Saudi Public Assessment Report

Rinvoq®

(Clinical Summary Report for a New Indication)

Active Pharmaceutical Ingredient(s): Upadacitinib

ATC code/CAS no.: L04AA44

Pharmaceutical/Dosage Form: Extended release tablet

Dosage Strength: 15mg

Marketing Authorization Holder: AbbVie Inc. USA

Shelf life: 36 months

Storage conditions: Store below 25˚C, Store in the original blister or bottle in order to protect from moisture. Keep the bottle tightly closed.

Registration No.: 0403200025

Decision and Decision Date: Approved on 17.02.2020

Table of Contents

1. Terms, Definitions, Abbreviations

Terms	Definition
AD	Atopic Dermatitis
ADerm-IS	Atopic Dermatitis Impact Scale
ADerm-SS	Atopic Dermatitis Symptoms Scale
ADRs	Adverse drug reactions
AE	Adverse Event
AEs	Adverse events
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BE	Blinded Extension
BMI	Body mass index
CI	Confidence Intervals
CMH	Cochran-Mantel- Haenszel
CPK	Creatine Phosphokinase
CSR	Clinical study report
CYP3A	Cytochrome P450 3A isoform subfamily
DB	Double-blind
DLQI	Dermatology Life Quality Index
EASI 50/75/90/100	50%/75%/90% improvement (reduction) in Eczema Area and Severity Index
EMA	European Medicine Agency
EU	European union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HADS-A	Hospital Anxiety and Depression Scaleanxiety
HADS-D	Hospital Anxiety and Depression Scale-depression
hsCRP	High-sensitivity C-reactive protein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INN	International Nonproprietary Names

ITT-M	Intent-to-treat population for the main study
JAK	Janus kinase
LDL	Low-density lipoprotein
MCID	Minimal clinically important difference
MI	Multiple Imputation
MMRM	Mixed-Effect Model Repeat Measurement
MTX	Methotrexate
NA	Not Available
NRI	Non-Responder Imputation
NRI-C	Non-responder imputation due to coronavirus 2019 pandemic
NRS	Numerical rating scale
OL	Open label
PBO	Placebo
PD	Pharmacodynamics
PK	Pharmacokinetics
POEM	Patient Oriented Eczema Measure
PY	Patient year
QD	Once a day
RA	Rheumatoid Arthritis
SAE	Serious Adverse Events
SAEs	Serious adverse events
SCORAD	Scoring Atopic Dermatitis
SD	Standard Deviation
SDI	Saudi Drug Information System
SFDA	Saudi Food and Drug Authority
SOC	Standard of care
SPC	Summary of Product Characteristics
STAT	Signal Transducers and Activators of Transcription
TB	Tuberculosis
TCI	Topical Calcineurin Inhibitors
TCS	Topical corticosteroids
TEAEs	Treatment-emergent adverse event

TGA	Therapeutic Goods Administration
TSS	Total symptom score
UPA	Upadacitinib
US	United states
USAN	United States Adopted Names
vIGA-AD	The Validated Investigator Global Assessment for Atopic Dermatitis

2. Background

2.1 Submission Details

Type of submission: Variation (New Indication)

Pharmacological class: Janus kinase (JAK) inhibitor

Submitted Indication: Treatment of moderate to severe atopic dermatitis (AD) in adults and adolescents 12 years and older who are candidates for systemic therapy for Rinvoq.

Submitted Dosage: 15mg

2.2 Regulatory Background

This product is considered a new chemical entity when authorized by Saudi food and drug authority (SFDA) in November 2019 for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate (MTX).

Regulatory pathway:
This product was evaluated under the regular review pathway followed by several type II variations requests, the recently submitted variation request aimed at adding a new indication.

Regulatory status in other countries:

The new indication of Rinvoq as a treatment of moderate to severe atopic dermatitis is authorized in the following countries:

Country	Product name	Dosage form/Strength	Approval Authority	Date of Approval
European union (EU)	Rinvoq	15mg and 30mg prolonged release tablet	European Medicine Agency (EMA)	23 August 2021
United states (US)	Rinvoq	15mg and 30mg prolonged release tablet	Food and Drug Administration (FDA)	14 January 2022
Australia	Rinvoq	15 mg and 30 mg modified release tablet	Therapeutic Goods Administration (TGA)	17 September 2021

2.3 Product Information

The officially approved Summary of Product Characteristics (SPC) can be accessed via Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

3.2 Clinical Aspects

3.2.1 Clinical Pharmacology

The suggested mechanism of action and drugs in the same pharmacological class:

Upadacitinib is a (JAK) inhibitor. JAKs are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STAT) within the signaling pathway, which modulate intracellular activity, including gene expression.

In a cell-free isolated enzyme assay, upadacitinib had greater inhibitory potency at JAK1 and JAK2 relative to JAK3 and TYK2. In human leukocyte cellular assays, upadacitinib inhibited cytokine-induced STAT phosphorylation mediated by JAK1 and JAK1/JAK3 more potently than JAK2/JAK2 mediated STAT phosphorylation.

The JAK1 inhibition with upadacitinib modulates the signaling of the JAK-dependent cytokines underlying the signs and symptoms of atopic dermatitis, including chronic eczematous rash and pruritus.

There are two JAK inhibitors, tofacitinib and baricitinib; both are non-selective (inhibiting JAK-1, JAK-2, JAK-3). Baricitinib is used to treat rheumatoid arthritis and atopic dermatitis. Tofacitinib is approved for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. Both are approved by SFDA and are currently available in the Saudi market.

3.2.1.1 Pharmacodynamic studies

No new pharmacodynamics (PD) studies were submitted in this application.

3.2.2 Clinical Efficacy

3.2.2.1 List of submitted clinical efficacy studies

Study ID*	No. of study centres / locations	Design	Study Objective	Subjs by arm entered/ compl.	Duration	Diagnosis
M16-048	36 sites	Phase 2b, multicenter, 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a DB treatment period of 72 weeks	To assess the safety and efficacy of multiple doses of Upadacitinib (UPA) monotherapy versus Placebo (PBO) in the treatment of adult with moderate to severe AD	Planned: 160 Subjects per arm: 7.5 mg: 42 subjects 15 mg :42 subjects 30 mg: 42 subjects Placebo: 41 subjects Analyzed: 167	Period 1: 16 weeks Period 2: 72 weeks	Adult subjects ≥ 18 yrs. old and ≤ 75 yrs. old with diagnosis of chronic AD who had an inadequate response to treatment with TCS, Topical Calcineurin Inhibitors (TCI), or for whom topical treatments were medically inadvisable
M16-045	151 sites	Phase III, multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term Blinded Extension (BE) period up to Week 136	To assess the efficacy and safety of UPA for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy	Planned: 810 Subjects per arm: 15 mg: 281 subjects 30 mg: 285 subjects Placebo: 281 subjects Analyzed: 847	DB Period: 16 weeks BE Period: Up to Week 136	Subjects ≥ 12 yrs. old and ≤ 75 yrs. old with a diagnosis of chronic AD who had an inadequate response to treatment with TCS, TCI, or for whom topical treatments were medically inadvisable
M18-891	154 sites	Phase III, multicenter period: 16-week	To assess the efficacy and safety of UPA for	Planned: 810 Subjects per arm:	DB Period: 16 weeks BE Period:	Subjects ≥ 12 yrs. old and ≤ 75 yrs.

		randomized, DB, parallel-group, controlled treatment period followed by a long-term BE period up to Week 136	the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy	15 mg: 276 subjects 30 mg: 282 subjects Placebo: 278 subjects Analyzed: 836	Up to Week 136	old with a diagnosis of chronic AD who had an inadequate response to treatment with TCS, TCI, or for whom topical treatments were medically inadvisable
M16-047	171 sites	Phase III, multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period followed by a long-term BE period up to Week 136	To assess the efficacy and safety of UPA combined with TCS for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy	Planned: 810 Subjects per arm: 15 mg+TCS : 300 subjects 30 mg+ TCS: 297 subjects Placebo+ TCS: 304subjects Analyzed: 901	DB Period: 16 weeks BE Period: Up to Week 136	Subjects ≥ 12 yrs. old and ≤ 75 yrs. old with a diagnosis of chronic AD who had an inadequate response to treatment with TCS or TCI
M17-377	42 study sites located in Japan	Phase III, multicenter 2-period: 16-week randomized, DB, parallel-group, controlled treatment period, followed by a long-term BE (up to Week 52), followed by an OL extension up to Week 136)	To assess the safety of UPA combined with TCS in adolescent and adult subjects in Japan with moderate to severe AD who are candidates for systemic therapy	Planned: 264 subjects Subjects per arm: 15 mg+TCS: 91 subjects 30 mg+ TCS: 91 subjects Placebo+ TCS: 90 subjects Analyzed: 272 subjects	DB Period: 16 weeks BE Period: Up to Week 52 Open label (OL)Period : Up to Week 136	Subjects ≥ 12 yrs. old and ≤ 75 yrs. old with a diagnosis of chronic AD who had an inadequate response to treatment with TCS or TCI

3.2.2.2 Data integrity and GCP

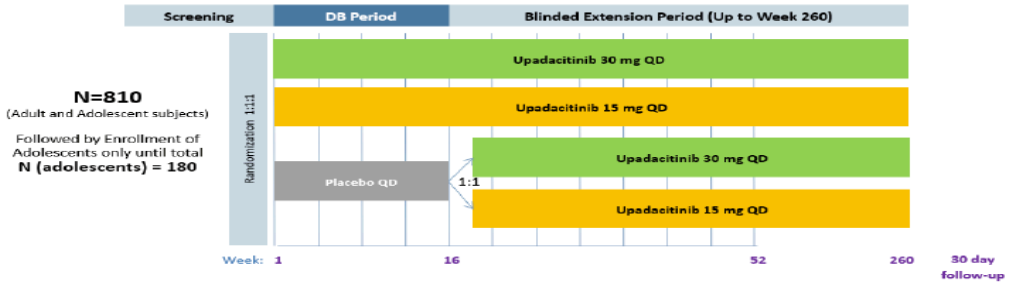
The applicant assured that the studies were carried out in accordance with the principles of good clinical practice (GCP), as documented by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), US FDA, EMA and the Japan Pharmaceutical and Medical Devices Agency. All patients gave written, informed consent.

