Safety and Efficacy of Upadacitinib in Combination With Topical Corticosteroids in Adolescents and Adults With Moderate-to-Severe Atopic Dermatitis: Results From the Pivotal Phase 3, Randomized, Double-Blind, Placebo-Controlled AD Up Study

Kristian Reich, MD, PhD[1]; Henrique D. Teixeira, PhD[2]; Marjolein De Bruin-Weller, MD, PhD[3]; Thomas Bieber, MD, PhD[4]; Weily Soong, MD[5]; Kenji Kabashima, MD, PhD[6]; Thomas Werfel, MD[7]; Jiewei Zeng, PhD[2]; Xiaohong Huang, PhD[2]; Xiaofei Hu, PhD[2]; Barry Ladizinski, MPH, MBA[2]; Alvina D. Chu, MD[2]; Jonathan I. Silverberg, MD, PhD, MPH[8]

[1]Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, and *Skin*flammation Center, Hamburg, Germany; [2]AbbVie Inc., North Chicago, IL, USA; [3]Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, Netherlands; [4]Department of Dermatology and Allergy, University Hospital of Bonn, Bonn, Germany; [5]Alabama Allergy & Asthma Center, Birmingham, AL, USA; [6]Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [7]Division of Immunodermatology and Allergy Research, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany; [8]Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington DC, USA

Introduction: Topical corticosteroids (TCS) are the mainstay of atopic dermatitis (AD) management. Upadacitinib (UPA) is a novel, oral, selective Janus kinase (JAK) inhibitor with greater inhibitory potency for JAK1 than JAK2, JAK3, or tyrosine kinase 2 that is being developed for AD. The trial AD Up was designed to assess the efficacy and safety of UPA vs placebo (PBO), both in combination with TCS, in adolescents and adults with moderate-to-severe AD.

Methods: AD Up (NCT03568318) is a pivotal, phase 3, randomized, double-blind, placebo-controlled, multicenter study. Adolescents (age 12-17 years; weight ≥40 kg) and adults (age 18-75 years) with chronic AD (≥10% of body surface area affected, Eczema Area and Severity Index [EASI] ≥16, validated Investigator's Global Assessment for AD [vIGA-AD] score ≥3, and Worst Pruritus numerical rating scale (NRS) score ≥4 (based on the rolling average) were randomized 1:1:1 to receive UPA 15 mg, UPA 30 mg, or PBO once daily (QD), all in

combination with TCS. Starting at the baseline visit and up to week 52, TCS were to be applied as follows:

(1) Active lesions for ≤3 consecutive weeks: Medium-potency TCS (or low-potency TCS or topical calcineurin inhibitors [TCIs]) were to be applied to sensitive skin areas QD
(2) After lesions were "clear" or "almost clear" or after 3 consecutive weeks of medium-potency TCS: Low-potency TCS QD were to be applied for 7 days, and stopped if there were no longer active lesions
(3) If lesions returned or persisted: This step-down approach was repeated until lesion resolution or evidence of local or systemic TCS toxicity.

Coprimary endpoints were the proportions of patients achieving ≥75% reduction in EASI (EASI-75) and vIGA-AD score of "clear" (0) or "almost clear" (1) with ≥2 grades of reduction from baseline (vIGA-AD 0/1), both at week 16. Key secondary multiplicity-controlled efficacy endpoints included proportions of patients achieving EASI-90 at week 16, EASI-75 at week 2, and Worst Pruritus NRS improvement ≥4 at weeks 1 and 16. The number of TCS-free days with EASI-75 response through week 16 was also

assessed in a prespecified analysis (not multiplicity controlled). Safety assessments included adverse events (AEs).

Results: Of 597 patients randomized (300 to UPA 15 mg+TCS, 297 to UPA 30 mg+TCS, and 304 to PBO+TCS), 95.7%, 96.0%, and 92.1%, respectively, completed 16 weeks of treatment. Demographics and baseline characteristics were balanced among groups, including mean (SD) EASI (29.2 [11.8], 29.7 [11.8], and 30.3 [13.0]) and proportion of patients with severe vIGA-AD (52.3%, 52.9%, and 53.6%). The coprimary and all selected key secondary endpoints were met for both UPA doses tested. At week 16, significantly greater proportions of patients treated with UPA 15 mg+TCS or UPA 30 mg+TCS than PBO+TCS achieved the coprimary endpoints of EASI-75 (64.6% and 77.1% vs 26.4%; *P*<.001 for both doses) and vIGA-AD 0/1 (39.6% and 58.6% vs 10.9%; *P*<.001 for both doses (**Table 1**). Likewise, response rates for all selected key secondary endpoints were significantly higher for UPA 15 mg+TCS and UPA 30 mg+TCS than PBO+TCS (**Table 1**). Mean numbers of TCS-free days with EASI-75 response through week 16 were greater for UPA 15 mg+TCS (33.5) and UPA 30 mg+TCS (47.5) than PBO+TCS (7.9; nominal *P*<.001 for both). During the double-blind period reported here, UPA 15 and UPA 30 mg were well tolerated in combination with TCS, and no new safety signals compared with the known safety profile of UPA were observed, except for higher incidences of acne (**Table 2**). Among AEs of special interest, there were no active tuberculosis, lymphoma, adjudicated gastrointestinal perforations, adjudicated major adverse cardiovascular events (MACE), or adjudicated venous thromboembolic events. Incidences for the remaining AEs of special interest are listed in **Table 2**. Incidences of AEs leading to discontinuation of study drug and serious AEs were similar among treatment groups (**Table 2**). Efficacy and safety results for adolescents were consistent with the overall results.

