Supplementary Online Content

Blauvelt A, Teixeira HD, Simpson EL, et al. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol.* Published online August 4, 2021. doi:10.1001/jamadermatol.2021.3023

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods.

COVID-19-Related Methods

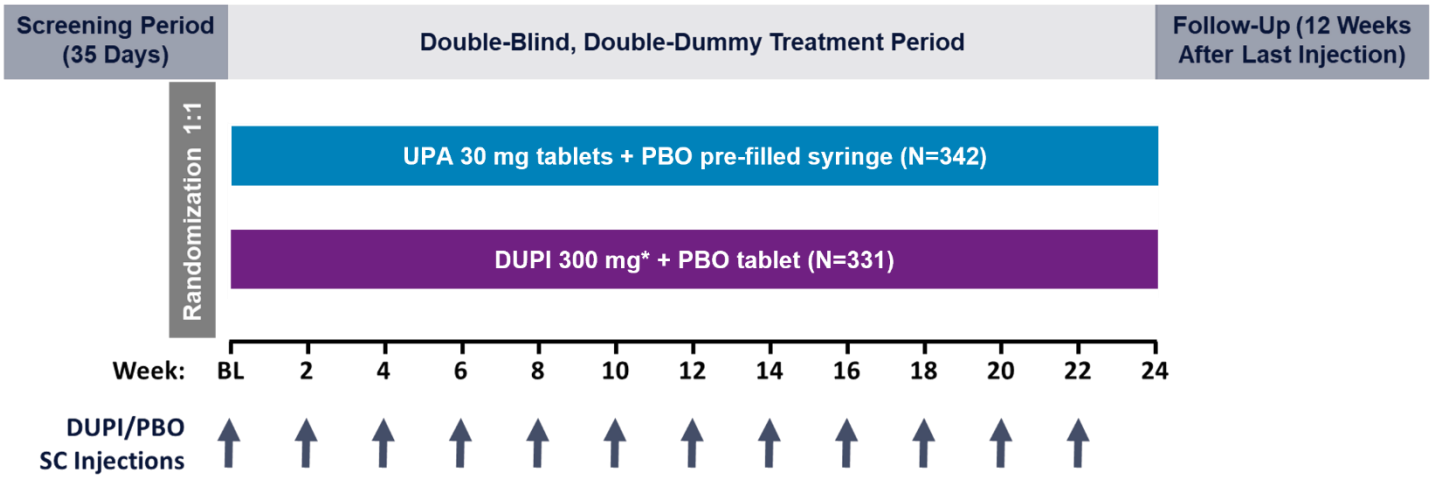
With the advent of the coronavirus disease 2019 (COVID-19) pandemic, operational accommodations for clinical trial continuity were incorporated for temporary site disruptions and secure-in-place measures, including remote visits, local laboratory collections, and courier delivery of study drug to the patient, where allowed and in accord with local regulations. Remote efficacy assessments of the skin were not allowed, and in-person visits were required at baseline and week 24.

NRI-C categorized any patient who did not have an evaluation during a pre-specified visit window as a non-responder for the visit. The only exceptions were (1) when the patient was a responder both before and after the visit window, the patient was categorized as a responder for the visit, and (2) missing data due to COVID-19 infection or logistical restriction was handled by MI. Patients were counted as non-responders after the start of rescue therapy and were not imputed by MI. Results for continuous endpoints are based on the Mixed-Effect Model Repeat Measurement (MMRM).

The primary approach for evaluating categorical endpoints was NRI-C (Non-Responder Imputation incorporating Multiple Imputation [MI] to handle missing data due to COVID-19). For the NRI-C approach, the “before-and-after window imputation” rule is defined as: if a patient does not have an evaluation within a specific visit window and when the patient is a responder both before and after this specific visit window (using the adjacent records), the patient is categorized as a responder for the visit.