Protocol deviation (study M16-045/ M18-891/ M16-047)

The most common protocol deviation was the subject entered into the study even though he/she did not satisfy the eligibility criterion #7 (atopic disease activity criteria). As mentioned in clinical study report (CSR), none of the deviations affected the study outcome or interpretation of the study results or conclusions.

The applicant submitted all required study reports for the proposed indication. Deviations from the eligibility criterion #7 are unlikely to affect the results as other criteria for disease severity were met for subjects with deviations. The deviation was due to insufficient understanding of the technique used to measure the worst pruritus numerical rating scale (NRS) score, which was resolved by training site personnel.

Study 1

Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis.	
Study identifier	M16-045 NCT03569293 (published in the lancet)
Design	Phase 3, randomized, DB, placebo-controlled multicenter study that evaluates the efficacy and safety of upadacitinib in adolescents (12 to 17 years of age at the time of the screening visit) and adults (18 to 75 years of age) with moderate to severe AD who were candidates for systemic therapy. Figure 1: Study Design Schematic  DB = double-blind; QD = once daily Note: This schematic applies to both the main study and adolescent sub-study. Main Criteria for Inclusion – Male and female ≥ 12 years old and ≤ 75 years old – At Screening, had a clinical diagnosis of AD and they had a documented history of inadequate response to treatment with topical AD treatments or use of systemic treatment for AD and met the following disease activity criteria: – (EASI) score ≥ 16 – The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score ≥ 3 ≥ 10% BSA of AD involvement at the Screening and Baseline visits and a Baseline weekly average of daily Worst Pruritus NRS ≥ 4.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		35 days 16 weeks 244 weeks
Hypothesis	Superiority		
Treatments arms	Upadacitinib 15 mg once a day (QD) film-coated tablet for oral administration (281 subjects)		
	Upadacitinib 30 mg QD film-coated tablet for oral administration (285 subjects)		
	Placebo QD film-coated tablet for oral administration (281 subjects)		
Randomization	Randomization ratio: 1:1:1 Randomization was stratified by baseline disease severity, age, and geographic region.		
Blinding	Study sites and subjects will remain blinded for the duration of the study.		
Endpoints and definitions	Co-Primary Endpoint	EASI75	Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index (EASI 75) from Baseline at Week 16.
		vIGA-AD	Proportion of subjects achieving vIGA-AD of 0 or 1 with at least two grades of reduction from Baseline at Week 16.
	Key secondary End points	Key secondary endpoints for EU/EMA regulatory purposes: • Improvement (reduction) in Worst Pruritus (NRS) ≥ 4 from Baseline at Week 16 for subjects with Worst Pruritus NRS ≥ 4 at Baseline • EASI 90 at Week 16 • Percent change from Baseline of Worst Pruritus NRS at Week 16 • Percent change in EASI from Baseline at Week 16 • Proportion of subjects achieving EASI 75 at Week 2 • Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Week 1 for subjects with Worst Pruritus NRS ≥ 4 at Baseline • Proportion of subjects achieving an improvement (reduction) in Patient Oriented Eczema Measure (POEM) ≥ 4 from Baseline at Week 16 for subjects with POEM ≥ 4 at Baseline • Proportion of subjects age ≥ 16 years old at screening achieving an improvement (reduction) in Dermatology Life Quality Index (DLQI) ≥ 4 from Baseline at Week 16 for subjects with DLQI ≥ 4 at Baseline • Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 2 for subjects with	

		Worst Pruritus NRS ≥ 4 at Baseline (upadacitinib 30 mg vs. placebo) • Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 3 for subjects with Worst Pruritus NRS ≥ 4 at Baseline (upadacitinib 15 mg vs. placebo) • Proportion of subjects experiencing a flare, characterized as a clinically meaningful worsening in EASI, defined as an increase of EASI by ≥ 6.6 from Baseline for subjects with EASI ≤ 65.4 at Baseline, during double-blind treatment period (DB Period) • Percent change in Scoring Atopic Dermatitis (SCORAD) from Baseline at Week 16 • Proportion of subjects achieving a Hospital Anxiety and Depression Scaleanxiety (HADS-A) < 8 and Hospital Anxiety and Depression Scale-depression (HADS-D) < 8 at Week 16 among subjects with HADS-A ≥ 8 or HADS-D ≥ 8 at Baseline • Proportion of subjects achieving an improvement (reduction) in Atopic Dermatitis Impact Scale (ADerm-IS) sleep domain score ≥ 12 (minimal clinically important difference [MCID]) from Baseline at Week 16 for subjects with ADerm-IS sleep domain score ≥ 12 at Baseline • Proportion of subjects achieving an improvement (reduction) in Atopic Dermatitis Symptom Scale (ADerm-SS) skin pain score ≥ 4 (MCID) from Baseline at Week 16 for subjects with ADerm-SS skin pain score ≥ 4 at Baseline • Proportion of subjects achieving an improvement (reduction) in ADerm-SS 7-item total symptom score (TSS-7) ≥ 28 (MCID) from Baseline at Week 16 for subjects with ADerm-SS TSS-7 ≥ 28 at Baseline; ADerm-SS TSS-7 is defined as the algebraic sum of the responses to items 1 – 7 of the ADerm-SS • Proportion of subjects achieving an improvement (reduction) in ADerm-IS emotional state domain score ≥ 11 (MCID) from Baseline at Week 16 for subjects with ADerm-IS emotional state domain score ≥ 11 at Baseline • Proportion of subjects achieving an improvement (reduction) in ADerm-IS daily activities domain score ≥ 14 (MCID) from Baseline at Week 16 for subjects with ADerm-IS daily activities domain score ≥ 14 at Baseline • Proportion of subjects achieving EASI 100 at Week 16 • Proportion of subjects age ≥ 16 years old at screening achieving DLQI score of 0 or 1 at Week 16 for subjects with DLQI > 1 at Baseline. **Key secondary endpoints for US/FDA regulatory purposes:**

		• Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Week 16 for subjects with Worst Pruritus NRS ≥ 4 at Baseline • Proportion of subjects achieving EASI 90 at Week 16 • Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Week 4 for subjects with Worst Pruritus NRS ≥ 4 at Baseline • Proportion of subjects achieving EASI 75 at Week 2 • Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Week 1 for subjects with Worst Pruritus NRS ≥ 4 at Baseline • Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 2 for subjects with Worst Pruritus NRS ≥ 4 at Baseline (upadacitinib 30 mg vs. placebo) • Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 3 for subjects with Worst Pruritus NRS ≥ 4 at Baseline (upadacitinib 15 mg vs. placebo) • Proportion of subjects experiencing a flare, characterized as a clinically meaningful worsening in EASI, defined as an increase of EASI by ≥ 6.6 from Baseline for subjects with EASI ≤ 65.4 at Baseline, during DB Period • Proportion of subjects achieving an improvement (reduction) in ADerm-IS sleep domain score ≥ 12 (MCID) from Baseline at Week 16 for subjects with ADerm-IS sleep domain score ≥ 12 at Baseline • Proportion of subjects achieving an improvement (reduction) in ADerm-SS skin pain score ≥ 4 (MCID) from Baseline at Week 16 for subjects with ADerm-SS skin pain score ≥ 4 at Baseline • Proportion of subjects achieving an improvement (reduction) in ADerm-SS TSS-7 ≥ 28 (MCID) from Baseline at Week 16 for subjects with ADerm-SS TSS-7 ≥ 28 at Baseline • Proportion of subjects achieving an improvement (reduction) in ADerm-IS emotional state domain score ≥ 11 (MCID) from Baseline at Week 16 for subjects with ADerm-IS emotional state domain score ≥ 11 at Baseline • Proportion of subjects achieving an improvement (reduction) in ADerm-IS daily activities domain score ≥ 14 (MCID) from Baseline at Week 16 for subjects with ADerm-IS daily activities domain score ≥ 14 at Baseline • Proportion of subjects achieving EASI 100 at Week 16.
Database lock	13 April 2020	

Results and Analysis

Sample size determination:

- Approximately 810 adult and adolescent subjects were randomized to upadacitinib 30 mg, upadacitinib 15 mg, or placebo in a ratio of 1:1:1 (270 subjects per treatment group).
- The sample size was determined by assuming an EASI 75 response rate of 15% and vIGA-AD clear or almost clear with at least a 2-point reduction response rate of 10% in the placebo group. This sample size provided more than 90% power to detect the treatment differences of 32% and 21%, respectively, for the above 2 endpoints simultaneously using the two-sided test at a 0.05 significant level.
- The assumptions of placebo response rates for EASI 75 and IGA-AD 0/1 were based on the maximum placebo rate in upadacitinib AD Phase 2b study and dupilumab Phase 3 monotherapy studies (SOLO 1 and SOLO 2).

