were observed after switching from DUPI to UPA without a washout period. Safety findings for UPA were consistent with the known safety profile, with no new safety signals identified.

These findings indicate that UPA may address an unmet medical need in patients with moderate-to-severe AD who do not achieve an adequate response while taking DUPI.

AbbVie and the authors thank the participants, study sites, and investigators who participated in this clinical trial. AbbVie funded this trial and participated in the trial design, research, analysis, data collection, interpretation of data, and the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Elin M Grissom, PhD of AbbVie.

Financial arrangements of the authors with companies whose products may be related to the present report are listed as declared by the authors: **CG Bunick** has served as an investigator for has served as an investigator for AbbVie, Almirall, Apogee, Daiichi Sankyo, LEO Pharma, Ortho Dermatologics, Sun Pharma, Timber, and Palvella; a consultant for AbbVie, Almirall, Apogee, Arcutis, Connect BioPharma, Eli Lilly, EPI Health/Novan, Incyte, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Sanofi-Regeneron, Takeda, and UCB; and a speaker for and received honoraria from Allergan, Almirall, LEO Pharma, and UCB. **N Magnolo** has received honoraria for participation on advisory boards, as a speaker and/or for consultancy from AbbVie, Almirall, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi, and UCB Pharma. **A Moore** has received honoraria or research funds from Abbvie, Actavis, Acrotech, Arcutis, Bayer, Cara, Eli Lilly, Galderma, Incyte, Pfizer, Rapt, and Sanofi-Regeneron. **G Xinghua** has served as speaker for Eli Lilly, GSK, Janssen, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals Inc., Sanofi and; consultancy/advisory board member for AbbVie, Boehringer Ingelheim, Novartis, Pfizer, Sanofi – investigator; AbbVie, AstraZeneca, BMS, Eli Lilly, Huarun, JiaLan, LEO Pharma, Pfizer, Puqi and Sanofi. **C Lynde** has acted as a principal investigator, speaker and/or consultant for AbbVie, Amgen Anaptysbio, Avillion, Arcutis, Bristol-Myers Squibb, Celgene Cipher Genentech, GlenMark, Incyte, Janssen, Leo Pharma, Kyowa, Pfizer, and Merck. **N Ibrahim, A Grada, G Levy, B Calimlim, X Wu, Y Armendariz** are full-time employees of AbbVie Inc and may hold AbbVie stock and/or stock options. **K Eyerich** has received grants and personal fees from AbbVie; has received personal fees from Almirall, Bristol Myers Squibb, LEO Pharma, Lilly, Janssen, Novartis, UCB, and Sanofi; and has received grants from Lilly, LEO Pharma, Janssen, Novartis, and UCB.

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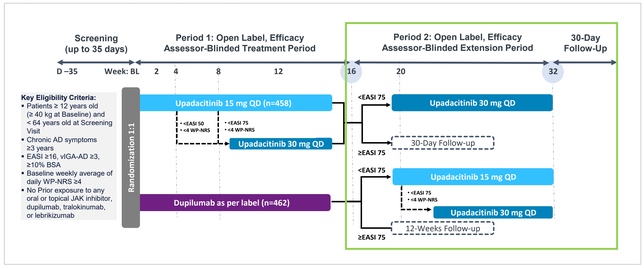
INTRODUCTION

- Level Up is a phase 3b/4 global, randomized, open-label, efficacy assessor blinded, head-to-head, multi-center study evaluating UPA vs DUPI in adolescents and adults with moderate-to-severe AD who had inadequate response to systemic therapy or when use of those therapies was inadvisable.
- Here we report results from Period 2 of the LEVEL UP study for patients switching from DUPI to UPA (DUPI/UPA).