‘Visit window’ was defined based on the date from the first dose (or from the randomization date for those who were never dosed). The detailed visit window for each variable was pre-defined in the study’s Statistical Programming Plan document. As an example, for EASI 75 at Week 16, the visit window for Week 16 EASI is day 100 to 127. If a patient had an observation between day 100 and 127, this observation was used for Week 16 EASI, without any imputation needed. If a patient did not have any observation between day 100 and 127, then this patient’s Week 16 EASI was considered missing and needed to be imputed. It was imputed as ‘EASI 75 non-responder’ unless if it satisfied the ‘before-and-after’ rule, in which all three of the following conditions were met: 1) There was at least one observation in the visit window before Week 16, i.e., Week 12 in the case of EASI (according to the visit window, this means having an observation between day 72 and 99); 2) There was at least one observation in the visit window after Week 16, i.e., Week 20 in the case of EASI (according to the visit window, this means having an observation between day 128 and 155); 3) The latest observation in 1) and the earliest observation in 2) were both ‘EASI 75 responders’. Then Week 16 EASI 75 for this patient was imputed as ‘responder’ following the ‘before-and-after’ rule.

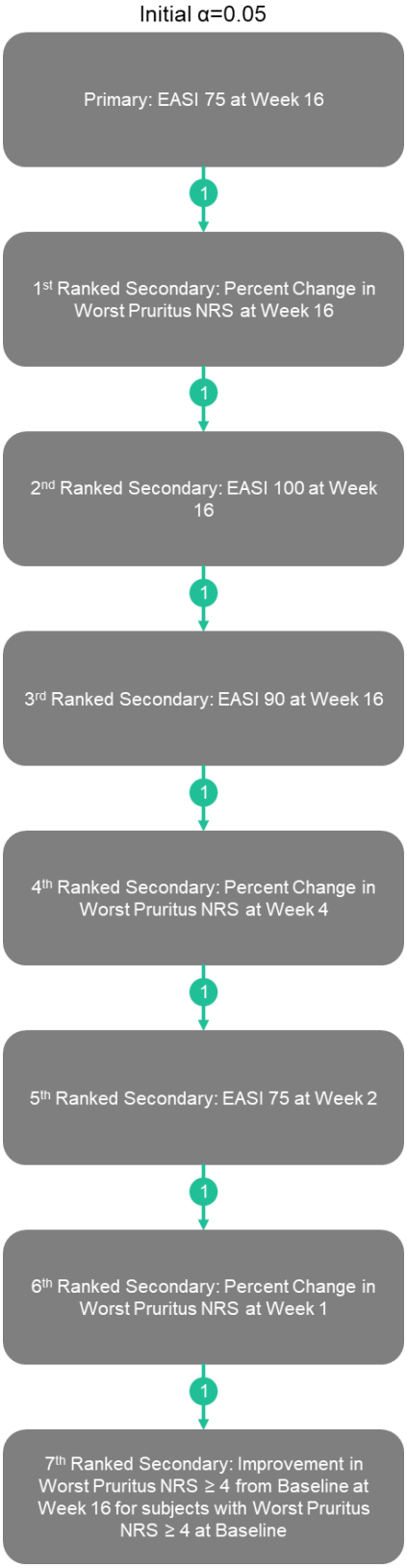
eFigure 1. Study Design



*Dupilumab 300 mg SC injection administered every other week starting at the Week 2 visit and until the Week 22 visit, after an initial dose of 600 mg at the Baseline visit
UPA, upadacitinib; PBO, placebo; DUPI, dupilumab; BL, baseline; SC, subcutaneous

eFigure 1. Study Design
Study design for Heads Up. Arrows indicate timing of dupilumab or placebo subcutaneous injection. UPA, upadacitinib; PBO, placebo; DUPI, dupilumab; BL, baseline; SC, subcutaneous. *Dupilumab 300 mg subcutaneous injection administered every other week starting at the week 2 visit and until the week 22 visit, after an initial dose of 600 mg at the baseline visit.