Statistical Analysis:

- They used the intent-to-treat population for the main study (ITT_M) Population for all efficacy analyses, consisting of all randomized subjects of the Main Study. The primary analysis was conducted after all subjects in the Main Study completed Week 16 or discontinued prematurely.
- Cochran-Mantel- Haenszel (CMH) method is used for categorical variables and Mixed-Effect Model Repeat Measurement (MMRM) method for continuous variables.
- Overall type I error rate was controlled at the 0.05 (two-sided) level using a pre-specified graphical approach.
- The Non-Responder Imputation, while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 non-responder imputation due to coronavirus 2019 pandemic (NRI-C), was the primary approach for missing data handling in the analysis for the categorical endpoints. The Non-Responder Imputation (NRI) without special data handling for missing due to COVID-19 (NRI-NC), MI, and tipping point approaches were used as sensitivity analyses. For continuous endpoints, missing data will be handled using (MMRM).
- No adjustment was made for multiple centres.
- Subgroup analysis of the co-primary efficacy endpoints was conducted on the ITT_M Population for the following subgroup: age, sex, BMI, race, weight, geographic regions, bassline vIGA, bassline EASI, hsCRP, previous systemic therapy, subjects

who reported intolerance to at least one prior TCS or TCI therapy, and subjects that reported an inadequate response to at least one prior topical treatment.

Results:

Subject's disposition

A total of 847 subjects were randomized at 151 study sites located in 24 countries. All 847 subjects (100%) received the study drug. A total of 778 subjects (91.9%) completed the study drug through the DB Period (Week 16), and 782 subjects (92.3%) completed study participation through Week 16. Across all trials, discontinuation was slightly higher in the placebo groups.

Demographic Data

The overall demographic characteristics were generally balanced across the upadacitinib (30 mg and 15 mg) and placebo groups. Over half of the subjects (53.8%) were male, 65.5% were white, and 52.2% were 18 to 39 years of age; 50.1% of subjects had a body mass index (BMI) of < 25 kg/m2 at screening. The adolescent group characteristics were generally balanced across the upadacitinib (30 mg and 15 mg) and placebo groups. Over half of adolescent subjects (51.6%) were female, 66.1% were white, and 71.3% of subjects had a BMI of < 25 kg/m2 at screening.

Disease Severity

Baseline disease characteristics were generally balanced across the upadacitinib and placebo groups overall and in adolescents. Subjects had been diagnosed with AD for approximately 20.7 years overall and 12.7 years for adolescents. Disease activity consistently reflected moderate to severe AD across the treatment groups.

Table 1: Disease-Related Baseline Characteristics (ITT_M population) (Continued)

	Overall					Adolescents				
	PBO (N = 281)	UPA 15 mg (N = 281)	UPA 30 mg (N = 285)	UPA Total (N = 566)	Total (N = 847)	PBO (N = 40)	UPA 15 mg (N = 42)	UPA 30 mg (N = 42)	UPA Total (N = 84)	Total (N = 124)
vIGA-AD										
Score = 3 (moderate), n (%)	156 (55.5)	154 (54.8)	154 (54.0)	308 (54.4)	464 (54.8)	24 (60.0)	24 (57.1)	25 (59.5)	49 (58.3)	73 (58.9)
Score = 4 (severe), n (%)	125 (44.5)	127 (45.2)	131 (46.0)	258 (45.6)	383 (45.2)	16 (40.0)	18 (42.9)	17 (40.5)	35 (41.7)	51 (41.1)

Prior and concomitant medication

Topical betamethasone was the most frequently reported prior medication (38.6% of subjects), and emollients and protectives were the most frequently reported concomitant medications (27.5% and 27.4% of subjects in the DB Period and BE Period).

Extent of exposure to Upadacitinib

Overall, the extent of exposure to upadacitinib in adolescents was similar to the overall population in the Main Study. In total, 139 subjects (17.3%), including 20 adolescent subjects (16.8%) were treated with upadacitinib for a minimum of 52 weeks.

Table 2: Extent or Exposure Upadacitinib ALL UPA (ALL UPA_M Population)

	Overall			Adolescents		
	UPA 15 mg (N = 398)	UPA 30 mg (N = 406)	UPA Total (N = 804)	UPA 15 mg (N = 60)	UPA 30 mg (N = 59)	UPA Total (N = 119)
Duration (days)						
Mean (SD)	232.8 (121.07)	231.4 (124.19)	232.1 (122.58)	231.0 (113.74)	245.4 (123.55)	238.2 (118.42)
Median (Min, Max)	221.5 (6, 559)	211.0 (1, 552)	217.0 (1, 559)	224.5 (6, 559)	224.0 (27, 552)	224.0 (6, 559)
Duration interval, n (%)						
≥ 4 weeks	388 (97.5)	393 (96.8)	781 (97.1)	59 (98.3)	58 (98.3)	117 (98.3)
≥ 12 weeks	358 (89.9)	365 (89.9)	723 (89.9)	55 (91.7)	55 (93.2)	110 (92.4)
≥ 24 weeks	256 (64.3)	264 (65.0)	520 (64.7)	39 (65.0)	42 (71.2)	81 (68.1)
≥ 36 weeks	158 (39.7)	163 (40.1)	321 (39.9)	23 (38.3)	27 (45.8)	50 (42.0)
≥ 48 weeks	80 (20.1)	93 (22.9)	173 (21.5)	9 (15.0)	16 (27.1)	25 (21.0)
≥ 52 weeks	65 (16.3)	74 (18.2)	139 (17.3)	8 (13.3)	12 (20.3)	20 (16.8)
≥ 72 weeks	10 (2.5)	6 (1.5)	16 (2.0)	1 (1.7)	2 (3.4)	3 (2.5)
≥ 104 weeks	0	0	0	0	0	0
≥ 130 weeks	0	0	0	0	0	0

Max = maximum; Min = minimum; SD = standard deviation; UPA = upadacitinib

Note: Exposure = date of last study medication in double-blind period - date of first study medication in double-blind period + 1.

Cross reference: Table 14.1__8.3.1, Table 14.1__8.3.2

Treatment Compliance

Compliance rates were high in DB Period with mean compliance greater than 96% and median compliance greater than 99% in all three groups.

Efficacy Results

Primary efficacy endpoints-Week 16 (ITT_M Population)

The trial achieved the co-primary endpoints. A statistically significantly larger proportion of subjects in the upadacitinib groups achieved EASI75 69.6% in the 15 mg group and 79.7% in the 30 mg compared with 16.3% in the placebo group. The adjusted difference in response rate vs. placebo is 53.3% (P< 0.001) for the 15 mg group and 63.4 (P<0.001) for the 30 mg group compared to the placebo group.

The vIGA-AD score of 0 or 1 (clear or almost clear) was achieved with a clinically meaningful reduction (at least 2-grade reductions from baseline) at week 16 in 48.1% of the 15 mg group and 62% of the 30 mg group. The adjusted response rate difference against placebo was 39.8% (p < 0.001) in the UPA 15 mg group and 53.6% (p < 0.001) in the UPA 30 mg group compared with the placebo group based on the primary approach of NRI-C.

Table 3: Co-Primary Endpoints: EASI 75 and vIGA-AD or 1 at Week 16 (ITT_M population)

EMA Testing [a]	FDA Testing[a]	Primary Endpoint[b]	PBO (N = 281) n (%)	UPA 15 mg (N = 281) n (%); Adj Diff (P-value)	UPA 30 mg (N = 285) n (%); Adj Diff (P-value)
V1	V1	EASI 75 at Week 16	46 (16.3)	196 (69.6); 53.3 (< 0.001***)	227 (79.7); 63.4 (< 0.001***)
V2	V2	vIGA-AD clear or almost clear at Week 16	24 (8.4)	135 (48.1); 39.8 (< 0.001***)	177 (62.0); 53.6 (< 0.001***)

Adj Diff = adjusted difference; EASI = Eczema Area and Severity Index; EMA = European Medicines Agency; FDA = Food and Drug Administration; NRI-C = Non-Responder Imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO = placebo; UPA = upadacitinib; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis

*** p-value ≤ 0.001 according to the Cochran-Mantel Haenzel test; UPA vs PBO.

a. Variables in the EMA and FDA graphical approach for overall type-I error control details in SAP Section 4.6.

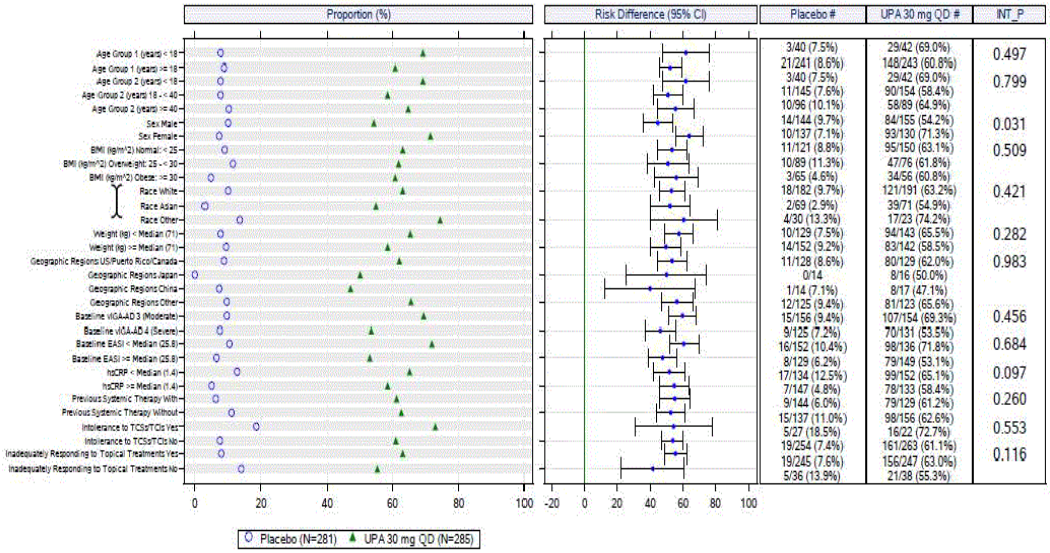
b. Results are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C).