METHODS

- Patients were randomized to UPA 15 mg or DUPI per its label for 16 weeks of treatment (Period 1), with a 16-week extension period to 32 weeks (Period 2) for patients not achieving at least 75% reduction in Eczema Area and Severity Index from baseline (EASI 75) at Week 16.
- Starting 4 weeks following dose escalation to upadacitinib 30 mg QD in Period 2, patients who do not achieve EASI 75 or a ≥4-point improvement in Worst Pruritus Numerical Rating Scale (WP-NRS) from Baseline (ΔWP-NRS≥4) have the option to add topical therapy (except for topical JAK inhibitors).
- Efficacy analysis for Period 2 was based on observed case (OC) analysis while patients were on treatment. Only summary statistics have been provided for Period 2 data; no statistical tests were performed to compare the results between treatment groups. Patients who initiated topical rescue treatments during Period 2 were imputed as non-responders for the remainder of the period.

Figure 1. Level Up Study Design



BL, baseline; AD, atopic dermatitis; EASI, Eczema Area and Severity Index; vIGA-AD, Validated Investigators Global Scale for Atopic Dermatitis; BSA, body surface area; WP-NRS, Worst Pruritus Numerical Rating Scale.

RESULTS

- A total of 355 patients entered Period 2 of the study, of which 208 received dupilumab in Period 1, and switched to upadacitinib in Period 2 (DUPI/UPA) and 147 continued with upadacitinib (UPA/UPA 30). Demographics and baseline characteristics were generally balanced between treatment groups (Table 1).
- In the DUPI/UPA group, 47.6% (99/208) of patients escalated to UPA 30 in Period 2; 52.4% (109/208) were never dose escalated.

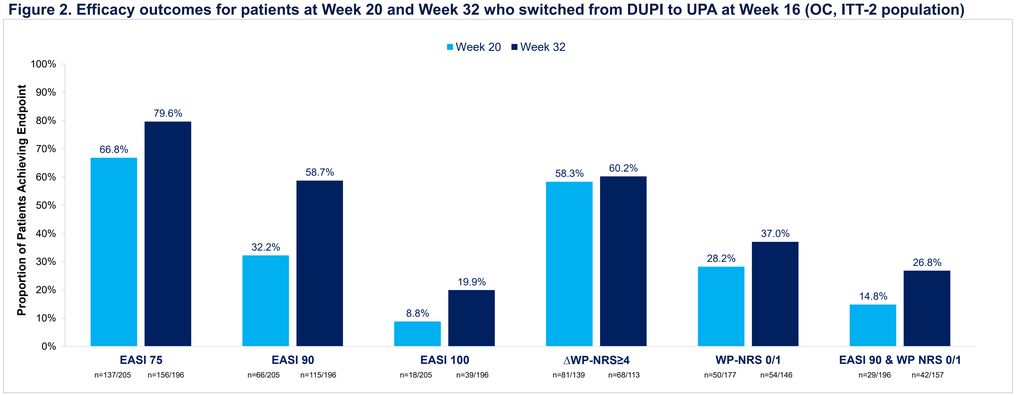
Table 1. Demographics and baseline characteristics

Demographics and characteristics	DUPI/UPA (N=208)	UPA/UPA 30 mg (N=147)	Total (N=355)
Female, n (%)	84 (40.4)	60 (40.8)	144 (40.6)
Age (years), mean ±SD	29.9 ±12.3	30.8 ±11.8	30.2±12.1
Age categories (years), n (%)			
12 to <18	30 (14.4)	15 (10.2)	45 (12.7)
18 to <40	140 (67.3)	100 (68.0)	240 (67.6)
40 to <64	37 (17.8)	32 (21.8)	69 (19.4)
=64	1 (0.5)	0	1 (0.3)
BMI (kg/m^2) for adolescents, mean ±SD	22.7 ±4.6	22.6 ±2.8	22.7 ±4.0
BMI (kg/m^2) for overall, mean ±SD	25.7 ±5.7	26.0 ±6.5	25.9 ±6.0
Baseline EASI, n (%)			
< median (23.5)	103 (49.5)	74 (50.3)	177 (49.9)
≥ median (23.5)	105 (50.5)	73 (49.7)	178 (50.1)
BSA (%), mean ±SD	38.3 ±20.1	39.3 ±21.9	38.8 ±20.9
Baseline vIGA-AD, n (%)			
3 (moderate)	119 (57.2)	80 (54.4)	199 (56.1)
4 (severe)	89 (42.8)	67 (45.6)	156 (43.9)
Previous systemic therapy, n (%)			
With	158 (76.0)	131 (89.1)	289 (81.4)
Without	50 (24.0)	16 (10.9)	66 (18.6)
EASI, mean ±SD	27.6 ±10.2	29.2 ±12.5	28.3 ±11.2
WP-NRS (weekly average), mean ±SD	7.7 ±1.4	7.8 ±1.3	7.7 ±1.4
Prior AD treatment, n (%)			
With	206 (99.0)	147 (100)	353 (99.4)
Without[a]	2 (1.0)	0	2 (0.6)