eFigure 2. Graphical Approach for Multiplicity Adjustment



eFigure 2. Graphical Approach for Multiplicity Adjustment**.** Arrows specify a transfer path. Once an endpoint is rejected (ie deemed significant) at its assigned significance level, its significance level will be transferred to subsequent endpoint(s) following the arrow. The numbers on the arrows denote the weights for transferring and (possibly) splitting significance levels; specifically, a weight of 1 denotes 100% transfer of significance level. EASI, eczema area and severity index; NRS, numerical rating scale

eTable 1. Eligibility Criteria

Eligibility criteria	
Consent and Demographics	
1	Patients must be ≥ 18 years old and ≤ 75 years old at Screening Visit.
2	Patients and/or their legally authorized representative must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures and comply with the requirements of this study protocol.
3	Patient is judged to be in general good health (other than AD) as determined by the Principal Investigator, based upon the results of medical history, laboratory profile, physical examination, chest x-ray, and a 12-lead electrocardiogram performed during Screening.
AD Disease Activity	
4	Chronic AD with onset of symptoms at least 3 years prior to baseline and patient meets Hanifin and Rajka criteria[9]
5	Patient meets all of the following disease activity criteria: • EASI ≥ 16 at the Screening and Baseline Visits; • vIGA-AD ≥ 3 (moderate) at the Screening and Baseline Visits; • ≥ 10% body surface area of AD involvement at the Screening and Baseline Visits; • Baseline weekly average of daily worst pruritus NRS ≥ 4. Note: The baseline weekly average of daily worst pruritus NRS will be calculated from the 7 consecutive days immediately preceding the Baseline Visit. A minimum of 4 daily scores out of the 7 days is needed.
6	Patient has applied a topical emollient (moisturizer) twice daily for ≥ 7 days before the Baseline Visit. Note: Patient may use prescription moisturizers or moisturizers containing ceramide, urea, filaggrin degradation products, or hyaluronic acid if such moisturizers were initiated before the Screening Visit.
7	Documented history (within 6 months of the Baseline Visit) of inadequate response to TCS or TCI OR documented systemic treatment for AD within 6 months prior to the Baseline Visit, OR for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).
Contraception	
8	Females of childbearing potential must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Baseline Visit prior to study drug dosing. Note: Patients with borderline pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to determine eligibility.
9	If female, patient must be postmenopausal OR permanently surgically sterile OR, for females of childbearing potential, practicing at ≥ 1 protocol-specified method of birth control, that is effective from the Baseline Visit through at least 12 weeks after the last injection.
10	Female patients must not be pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 12 weeks after the injection.
11	Additional local requirements as required.
Prior/Concomitant Therapy	
12	No prior exposure to any JAK inhibitor (including but not limited to ruxolitinib, tofacitinib, baricitinib, upadacitinib, abrocitinib [PF-04965842], and filgotinib).
13	No prior exposure to dupilumab.
14	Patients must not have used the following AD treatments within the specified timeframe prior to Baseline Visit: • Systemic therapy for AD, including but not limited to corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE-4) inhibitors, interferon-γ, and mycophenolate mofetil within 4 weeks; • Targeted biologic treatments (within 5 half-lives [if known]) or within 12 weeks, whichever is longer;

	• Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks; • Oral or parenteral traditional Chinese medicine within 4 weeks; • Marijuana use within 2 weeks; • Topical treatments (with the exception of topical emollient treatments, described in Eligibility Criterion 8), including but not limited to TCS, TCIs, or topical PDE-4 inhibitors within 7 days.
15	Patients must not have received any live vaccine within 4 weeks (or longer if required locally) prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4 weeks (or longer if required locally) after the last dose of study drug.
16	No systemic use of known strong CYP3A inhibitors or strong CYP3A inducers from Screening through the end of the study.
17	No treatment with any investigational drug of chemical or biologic nature within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to Baseline Visit or is currently enrolled in another clinical study.
Medical History	
18	Patients must not have laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug: • Serum aspartate transaminase > 2 × upper limit of normal (ULN); • Serum alanine transaminase > 2 × ULN; • Estimated glomerular filtration rate of < 40 mL/min/1.73 m^2 by simplified 4-variable Modification of Diet in Renal Disease formula for adult patients or by Schwartz equation for adolescent patients; • Total white blood cell count < 2,500/μL; • Absolute neutrophil count < 1,500/μL; • Platelet count < 100,000/μL; • Absolute lymphocyte count < 800/μL; • Hemoglobin < 10 g/dL.
19	No current or past history of the following: • Other active skin diseases or skin infections (bacterial, fungal, or viral) requiring systemic treatment within 4 weeks of the Baseline Visit or that would interfere with the appropriate assessment of AD lesions; • History of recurrent herpes zoster, or ≥ 1 episode of disseminated herpes zoster; • History of ≥ 1 episode of disseminated herpes simplex (including eczema herpeticum); • History of known invasive infection (e.g., listeriosis and histoplasmosis); • Active HIV or immunodeficiency syndrome. Active HIV is defined as confirmed positive anti-HIV antibody test; • Patient has active TB or meets TB exclusionary parameters (Bacillus Calmette–Guérin vaccination, cohabitation with individuals who have had TB, and travel to, residence in, or work in TB endemic locations); • Non-skin related active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the Baseline Visit; Chronic recurring infection and/or active viral infection that, based on the investigator's clinical assessment, makes the patient an unsuitable candidate for the study; • Active hepatitis B virus (HBV) or hepatitis C virus (HCV); ○ HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV DNA polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive (+) patients (and for hepatitis B surface antibody positive [+] where mandated per local requirements); ○ HCV: HCV ribonucleic acid (RNA) detectable in any patient with anti-HCV antibody (HCV Ab).