Note: vIGA-AD of clear or almost clear included reduction ≥ 2 grades at Week 16 from Baseline

Subgroup

Treatment effects in all pre-specified subgroups (across demographic and baseline characteristics), including adolescents, consistently favored both upadacitinib doses compared to placebo in EASI 75 and vIGA-AD with all 95% confidence intervals (C.I) excluding zero.

Figure 1: Proportion of Subjects Achieving vIGA-AD of 0 or 1 with at Least 2 Grades of reduction from Baseline at week 16 by Subgroup in the Upadacitinib 30 mg Group (NRI-C, ITT_M Population)

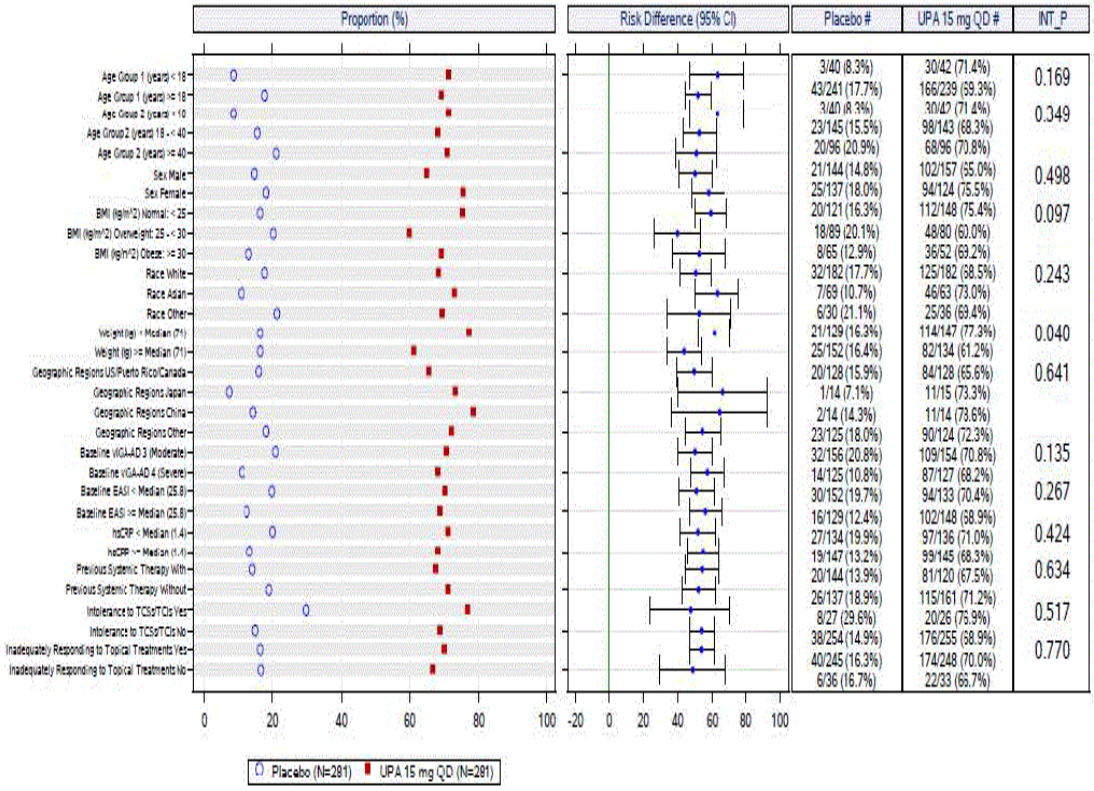


BMI = body mass index; CI = confidence interval for adjusted difference, calculated according to the Cochran-Mantel-Haenszel test adjusted for strata; EASI = Eczema Area and Severity Index; hsCRP = high-sensitivity C-reactive protein; INT_P = P-value for interaction between subgroup and treatment was calculated using a logistic regression with visit measurement at Week 16 as response variable, treatment, subgroup, strata, and treatment by subgroup interaction as factors; ITT_M = Intent-to-Treat Population for the Main Study; NRI-C = non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids; QD = once daily; UPA = upadacitinib; vIGA-AD = validated Investigator Global assessment for Atopic Dermatitis

Placebo and UPA 30 mg QD represents n/N (xx.x%).

Cross reference: Figure 14.2__21.1.4

Figure 2: Proportion of Subjects Achieving EASI 75 at week 16 by Subgroup in the Upadacitinib 15 mg Group ((NRI-C, ITT_M Population)



BMI = body mass index; CI = confidence interval for adjusted difference, calculated according to the Cochran-Mantel-Haenszel test adjusted for strata; EASI = Eczema Area and Severity Index; hsCRP = high-sensitivity C-reactive protein; INT_P = P-value for interaction between subgroup and treatment was calculated using a logistic regression with visit measurement at Week 16 as response variable, treatment, subgroup, strata, and treatment by subgroup interaction as factors; ITT_M = Intent-to-Treat Population for the Main Study; NRI-C = non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids; QD = once daily; UPA = upadacitinib; vIGA-AD = validated Investigator Global assessment for Atopic Dermatitis

Placebo and UPA 15 mg QD represents n/N (xx.x%).

Table 4: Proportion of Subjects Achieving EASI 75 at Week 16 by Subgroup (NRI-C) (ITT_M Population)

Subgroup Category Treatment	N	---- Responder ---- n (%) [95% CI]&	Missing Due to COVID-19 n	Response Rate Diff Compared to Placebo Diff(%)	Adjusted Diff(%)	[95% CI]#	P-value@
Age Group 1 (years)							
< 18							
Placebo	40	3 (8.3) [0.0, 17.2]	1				
UPA 15 mg QD	42	30 (71.4) [57.8, 85.1]	0	63.1	63.0	[47.1, 78.8]	<0.001***
UPA 30 mg QD	42	35 (83.3) [72.1, 94.6]	0	75.0	75.1	[61.3, 88.9]	<0.001***
Test of interaction between subgroup and UPA 15 mg QD vs. Placebo: P-value $ = 0.169							
Test of interaction between subgroup and UPA 30 mg QD vs. Placebo: P-value $ = 0.127							

Note: EASI = Eczema Area and Severity Index; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis.
NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
& 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.
# @ 95% CI for adjusted difference and P-value are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (Baseline vIGA-AD categories and age [adolescent vs. adult]) for the comparison of two treatment groups with exceptions: 1) Age subgroup analyses are stratified by Baseline vIGA-AD categories; 2) Baseline vIGA-AD subgroup analysis is stratified by age [adolescent vs. adult]. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19. For any subgroup, if there are zero subjects within a stratum in any treatment group, the CMH model will not be adjusted for the stratification factors.
$ P-value for interaction between subgroup and treatment is calculated using a logistic regression with visit measurement at Week 16 as response variable, treatment, subgroup, Baseline vIGA-AD categories, age [adolescent vs. adult], and treatment by subgroup interaction as factors with exceptions: 1) Age subgroup analyses are stratified by Baseline vIGA-AD categories; 2) Baseline vIGA-AD subgroup analysis is stratified by age [adolescent vs. adult]. Logistic regression is based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19. For multiple imputation data, one-sided P-value is calculated based on Student's t-distribution from PROC MIANALYZE procedure according to the Chi-square test using the Wilson-Hilferty transformation.
***, **, * Statistically significant at the 0.001, 0.01, 0.05 level, respectively.

Subgroup Category Treatment	N	---- Responder ---- n (%) [95% CI]&	Missing Due to COVID-19 n	Response Rate Diff Compared to Placebo Diff(%)	Adjusted Diff(%)	[95% CI]#	P-value@
Age Group 1 (years) (Cont.)							
>= 18							
Placebo	241	43 (17.7) [12.8, 22.6]	3				
UPA 15 mg QD	239	166 (69.3) [63.4, 75.2]	1	51.6	51.6	[44.1, 59.2]	<0.001***
UPA 30 mg QD	243	192 (79.1) [73.9, 84.2]	2	61.4	61.5	[54.4, 68.5]	<0.001***
Test of interaction between subgroup and UPA 15 mg QD vs. Placebo: P-value $ = 0.169							
Test of interaction between subgroup and UPA 30 mg QD vs. Placebo: P-value $ = 0.127							

Subgroup Category Treatment	N	---- Responder ---- n (%) [95% CI]&	Missing Due to COVID-19 n	Response Rate Diff Compared to Placebo Diff(%)	Adjusted Diff(%)	[95% CI]#	P-value@
Age Group 2 (years) (Cont.)							
18 - < 40							
Placebo	145	23 (15.5) [9.6, 21.5]	1				
UPA 15 mg QD	143	98 (68.3) [60.6, 75.9]	1	52.7	52.7	[43.0, 62.4]	<0.001***
UPA 30 mg QD	154	119 (77.3) [70.7, 83.9]	0	61.7	61.8	[52.9, 70.6]	<0.001***
>= 40							
Placebo	96	20 (20.9) [12.6, 29.2]	2				
UPA 15 mg QD	96	68 (70.8) [61.7, 79.9]	0	49.9	50.9	[39.1, 62.8]	<0.001***
UPA 30 mg QD	89	73 (82.2) [74.2, 90.2]	2	61.3	62.0	[50.7, 73.3]	<0.001***
Test of interaction between subgroup and UPA 15 mg QD vs. Placebo: P-value $ = 0.349							