[a]Patients listed without prior AD treatment were due to missing data. AD, atopic dermatitis; BMI, body mass index; DUPI, dupilumab; EASI, Eczema Area and Severity Index; SD, standard deviation; UPA, upadacitinib; vIGA-AD, Validated Investigator Global Assessment scale for Atopic Dermatitis; WP-NRS, Worst Pruritus Numeric Rating Scale.

- Of those patients who switched from DUPI to UPA, 79.6%, 58.7%, and 19.9% of them achieved a EASI 75, 90, and 100, respectively. Response was seen as early as 4 weeks post-switch (Week 20), with increased responses by 16 weeks post-switch (Week 32; Figure 2).
- DUPI/UPA patients also had improvements in measures of itch, where most achieved ΔWP-NRS≥4 by Week 20, with a greater proportion reaching this endpoint at Week 32.
- The proportion of patients achieving WP-NRS 0/1 increased by 4 weeks post-switch (Week 20), with additional increases by Week 32 (Figure 2).
- 26.8% of patients reached the stringent endpoint of simultaneous achievement of both EASI 90 and WP-NRS 0/1 by 16 weeks post-switch from DUPI to UPA (Week 20, Week 32; Figure 2) with response rates seen as early as 4 weeks post-switch.
- Week 20 results include patients on UPA 15 mg as dose escalations did not occur until Week 20 or later if protocol criteria were met; Week 32 results include patients on UPA 15 mg and those who dose escalated to UPA 30 mg.
- Efficacy measures for patients in the UPA/UPA 30 group indicated that a proportion of patients achieved clinically meaningful improvements in both skin and itch outcomes after continuing treatment (data not shown; will be included in future publications).

Figure 2. Efficacy outcomes for patients at Week 20 and Week 32 who switched from DUPI to UPA at Week 16 (OC, ITT-2 population)



EASI, Eczema Area and Severity Index; WP-NRS, Worst Pruritus Numerical Rating Scale. Patients receiving topical rescue were imputed as non-responders. WP-NRS 0/1 is assessed among patients with WP-NRS>1 at baseline, WP-NRS reduction (improvement) ≥ 4 is assessed among patients with Baseline WP-NRS ≥ 4.

Table 2. Selected additional endpoints for DUPI/UPA patients in Period 2

Selected Additional Endpoints	DUPI/UPA N=208 (%) [95% CI] n
EASI 75 at Week 32, among patients who did not achieve EASI 75 at Week 16	(**79.6**) [73.9, 85.2] 156/196
EASI 90 at Week 32, among patients who did not achieve EASI 75 at Week 16	(**58.7**) [51.8, 65.6] 115/196
EASI 100 at Week 32, among patients who did not achieve EASI 75 at Week 16	(**19.9**) [14.3, 25.5] 39/196
WP-NRS improvement ≥ 4 at Week 32, among patients with Baseline WP-NRS ≥ 4 and did not achieve WP-NRS reduction ≥ 4 at Week 16 (ΔWP-NRS≥4)	(**60.2**) [51.2, 69.2] 68 /113
WP-NRS 0/1 at Week 32, among patients with Baseline WP-NRS > 1 and did not achieve WP-NRS 0/1 at Week 16	(**37.0**) [29.2, 44.8] 54 /146
EASI 90 and WP-NRS 0/1 at Week 32, among patients who did not simultaneously achieve EASI 90 and WP-NRS 0/1 at Week 16	(**26.8**) [19.8, 33.7] 42/157

CI, confidence interval; DUPI, dupilumab; EASI, Eczema Area and Severity Index; UPA, upadacitinib; WP-NRS, Worst Pruritus Numeric Rating Scale.