20	Patient must not have any of the following medical conditions:
	• Any of the following cardiovascular conditions:
	  ○ Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
	  ○ Uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg;
	  ○ Any other unstable clinical condition which, in the opinion of the investigator, would put the patient at risk by participating in the protocol.
	• Patient has been a previous recipient of an organ transplant which requires continued immunosuppression;
	• History of gastrointestinal perforation (other than due to appendicitis or mechanical injury), diverticulitis, or significantly increased risk for GI perforation per investigator judgment;
	• Conditions that could interfere with drug absorption including but not limited to short bowel syndrome;
	• History of any malignancy except for successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix;
	• History of clinically significant medical conditions or any other reason, which in the opinion of the investigator, would interfere with the patient's participation in this study or would make the patient an unsuitable candidate to receive study drug or would put the patient at risk by participating in the study.

Miscellaneous	
21	No history of an allergic reaction or significant sensitivity to constituents of the study drugs (or its excipients) and/or other products in the same class.
22	No history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months preceding the Baseline Visit.

eTable 1. Eligibility Criteria
Protocol-defined inclusion and exclusion criteria for Heads Up.

eTable 2. Number of Patients Becoming Responders After Implementation of the “Before-and-After” Imputation Rule

Endpoint	DUPI 300 MG	UPA 30 MG
EASI 75 at Week 16	1	3
Improvement of WP-NRS ≥4 at Week 16	0	0
EASI 75 at Week 24	0	0
Improvement of WP-NRS ≥4 at Week 24	0	0

eTable 3. Distance From Adjacent EASI Scores to the Week 16 Analysis Window for EASI 75

Treatment	Study Day* of the Adjacent Week 12 EASI Score	Days from the Adjacent Week 12 EASI Score to Lower Bound of Week 16 Analysis Window = Day 100	Study Day* of the Adjacent Week 20 EASI Score	Days from the Adjacent Week 20 EASI Score to Upper Bound of Week 16 Analysis Window = Day 127
UPA 30 MG	84	16	147	20
UPA 30 MG	84	16	141	14
UPA 30 MG	95	5	144	17
DUPI 300 MG	85	15	140	13

*: Study day is defined as days to the date of first dose of study drug, or to the randomization date if no study drug is taken.

The results of this study were impacted minimally after the implementation of the "before-and-after" imputation rule. For the ranked endpoints such as EASI 75 and Improvement of Worst Pruritus NRS (WP-NRS) ≥4 at Week 16, 4 patients (3 in UPA 30 mg group and 1 in DUPI 300 mg group) with missing data at Week 16 became responders using the "before- and after-window imputation" rule for EASI 75, no patients with missing data at week 16 became responders using the rule for Improvement of WP-NRS ≥4 (**eTable 5**). For patients patients who were imputed as responders for EASI 75 at Week 16, the distance from their adjacent EASI scores to the Week 16 analysis window are given in **eTable 6**. For EASI 75 and Improvement of WP-NRS ≥4 at Week 24, no patients with missing data became responders using the "Before- and after-window imputation" rule.