Subgroup Category Treatment	N	---- Responder ---- n (%) [95% CI]&	Missing Due to COVID-19 n	Response Rate Diff Compared to Placebo Diff(%)	Adjusted Diff(%)	[95% CI]#	P-value@
Geographic Regions							
US/Puerto Rico/Canada							
Placebo	128	20 (15.9) [9.5, 22.3]	1				
UPA 15 mg QD	128	84 (65.6) [57.4, 73.9]	0	49.7	49.6	[39.3, 59.9]	<0.001***
UPA 30 mg QD	129	104 (80.6) [73.8, 87.4]	0	64.7	64.7	[55.6, 73.8]	<0.001***
Test of interaction between subgroup and UPA 15 mg QD vs. Placebo: P-value $ = 0.641							
Test of interaction between subgroup and UPA 30 mg QD vs. Placebo: P-value $ = 0.990							

Subgroup Category Treatment	N	---- Responder ---- n (%) [95% CI]&	Missing Due to COVID-19 n	Response Rate Diff ---------- Compared to Placebo ---------- Diff(%)	Adjusted Diff(%)	[95% CI]#	P-value@
Geographic Regions (Cont.)							
Japan							
Placebo	14	1 (7.1) [0.0, 20.6]	0				
UPA 15 mg QD	15	11 (73.3) [51.0, 95.7]	0	66.2	66.2	[40.1, 92.3]	<0.001***
UPA 30 mg QD	16	9 (56.3) [31.9, 80.6]	0	49.1	49.1	[21.3, 76.9]	0.001**
China							
Placebo	14	2 (14.3) [0.0, 32.6]	0				
UPA 15 mg QD	14	11 (78.6) [57.1, 100.0]	0	64.3	64.3	[36.0, 92.5]	<0.001***
UPA 30 mg QD	17	13 (76.5) [56.3, 96.6]	0	62.2	62.2	[34.9, 89.4]	<0.001***

Test of interaction between subgroup and UPA 15 mg QD vs. Placebo: P-value $ = 0.641
Test of interaction between subgroup and UPA 30 mg QD vs. Placebo: P-value $ = 0.990

Subgroup Category Treatment	N	---- Responder ---- n (%) [95% CI]&	Missing Due to COVID-19 n	Response Rate Diff ---------- Compared to Placebo ---------- Diff(%)	Adjusted Diff(%)	[95% CI]#	P-value@
Geographic Regions (Cont.)							
Other							
Placebo	125	23 (18.0) [11.1, 24.9]	3				
UPA 15 mg QD	124	90 (72.3) [64.3, 80.2]	1	54.2	54.3	[43.9, 64.7]	<0.001***
UPA 30 mg QD	123	101 (82.2) [75.4, 89.1]	2	64.2	64.1	[54.5, 73.8]	<0.001***

Test of interaction between subgroup and UPA 15 mg QD vs. Placebo: P-value $ = 0.641
Test of interaction between subgroup and UPA 30 mg QD vs. Placebo: P-value $ = 0.990

Key secondary endpoints

The superiority of each upadacitinib dose vs. placebo was demonstrated by all secondary endpoints of skin clearance and disease improvement, including EASI 90 and EASI 100 at Week 16, EASI 75 at Week 2, percent change in EASI at Week 16, percentage of subjects with a flare during the DB Period and percent change in SCORAD at Week 16 as presented below.

Table 5: Results of key Secondary Endpoints – EMA and FDA (ITT_M Population)

EMA Testing[a]	FDA Testing[a]	Secondary Endpoint	PBO (N = 281) n (%) or LS Mean (SE)	UPA 15 mg (N = 281) n (%) or LS Mean (SE); Adj Diff (P-value)	UPA 30 mg (N = 285) n (%) or LS Mean (SE); Adj Diff (P-value)
V3	V3	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Week 16	N = 272 32 (11.8)	N = 274 143 (52.2); 40.5 (< 0.001***)	N = 280 168 (60.0); 48.2 (< 0.001***)
V4	V4	EASI 90 at Week 16	N = 281 23 (8.1)	N = 281 149 (53.1); 45.1 (< 0.001***)	N = 285 187 (65.8); 57.8 (< 0.001***)
V5	NA	Percent change in Worst Pruritus NRS at Week 16	N = 123 –26.06 (5.407)	N = 225 –62.79 (4.490); –36.74 (< 0.001***)	N = 236 –72.04 (4.412); –45.98 (< 0.001***)
NA	V5	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Week 4	N = 272 12 (4.4)	N = 274 141 (51.5); 47.1 (< 0.001***)	N = 280 187 (66.8); 62.3 (< 0.001***)
V6	NA	Percent change in EASI at Week 16	N = 128 –40.71, (2.280)	N = 244 –80.24, (1.910); –39.53 (< 0.001***)	N = 259 –87.74 (1.875); –47.03 (< 0.001***)
V7	V6	EASI 75 at Week 2	N = 281 10 (3.6)	N = 281 107 (38.1); 34.5 (< 0.001***)	N = 285 135 (47.4); 43.9 (< 0.001***)
V8	V7	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Week 1	N = 272 1 (0.4)	N = 274 41 (15.0); 14.6 (< 0.001***)	N = 280 55 (19.6); 19.2 (< 0.001***)
V9	NA	Improvement in POEM ≥ 4 at Week 16	N = 276 63 (22.8)	N = 278 209 (75.0); 52.3 (< 0.001***)	N = 280 228 (81.4); 58.6 (< 0.001***)
V10	NA	Improvement in DLQI ≥ 4 at Week 16	N = 250 73 (29.0)	N = 254 192 (75.4); 46.7 (< 0.001***)	N = 256 210 (82.0); 53.2 (< 0.001***)
V11	V8	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Day 2	N = 270 10 (3.7)	NA	N = 279 33 (11.8); 8.1 (< 0.001***)

Table 6: Result of key Secondary Endpoints –EMA and FDA (ITT_M Population) (Continued)

EMA Testing[a]	FDA Testing[a]	Secondary Endpoint	PBO (N = 281) n (%) or LS Mean (SE)	UPA 15 mg (N = 281) n (%) or LS Mean (SE); Adj Diff (P-value)	UPA 30 mg (N = 285) n (%) or LS Mean (SE); Adj Diff (P-value)
V12	V9	Improvement (reduction) in Worst Pruritus NRS ≥ 4 at Day 3	N = 270 9 (3.3)	N = 275 45 (16.4); 13.0 (< 0.001***)	NA
V13	V10	Flare during DB Period	N = 274 69 (25.2)	N = 279 3 (1.1); –24.1 (< 0.001***)	N = 285 0; –25.2 (< 0.001***)
V14	NA	Percent change in SCORAD at Week 16	N = 125 –32.68 (2.329)	N = 239 –65.71 (1.777); –33.03 (< 0.001***)	N = 253 –73.07 (1.729); –40.39 (< 0.001***)
V15	NA	HADS-A < 8 and HADS-D < 8 at Week 16	N = 126 18 (14.3)	N = 145 66 (45.5); 31.5 (< 0.001***)	N = 144 71 (49.2); 34.9 (< 0.001***)
V16-H a.	V11-H a.	Improvement in ADerm-IS Sleep Domain Score ≥ 12 at Week 16	N = 220 29 (13.2)	N = 218 120 (55.0); 41.8 (< 0.001***)	N = 218 144 (66.1); 52.9 (< 0.001***)
V16-H b.	V11-H b.	Improvement in ADerm-SS Skin Pain Score ≥ 4 at Week 16	N = 233 35 (15.0)	N = 237 127 (53.6); 38.7 (< 0.001***)	N = 249 158 (63.5); 48.6 (< 0.001***)
V16-H c.	V11-H c.	Improvement in ADerm-SS TSS-7 ≥ 28 at Week 16	N = 226 34 (15.0)	N = 233 125 (53.6); 38.3 (< 0.001***)	N = 246 167 (67.9); 52.9 (< 0.001***)
V16-H d.	V11-H d.	Improvement in ADerm-IS Emotional State Domain Score ≥ 11 at Week 16	N = 212 42 (19.8)	N = 227 142 (62.6); 42.7 (< 0.001***)	N = 226 164 (72.6); 52.5 (< 0.001***)
V16-H e.	V11-H e.	Improvement in ADerm-IS Daily Activities Domain Score ≥ 14 at Week 16	N = 197 40 (20.3)	N = 203 132 (65.0); 44.7 (< 0.001***)	N = 205 150 (73.2); 53.1 (< 0.001***)
V17	V12	EASI 100 at Week 16	N = 281 5 (1.8)	N = 281 47 (16.7); 15.0 (< 0.001***)	N = 285 77 (27.0) 25.3; (< 0.001)

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Table 7: Skin Clearance and Disease Activity in DB Period, Including Adolescents (ITT_M Population)