- The proportions of patients with treatment-emergent adverse events (TEAE) were similar for both the DUPI/UPA and UPA/UPA 30 mg groups (48.1% and 48.3%, respectively; Table 3).
- The most frequently reported TEAEs included nasopharyngitis, acne, upper respiratory tract infection, and atopic dermatitis. (Table 4)
- One patient reported a serious infection (pneumonia) for UPA/UPA, and there were no serious infections for DUPI/UPA.(Table 5)
- Two patients had opportunistic infections (excluding tuberculosis and herpes zoster) for UPA/UPA 30 mg, and one patient for DUPI/UPA; all were non-serious events of eczema herpeticum which did not lead to study drug discontinuation. (Table 5)
- All events of herpes zoster and hepatic disorder were non-serious, mild to moderate in severity and did not lead to study drug discontinuation. (Table 5)
- No malignancies, adjudicated major adverse cardiac events, adjudicated venous thromboembolic events (VTEs), adjudicated gastrointestinal perforations, or active tuberculosis were reported in either treatment group. (Table 5)

Table 3. Treatment-Emergent Adverse Events (TEAEs) in Period 2

Patients with any treatment-emergent	DUPI/UPA (N=208) n (%)	UPA/UPA 30 mg (N=147) n (%)
Adverse event (AE)	100 (48.1)	71 (48.3)
Serious AEs	0	4 (2.7)
AEs leading to discontinuation of study drug	2 (1.0)	1 (0.7)
AEs with reasonable possibility of being drug-related	41 (19.7)	28 (19.0)
Severe AE (CTCAE toxicity Grade ≥3)	2 (1.0)	7 (4.8)
All deaths	0	0

AE, adverse event; SAE CTCAE, Common Terminology Criteria for Adverse Events; DUPI, dupilumab; UPA, upadacitinib.

Table 4. TEAEs Reported by ≥5% of Patients in Period 2

Preferred Term	DUPI/UPA (N=208) n (%)	UPA/UPA 30 mg (N=147) n (%)
Nasopharyngitis	18 (8.7)	12 (8.2)
Acne	14 (6.7)	5 (3.4)
Upper respiratory tract infection	12 (5.8)	7 (4.8)
Atopic dermatitis	12 (5.8)	10 (6.8)

Table 5. Treatment-Emergent Adverse Events of Special Interest (AESI) in Period 2

Patients with any treatment-emergent AESI	DUPI/UPA (N=208) n (%)	UPA/UPA 30 mg (N=147) n (%)
Serious infections	0	1 (0.7)
Opportunistic infection, excluding TB and HZ[a]	1 (0.5)	2 (1.4)
Herpes zoster	2 (1.0)	4 (2.7)
Active TB	0	0
Malignancy	0	0
Adjudicated GI perforations	0	0
Adjudicated MACE[b]	0	0
Adjudicated VTE[c]	0	0
Anemia	1 (0.5)	2 (1.4)
Neutropenia	2 (1.0)	1 (0.7)
Lymphopenia	0	0
Renal dysfunction	0	0
Hepatic disorder	2 (1.0)	2 (1.4)
Elevated CPK	1 (0.5)	5 (3.4)
Bone fracture	0	0
Retinal detachment	0	0
Serious hypersensitivity reactions	0	0

[a]All cases of opportunistic infection with UPA were eczema herpeticum. [b]Defined as cardiovascular death, nonfatal myocardial infarction, and non-fatal stroke. [c]Defined as deep vein thrombosis and pulmonary embolism (fatal and non-fatal). AE, adverse event; AESI, adverse event of special interest; CPK, creatine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events; DUPI, dupilumab; GI, gastrointestinal; HZ, herpes zoster; MACE, major adverse cardiovascular event; SAE, serious adverse event; TB, tuberculosis; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolic event.