*Study Day day is defined as days to the date of first dose of study drug, or to the randomization date is if no study drug is taken.

eTable 4. Proportion of Patients Receiving 1 or More Rescue Therapy

Category, n (%)	DUPI 300 mg (N = 331)	UPA 30 mg (N = 342)
Before Week 16		
Any Rescue Therapy	70 (21.1)	61 (17.8)
Topical Corticosteroid Therapy	63 (19.0)	57 (16.7)
Topical Calcineurin Inhibitor Therapy	17 (5.1)	9 (2.6)
Other Topical Therapy	0	0
Systemic Biologic Therapy	0	0
Systemic Non-Biologic Immunomodulating Therapy	1 (0.3)	2 (0.6)
Other Systemic Therapy	0	0
Phototherapy	1 (0.3)	0
Overall Through Week 24		
Any Rescue Therapy	85 (25.7)	87 (25.4)
Topical Corticosteroid Therapy	75 (22.7)	79 (23.1)
Topical Calcineurin Inhibitor Therapy	22 (6.6)	14 (4.1)
Other Topical Therapy	0	0
Systemic Biologic Therapy	2 (0.6)	5 (1.5)
Systemic Non-Biologic Immunomodulating Therapy	1 (0.3)	8 (2.3)
Other Systemic Therapy	0	0
Phototherapy	1 (0.3)	0

DUPI, dupilumab; UPA, upadacitinib;
Patients are counted once in each row, regardless of the number of rescue medications they may have taken

eTable 4. Proportion of Patients Initiating Rescue Therapy
Proportion of patients initiating rescue therapy before and after week 16. Patients are counted once in each row, regardless of the number of rescue medications they may have taken. DUPI, dupilumab; UPA, upadacitinib.

eTable 5. Efficacy at Week 24 (Unranked)

Endpoint	DUPI 300 mg (N = 331)	UPA 30 mg (N = 342)	Difference (*P* value)
Proportion of patients achieving EASI75 (%) [95% CI]	61.2 [56.0, 66.5]	65.3 [60.2, 70.3]	4.0 (0.285)
Proportion of patients achieving EASI90 (%) [95% CI]	49.5 [44.1, 54.9]	56.6 [51.3, 61.8]	7.0 (0.068)
Proportion of patients achieving EASI100 (%) [95% CI]	13.6 [9.9, 17.3]	27.8 [23.0, 32.5]	14.1 (<0.001***)
Proportion of patients with Worst Pruritus NRS improvement ≥4[a] [95% CI]	41.4 [36.0, 46.8]	50.8 [45.4, 56.1]	9.4 (0.016*)

DUPI, dupilumab; UPA, upadacitinib; EASI, Eczema Area and Severity Index; NRS, numerical rating scale
[a]Analyzed for patients with Worst Pruritus NRS ≥4 at baseline, n=336 [DUPI] and n = 340 [UPA]
*: *P* < 0.05, ***: *P* < 0.001, UPA vs DUPI without multiplicity-control.

eTable 5. Week 24 Efficacy Results
DUPI, dupilumab; UPA, upadacitinib; EASI, Eczema Area and Severity Index; NRS, Numerical Rating Scale
[a]Analyzed for patients with Worst Pruritus NRS ≥4 at baseline, n=336 [DUPI] and n = 340 [UPA]
*: *P* < 0.05, ***: *P* < 0.001, UPA vs DUPI without multiplicity-control.