	Overall						Adolescents					
		Response		Response Rate Diff (Upadacitinib – Placebo)				Response		Response Rate Diff (Upadacitinib – Placebo)		
Treatment	N	n (%)	(95% CI)[a]	Adj Diff (%)	(95% CI)[b]	P-Value[c]	Treatment	N	n (%)	(95% CI)[a]	Diff (%)	(95% CI)[b]	P-Value[c]
EASI 100 at Week 16, NRI-C													
PBO	281	5 (1.8)	(0.2, 3.3)				PBO	40	0				
UPA 15 mg	281	47 (16.7)	(12.4, 21.1)	15.0	(10.4, 19.6)	< 0.001[#,$]	UPA 15 mg	42	4 (9.5)	(0.6, 18.4)	9.5	(0.6, 18.4)	0.035
UPA 30 mg	285	77 (27.0)	(21.9, 32.2)	25.3	(20.0, 30.6)	< 0.001[#,$]	UPA 30 mg	42	14 (33.3)	(19.1, 47.6)	33.3	(19.1, 47.6)	< 0.001
SCORAD 50 at Week 16, NRI-C													
PBO	281	42 (14.9)	(10.7, 19.1)				PBO	40	4 (10.7)	(0.8, 20.5)			
UPA 15 mg	281	186 (66.0)	(60.5, 71.6)	51.1	(44.3, 58.0)	< 0.001[&]	UPA 15 mg	42	28 (66.7)	(52.4, 80.9)	56.0	(38.7, 73.3)	< 0.001
UPA 30 mg	285	219 (76.7)	(71.8, 81.7)	61.8	(55.4, 68.2)	< 0.001[&]	UPA 30 mg	42	36 (85.7)	(75.1, 96.3)	75.0	(60.6, 89.5)	< 0.001
SCORAD 75 at Week 16, NRI-C													
PBO	281	11 (4.0)	(1.7, 6.3)				PBO	40	0	(0.0, 1.4)			
UPA 15 mg	281	107 (38.1)	(32.4, 43.8)	34.2	(28.1, 40.3)	< 0.001[&]	UPA 15 mg	42	13 (31.0)	(17.0, 44.9)	30.9	(16.8, 44.9)	< 0.001
UPA 30 mg	285	140 (49.1)	(43.3, 54.9)	45.1	(38.8, 51.3)	< 0.001[&]	UPA 30 mg	42	25 (59.5)	(44.7, 74.4)	59.4	(44.5, 74.3)	< 0.001
SCORAD 90 at Week 16, NRI-C													
PBO	281	2 (0.7)	(0.0, 1.8)				PBO	40	0				
UPA 15 mg	281	51 (18.2)	(13.7, 22.7)	17.5	(12.8, 22.1)	< 0.001[&]	UPA 15 mg	42	6 (14.3)	(3.7, 24.9)	14.3	(3.7, 24.9)	0.008
UPA 30 mg	285	81 (28.5)	(23.2, 33.7)	27.7	(22.4, 33.0)	< 0.001[&]	UPA 30 mg	42	14 (33.3)	(19.1, 47.6)	33.3	(19.1, 47.6)	< 0.001

Table 8: Skin Clearance and Disease Activity in DB Period, Including Adolescents (ITT_M Population) (Continued)

	Overall						Adolescents					
		Response		Response Rate Diff (Upadacitinib – Placebo)				Response		Response Rate Diff (Upadacitinib – Placebo)		
Treatment	N	n (%)	(95% CI)[a]	Adj Diff (%)	(95% CI)[b]	P-Value[c]	Treatment	N	n (%)	(95% CI)[a]	Diff (%)	(95% CI)[b]	P-Value[c]
vIGA score of 0/1 at Week 16, NRI-C[a,b]													
PBO	281	24 (8.4)	(5.2, 11.7)				PBO	40	3 (7.5)	(0.0, 15.7)			
UPA 15 mg	281	135 (48.1)	(42.3, 54.0)	39.8	(33.2, 46.4)	< 0.001[#,$]	UPA 15 mg	42	16 (38.1)	(23.4, 52.8)	30.6	(13.8, 47.4)	< 0.001
UPA 30 mg	285	177 (62.0)	(56.4, 67.7)	53.6	(47.2, 60.0)	< 0.001[#,$]	UPA 30 mg	42	29 (69.0)	(55.1, 83.0)	61.5	(45.4, 77.7)	< 0.001
EASI 75 at Week 2, NRI-C													
PBO	281	10 (3.6)	(1.4, 5.7)				PBO	40	1 (2.5)	(0.0, 7.3)			
UPA 15 mg	281	107 (38.1)	(32.4, 43.8)	34.5	(28.6, 40.5)	< 0.001[#,$]	UPA 15 mg	42	15 (35.7)	(21.2, 50.2)	33.2	(17.9, 48.5)	< 0.001
UPA 30 mg	285	135 (47.4)	(41.6, 53.2)	43.9	(37.7, 50.0)	< 0.001[#,$]	UPA 30 mg	42	22 (52.4)	(37.3, 67.5)	49.9	(34.0, 65.7)	< 0.001
EASI 75 at Week 16, NRI-C[a,b]													
PBO	281	46 (16.3)	(12.0, 20.7)				PBO	40	3 (8.3)	(0.0, 17.2)			
UPA 15 mg	281	196 (69.6)	(64.2, 75.0)	53.3	(46.4, 60.2)	< 0.001[#,$]	UPA 15 mg	42	30 (71.4)	(57.8, 85.1)	63.1	(46.8, 79.4)	< 0.001
UPA 30 mg	285	227 (79.7)	(75.0, 84.4)	63.4	(57.1, 69.8)	< 0.001[#,$]	UPA 30 mg	42	35 (83.3)	(72.1, 94.6)	75.0	(60.6, 89.4)	< 0.001
EASI 90 at Week 16, NRI-C													
PBO	281	23 (8.1)	(4.9, 11.3)				PBO	40	1 (2.8)	(0.0, 8.0)			
UPA 15 mg	281	149 (53.1)	(47.2, 58.9)	45.1	(38.6, 51.7)	< 0.001[#,$]	UPA 15 mg	42	18 (42.9)	(27.9, 57.8)	40.1	(24.2, 56.0)	< 0.001
UPA 30 mg	285	187 (65.8)	(60.2, 71.3)	57.8	(51.5, 64.1)	< 0.001[#,$]	UPA 30 mg	42	31 (73.8)	(60.5, 87.1)	71.1	(56.8, 85.4)	< 0.001

Study 2

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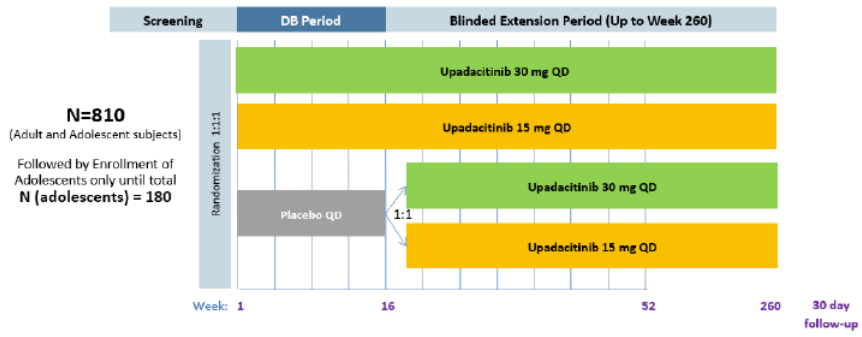
Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis.	
Study identifier	M18-891 NCT03607422 (published in the lancet)
Design	Phase 3, randomized, double-blind (DB), placebo-controlled multicenter study that evaluated the efficacy and safety of upadacitinib in adolescents (12 to 17 years of age at the time of the screening visit) and adults (18 to 75 years of age) with moderate to severe AD who were candidates for systemic therapy. Figure 4: Study Design Schematic  DB = double-blind; QD = once daily Note: This schematic applies to both the main study and adolescent sub-study. Main Criteria for Inclusion - Eligible subjects were to be ≥ 12 years old and ≤ 75 years old at the Screening and have had chronic AD with an onset of symptoms at least 3 years prior to Baseline and meet Hanifin and Rajka criteria, those subjects < 18 years of age were to have a body weight ≥ 40 kg at Baseline. - Subjects were to have had documented history (within 6 months of the Baseline Visit) of inadequate response to topical corticosteroids (TCS) or topical calcineurin inhibitors 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). - Subjects were also to have had at Screening and Baseline, EASI score ≥ 16, vIGA-AD score ≥ 3, and ≥ 10% body surface area of AD involvement, and a Baseline weekly average of daily Worst Pruritus Numerical Rating Scale (NRS) ≥ 4.
Duration of main phase:	35 days
Duration of Run-in phase:	16 weeks
Duration of Extension phase:	244 weeks

Hypothesis	Superiority	
Treatments arms	Upadacitinib 15 mg QD film-coated tablet for oral administration (276 subjects)	
	Upadacitinib 30 mg QD film-coated tablet for oral administration (282 subjects)	
	Placebo QD film-coated tablet for oral administration (278 subjects)	
Randomization	Randomization ratio: 1:1:1 Randomization was stratified by baseline disease severity, age, geographic region.	
Blinding	Study sites and subjects will remain blinded for the duration of the study.	
Endpoints and definitions	Primary Endpoints	Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index (EASI 75) from Baseline at Week 16.
		Proportion of subjects achieving vIGA-AD of 0 or 1 with at least two grades of reduction from Baseline at Week 16.
Database lock	8 May 2020	

Result and Analysis

Sample size determination

Approximately 810 adolescent and adult subjects were randomized to upadacitinib 30 mg, upadacitinib 15 mg, or placebo in a ratio of 1:1:1 in the Main Study (270 subjects per treatment group).

The regulatory requirement determined the sample size to characterize the safety profile adequately. Assuming an EASI 75 response rate of 15% and vIGA-AD 0 or 1 with at least a 2-point reduction response rate of 10% in the placebo arm, this sample size provided more than 90% power to detect the treatment differences of 32% and 21%, respectively, for the above 2 endpoints simultaneously using the two-sided test at a 0.05 significant level.