Conclusions: In this phase 3 study, UPA in combination with TCS was well tolerated, and it was superior to PBO in combination with TCS across the coprimary endpoints and all key endpoints measuring skin and itch improvement for patients with moderate-to-severe AD, including adolescents and adults.

Table 1. Coprimary and Selected Key Secondary Endpoints

Patients, %	Timeframe	PBO+TCS N = 304	UPA 15 mg+TCS N = 300	UPA 30 mg+TCS N = 297
Coprimary Efficacy Endpoints				
Patients achieving EASI 75	Week 16	26.4	64.6*	77.1*
Patients achieving vIGA-AD 0/1	Week 16	10.9	39.6*	58.6*
Selected Key Secondary Efficacy Endpoints				
Skin Improvement				
Patients achieving EASI 75	Week 2	6.9	31.0*	44.1*
Patients achieving EASI 90	Week 16	13.2	42.8*	63.1*
Itch				
		N = 294	N = 288	N = 291
Patients achieving Worst Pruritus NRS improvement ≥ 4[a]	Week 16	15.0	51.7*	63.9*
	Week 1	3.1	12.2*	19.2*

*P < .001 vs PBO+TCS.
[a]Based on weekly average. Among patients with worst pruritus NRS ≥ 4 at baseline.
EASI 75/90, ≥ 75%/90% improvement in Eczema Area and Severity Index; NRS, Numerical Rating Scale; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib; vIGA-AD 0/1, validated Investigator's Global Assessment for Atopic Dermatitis of clear (0) or almost clear (1) with ≥ 2 grades of reduction from baseline.

Table 2. Treatment-emergent Adverse Events in the Double-blind Period

Patients, n (%)	PBO+TCS N = 303	UPA 15 mg+TCS N = 300	UPA 30 mg+TCS N = 297
Any TEAE	190 (62.7)	200 (66.7)	215 (72.4)
Serious AEs	9 (3.0)	7 (2.3)	4 (1.3)
AEs leading to discontinuation of study drug	7 (2.3)	4 (1.3)	4 (1.3)
Deaths	0	0	0
AEs Special Interest			
Serious infections	3 (1.0)	3 (1.0)	0
Eczema herpeticum	0	3 (1.0)	4 (1.3)
Herpes zoster	3 (1.0)	3 (1.0)	5 (1.7)
NMSC	0	0	1 (0.3)
Malignancy excluding NMSC	0	0	1 (0.3)
Hepatic disorder	5 (1.7)	6 (2.0)	3 (1.0)
Anemia	1 (0.3)	0	3 (1.0)
Neutropenia	0	2 (0.7)	3 (1.0)
Lymphopenia	1 (0.3)	0	0
CPK elevation[a]	7 (2.3)	13 (4.3)	18 (6.1)
Renal dysfunction	0	1 (0.3)	0
Most Frequently Reported TEAEs (≥ 5% in any treatment group)			
Acne[b]	6 (2.0)	30 (10.0)	41 (13.8)
Nasopharyngitis	34 (11.2)	37 (12.3)	40 (13.5)
Upper respiratory tract infection	22 (7.3)	21 (7.0)	23 (7.7)
Oral herpes	5 (1.7)	10 (3.3)	23 (7.7)
Blood CPK increased	7 (2.3)	13 (4.3)	18 (6.1)
Headache	15 (5.5)	15 (5.0)	14 (4.7)
Dermatitis atopic	20 (6.6)	11 (3.7)	2 (0.7)

[a]Included laboratory CPK value ≥ 4× ULN with or without symptoms suggestive of myositis or rhabdomyolysis and CPK increases considered by the investigator to be an AE.
[b]Most (approximately 80%) acne events were grade 1, others were grade 2. Most events consisted primarily of inflammatory papules, pustules and comedones, and most events involved the face. All events were nonserious. None led to treatment discontinuation.
AE, adverse event; CPK, creatine phosphokinase; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PBO, placebo; TEAE, treatment emergent adverse event; UPA, upadacitinib.