eTable 6. Treatment-Emergent Adverse Events Through End of Monitoring Period*

TEAEs through end of monitoring period*, n (%)	DUPI 300 mg (N = 331)	UPA 30 mg (N = 342)
Adverse event (AE)	229 (69.2)	271 (79.2)
AE with reasonable possibility of being drug-related[a]	129 (39.0)	170 (49.7)
Severe AE	15 (4.5)	31 (9.1)
Serious AE (SAE)	7 (2.1)	14 (4.1)
SAE with reasonable possibility of being drug-related[a]	4 (1.2)	5 (1.5)
AE leading to discontinuation of study drug	4 (1.2)	11 (3.2)
AE leading to death[b]	0	1 (0.3)
Adverse Events of Special Interest		
Serious infections	2 (0.6)	4 (1.2)
Opportunistic infection, excluding tuberculosis (TB) and herpes zoster[c]	0	3 (0.9)
Herpes zoster	4 (1.2)	12 (3.5)
Active TB	0	0
Non-melanoma skin cancer (NMSC)[d]	1 (0.3)	0
Malignancy, excluding NMSC[e]	0	1 (0.3)
Lymphoma	0	0
Hepatic disorder[f]	5 (1.5)	12 (3.5)
Adjudicated gastrointestinal perforations	0	0
Anemia[g]	1 (0.3)	8 (2.3)
Neutropenia[g]	2 (0.6)	6 (1.8)
Lymphopenia[g]	0	2 (0.6)
Creatine phosphokinase (CPK) elevation	11 (3.3)	26 (7.6)
Renal dysfunction	1 (0.3)	1 (0.3)
Adjudicated major adverse cardiovascular events (MACE)	0	0
Adjudicated venous thromboembolic events (VTE)	0	0
TEAEs Reported by ≥5% in Either Treatment Group		

Acne[h]	11 (3.3)	64 (18.7)
Dermatitis atopic	32 (9.7)	37 (10.8)
Upper respiratory tract infection	17 (5.1)	26 (7.6)
Blood CPK increased	11 (3.3)	26 (7.6)
Nasopharyngitis	27 (8.2)	23 (6.7)
Folliculitis	4 (1.2)	22 (6.4)
Urinary tract infection	15 (4.5)	19 (5.6)
Headache	23 (6.9)	17 (5.0)
Conjunctivitis	35 (10.6)	5 (1.5)

*Through 30 days following the last dose of upadacitinib or 84 days following the last dose of dupilumab, regardless of any study drug interruption

[a]As assessed by investigator;

[b]40 y/o woman found deceased at home on study Day 70 who had bronchopneumonia associated with influenza A;

[c]All opportunistic infections were eczema herpeticum[d]Keratoacanthoma, no reasonable possibility of relationship to study drug as assessed by investigator;

[e]Invasive ductal breast carcinoma, reasonable possibility of relationship to study drug as assessed by investigator;

[f]Hepatic disorders: most were elevated transaminases; ALT and/or AST elevations were generally transient and CTCAE Grade 1 (>ULN – 3.0 ULN) or Grade 2 (>3.0 – 5.0 x ULN) in both treatment groups, Grade 3 (>5.0 – 20.0 x ULN) or Grade 4 (>20.0 x ULN) elevation observed in 3 DUPI patients, no Grade ≥3 for UPA, Study drug was interrupted and then restarted in 2 DUPI patients and 1 UPA patient; transaminase abnormalities (1 Grade 2 and 1 Grade 1) led to study drug discontinuation in 2 subjects treated with UPA. AST range: 13–1290 U/L; ALT range: 11-275 U/L;

[g]Anemia was reported on day 115 in the DUPI patient and ranged from day 13 to day 143 for UPA patients, neutropenia for DUPI patients was reported on days 15 and 26 and for UPA patients ranged from day 6 to day 140. Lymphopenia was reported in UPA patients on days 1 and 23, study drug was permanently discontinued in 1 UPA patient with anemia, 1 UPA patient with neutropenia, and 1 UPA patient with lymphopenia, for both treatments, the remainder of the hemoglobin, neutrophil, and lymphocyte abnormalities were transient and most were singular abnormalities without recurrence;[h]Most acne events consisted primarily of inflammatory papules, pustules and comedones, involving the face. All events were non-serious. None led to treatment discontinuation. Preferred terms; DUPI, dupilumab; UPA, upadacitinib

eTable 6. Treatment-Emergent Adverse Events Through Monitoring Period
Treatment-emergent adverse events through monitoring period* for all patients receiving ≥1 dose of study drug.
*30 days following the last dose of upadacitinib or 84 days following the last dose of dupilumab, regardless of any study drug interruption.