Statistical Analysis

- They used the ITT_M Population for all efficacy analyses, consisting of all randomized subjects of the Main Study. The primary analysis was conducted after all subjects in the Main Study completed Week 16 or discontinued prematurely.
- (CMH) method is used for categorical variables, and (MMRM) method for continuous variables.
- Overall type I error rate was controlled at the 0.05 (two-sided) level using a pre-specified graphical approach.

- The Non-Responder Imputation, while incorporating (MI) to handle missing data due to COVID-19 (NRI-C), was the primary approach for missing data handling in the analysis for the categorical endpoints. The NRI without special data handling for missing due to COVID-19 (NRI-NC), MI and tipping point approaches were used as sensitivity analyses. For continuous endpoints, missing data will be handled using (MMRM).
- No adjustment was made for multiple centres.

Results

Disposition of Subjects - DB Period (Through Week 16)

A total of 836 subjects were randomized at 154 study sites located in 23 countries. All 836 subjects (100%) received the study drug. A total of 764 subjects (91.4%) completed the study drug (with or without rescue therapy) through the DB Period (Week 16), and 768 subjects (91.9%) completed study participation through Week 16.

Demographic characteristics

The overall demographic characteristics were generally balanced across the upadacitinib (30 and 15 mg) and placebo groups. Over half of the subjects were male (56.3%), 69% were white, 58.3% were 18 to 39 years of age, and 49.9% had a body mass index (BMI) of < 25 kg/m2 at screening.

Disease-Related Baseline Characteristics

Subjects had been diagnosed with AD for a mean of approximately 20.2 years for the overall population and approximately 12.5 years for adolescents. Disease activity consistently reflected moderate to severe AD across the treatment groups.

Primary Efficacy results -week 16

A statistically significantly larger proportion of subjects in the upadacitinib groups achieved EASI 75 and achieved a vIGA-AD score of 0 or 1 (clear or almost clear) with a clinically meaningful reduction (at least 2 grade reductions from Baseline) at Week 16 compared with the placebo group.

Table 9: Co-Primary Endpoints: EASI 75 and vIGA-AD 0 or 1 at week 16 (ITT_M population)

EMA Testing[a]	FDA Testing[a]	Primary Endpoint[b]	PBO (N = 278) n (%)	UPA 15 mg (N = 276) n (%); Adj Diff (P-value)	UPA 30 mg (N = 282) n (%); Adj Diff (P-value)
V1	V1	EASI 75 at Week 16	37 (13.3)	166 (60.1); 46.9 (< 0.001***)	206 (72.9); 59.6 (< 0.001***)
V2	V2	vIGA-AD of 0 or 1 (clear or almost clear) at Week 16	13 (4.7)	107 (38.8); 34.0 (< 0.001***)	147 (52.0); 47.4 (< 0.001***)

Adj Diff = adjusted difference; EASI = Eczema Area and Severity Index; EMA = European Medicines Agency; FDA = Food and Drug Administration; ITT_M = Intent-to-Treat Population for the Main Study; NRI-C = Non-Responder Imputation incorporating Multiple Imputation to handle missing data due to coronavirus disease 2019; PBO = placebo; UPA = upadacitinib; V = variable; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis

a. Variables in the EMA and FDA graphical approach for overall type I error control details in SAP Section 4.6.

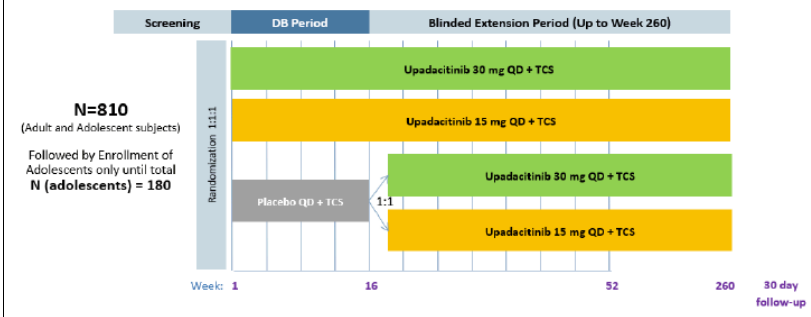
b. Results are based on NRI incorporating MI to handle missing data due to COVID-19 (NRI-C).

*** p-value ≤ 0.001; UPA vs. PBO.

Note: vIGA-AD of clear or almost clear included reduction ≥ 2 grades at Week 16 from Baseline.

Cross reference: Table 14.2__2.1.1, Table 14.2__3.1.1

Study 3

Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Combination with Topical Corticosteroids in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis.	
Study identifier	M16-047, NCT03568318 (published in the lancet)
Design	This was a Phase 3, randomized, DB, placebo-controlled multicenter study that evaluated the efficacy and safety of upadacitinib combined with TCS in adolescents (12 to 17 years of age at the time of the screening visit) and adults (18 to 75 years of age) with moderate to severe AD who were candidates for systemic therapy. Figure 5: Study Design Schematic  DB = double-blind; QD = once daily; TCS = topical corticosteroids Notes: This schematic applies to both the main study and adolescent sub-study. TCS inhibitors permitted for use in areas where TCS is generally not advisable. Number of Subjects (Planned and Analyzed): Planned: 810 subjects; Analyzed: 901 subjects Main Criteria for inclusion: Subjects were to be ≥ 12 years old and ≤ 75 years old at the screening visit and those subjects < 18 years of age were required to have a body weight ≥ 40 kg at Baseline. Subjects were in general good health (other than AD) as determined by the principal investigator based on results of medical history, laboratory profile, physical examination, chest x-ray, and a 12-lead electrocardiogram. Subjects with chronic AD had an onset of symptoms at least 3-years prior to Baseline and met Hanifin and Rajka criteria. At the Screening and Baseline, the had Eczema Area and Severity Index (EASI) score ≥ 16, vIGA-AD score ≥ 3, ≥ 10% body surface area of AD involvement and a baseline weekly average of daily Worst Pruritus numerical rating score (NRS) ≥ 4. Subjects must have had inadequate response to TCS or topical calcineurin inhibitor or documented systemic treatment for AD within 6 months. Subjects applied a topical emollient (moisturizer) twice daily for at least 7 days before Baseline.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	35 days 16 weeks 244 weeks
Hypothesis	Superiority	
Treatments arms	Upadacitinib 15 mg QD film-coated tablet for oral administration + TCS	
	Upadacitinib 30 mg QD film-coated tablet for oral administration + TCS	
	Placebo QD+ TCs	
Randomization	Randomization ratio: 1:1:1 Randomization was stratified by baseline disease severity, age, geographic region.	
Blinding	Study sites and subjects will remain blinded for the duration of the study.	
Endpoints and definitions	Primary Endpoints	Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index (EASI 75) from Baseline at Week 16.
		Proportion of subjects achieving validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) of 0 or 1 with at least two grades of reduction from Baseline at Week 16.
Database lock	10 April 2020	

Result and Analysis

Sample size determination

The regulatory requirement determined the sample size to characterize the safety profile adequately. Assuming an EASI 75 response rate of 24% and vIGA-AD 0 or 1 with at least a 2-point reduction response rate of 13% in the topical treatment with the placebo arm, this sample size will also provide more than 90% power to detect the treatment differences of 38% and 20%, respectively, for the above two primary endpoints simultaneously using the two-sided test at a 0.05 significant level.

Disposition of Subjects-week 16

A total of 901 subjects were randomized, and 900 subjects (including 115 adolescents) were treated with the study drug (1 adolescent was randomized but not treated) at 171 sites in 22 countries. Almost all subjects completed study treatment during the DB Period (94.8%).

Demographic characteristic

Most subjects were male (60.7%) and white (71.8%), with a mean age of 34.1 years (standard deviation [SD] 15.02 years). Adolescents had a mean age of 15.5 years (SD 1.75 years), with more female adolescents initially randomized to placebo compared to the upadacitinib groups. Subjects in this study represented a wide geographic distribution.

Disease-Related Baseline Characteristics

Subjects had a mean AD disease duration since diagnosis of 23.436 years (12.376 years for adolescents). Moderate to severe AD across was consistently observed across all treatment groups

Statistical Analysis

- They used the ITT_M Population for all efficacy analyses, consisting of all randomized subjects of the Main Study. The primary analysis was conducted after all subjects in the Main Study completed Week 16 or discontinued prematurely.
- (CMH) method is used for categorical variables, and (MMRM) method for continuous variables.
- Overall type I error rate was controlled at the 0.05 (two-sided) level using a pre-specified graphical approach.
- The Non-Responder Imputation, while incorporating (MI) to handle missing data due to COVID-19 (NRI-C), was the primary approach for missing data handling in the analysis for the categorical endpoints. The NRI without special data handling for missing due to COVID-19 (NRI-NC), MI and tipping point approaches were used as sensitivity analyses. For continuous endpoints, missing data will be handled using (MMRM).
- No adjustment was made for multiple centres.

Results

Primary efficacy result- DB period –Week 16

A statistically significant larger proportion of subjects in the upadacitinib groups achieved EASI 75 64.6% (adj diff: 38.1 (P<0.001***) in the 15 mg group, and 77.1% (adj diff: 50.6 P<0.001***) in the 30 mg group compared to 26.4% in the placebo group and achieved a vIGA-AD score of 0 or 1 (clear or almost clear) with a clinically meaningful reduction (at least 2 grade reduction from Baseline) in the 15 mg group in 39.6% (adj diff: 28.5 P<0.001***) and in 58.6% (adj diff: 47.6 P<0.001***) in the 30 mg group at Week 16 compared to 10.9% in the placebo group.

Table 10: Co-primary Endpoints (NRI, ITT_M Population)

EMA Testing[a]	FDA Testing[a]	Primary Endpoint	PBO + TCS (N = 304) n (%)	UPA 15 mg + TCS (N = 300) n (%); Adjusted Diff (P-value)	UPA 30 mg + TCS (N = 297) n (%); Adjusted Diff (P-value)
V1	V1	EASI 75 at Week 16	80 (26.4)	194 (64.6); 38.1 (<0.001***)	229 (77.1); 50.6 (<0.001***)
V2	V2	vIGA-AD Score 0/1 (clear or almost clear)[b] at Week 16	33 (10.9)	119 (39.6); 28.5 (<0.001***)	174 (58.6); 47.6 (<0.001***)

Adj Diff = adjusted difference; EASI = Eczema Area and Severity Index; EMA = European Medicines Agency; FDA = Food and Drug Administration; NRI-C = Non-Responder Imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO = placebo; TCS = topical corticosteroids; UPA = upadacitinib; V = variable; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis

*** p-value ≤ 0.001: UPA + TCS vs PBO. + TCS.

3.2.3 Overall conclusion of clinical efficacy

The three pivotal Phase III, randomized, double-blind, placebo-controlled studies were designed to compare the efficacy and safety of upadacitinib (30 mg and 15 mg) to placebo in subjects with moderate to severe AD. Totally including 2240 adult subjects and 344 adolescent subjects that completed the DB Period (Week 16).

Studies M16-045 and M18-891 had replicate study designs. In addition, pivotal combination study M16-047 had an identical design to the other two studies with a concomitant topical corticosteroid.

Overall, the design aspects were appropriate. Dose selection of these studies was based on the analyses of the 16-week safety, efficacy, and exposure-response data from Period 1 of the Phase 2 AD Study M16-048, which evaluated three doses of upadacitinib (7.5 mg, 15 mg, or 30 mg QD) versus placebo. Preliminary exposure-response analysis for period one of the phase two study showed that the percentage of subjects achieving EASI75, EASI90 or, IGA 0/1 increased with increasing upadacitinib plasma exposures. This trend was observed throughout the phase three trials, with a higher response in the 30mg group than in the 15mg group. Simulations using preliminary exposure-response models indicate that doses lower than 15mg QD are not predicted to provide adequate efficacy in subjects with moderate to severe AD. The basis for the choice of the two investigated doses is valid and the results observed are in line with phase two results. In addition, available Pharmacokinetics (PK), (PD), and safety data from upadacitinib studies in other disease indications were used to support the selection of these doses. The selection of the primary and secondary endpoints was suitable for the AD efficacy measures. The vIGA-AD,

SCORAD and EASI were validated and commonly used disease severity scales in AD clinical trials. The 16-week DB period is considered a sufficient duration to demonstrate the superiority between the two groups based on the previous AD clinical trials. All other approved products for AD used the same endpoints with similar durations to establish efficacy.

From a statistical perspective, the investigators selected suitable statistical analysis tests for both categorical and continuous data. Furthermore, they performed a subgroup analysis to show the treatment effects across demographic and baseline characteristics. The results showed consistent treatment effects in all pre-specified subgroups, all in favor of upadacitinib 30 mg and upadacitinib 15 mg compared to placebo, with all 95% (C.I) for the treatment differences excluding zero, except for the race of "other" subgroup, where the subgroup size was less than 10% of the total number subjects in the analysis population. In addition, they controlled multiplicity by using a pre-specified graphical approach. The studies were multicenter studies, which may affect the heterogeneity of the study and the results consistency between centers. However, all efficacy endpoints were analyzed overall and within each stratum of the three stratification factors: vIGA-AD, age (adolescent vs. adult) and region.

According to the study results, the co-primary endpoint of vIGA-AD 0/1 with at least 2 grades of reduction and EASI 75 at Week 16 were met as demonstrated by a statistically significantly greater percentage of subjects on upadacitinib 30 mg QD and upadacitinib 15 mg QD compared with placebo in each of the three Phase III studies.

Figure 3: vIGA-AD 0/1 at week 16 for Pivotal Phase 3 studies (NRI-C, ITT_M population)

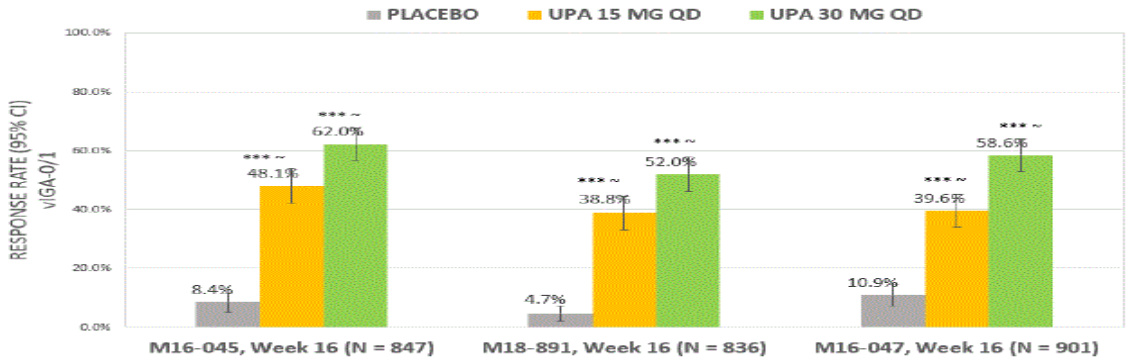
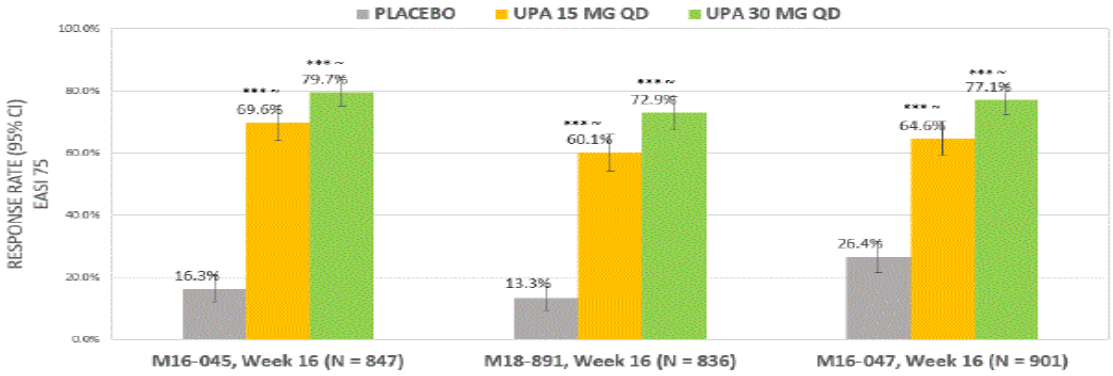


Figure 4: Improvement in EASI 75 at week 16 for the Pivotal Phase 3 studies (NRI-C, ITT_M Population)



*** $p < 0.001$ for upadacitinib vs. placebo.
~ Statistically significant in the multiplicity-controlled analysis.

In order to evaluate the effect of the protocol deviations, evaluation of the co-primary endpoint using per protocol analysis all showed a statistically significantly greater percentage of subjects on upadacitinib 30 mg QD and upadacitinib 15 mg QD compared with placebo in each of the three Phase III studies.

Per-protocol results- study M16045

Table 11: Proportion of subjects Achieving EASI 75 by visit in DB Period (NRI-C) (PP M Population)

TABLE 14.2 2.1.5

Proportion of Subjects Achieving EASI 75 by Visit in DB Period (NRI-C)
(PP M Population)

Time Point Strata Treatment	N	Responder n (%) [95% CI]&	Missing Due to COVID-19 n	Response Rate Diff Compared to Placebo Diff(%)	Adjusted Diff(%)	[95% CI]#	P-value@	Breslow-Day P-value
Week 16								
All								
Placebo	271	43 (15.9) [11.5, 20.3]	3					
UPA 15 mg QD	266	191 (71.8) [66.4, 77.2]	0	55.9	56.0	[49.2, 62.8]	<0.001***	0.230
UPA 30 mg QD	271	219 (80.8) [76.1, 85.5]	1	64.9	65.0	[58.6, 71.4]	<0.001***	0.099
vIGA-AD 3 (Moderate)								
Placebo	151	30 (20.1) [13.7, 26.5]	2					
UPA 15 mg QD	146	108 (74.0) [66.9, 81.1]	0	53.9		[44.3, 63.5]	<0.001***	
UPA 30 mg QD	145	117 (80.7) [74.3, 87.1]	0	60.6		[51.5, 69.7]	<0.001***	
vIGA-AD 4 (Severe)								
Placebo	120	13 (10.6) [5.0, 16.1]	1					
UPA 15 mg QD	120	83 (69.2) [60.9, 77.4]	0	58.6		[48.7, 68.6]	<0.001***	
UPA 30 mg QD	126	102 (80.9) [74.0, 87.8]	1	70.3		[61.5, 79.2]	<0.001***	

Note: EASI = Eczema Area and Severity Index; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis.
NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
& 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.
@ Across the strata, 95% CI for adjusted difference and P-value are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (Baseline vIGA-AD categories and age [adolescent vs. adult]) for the comparison of two treatment groups. Within each stratum, 95% CI for difference and P-value are calculated using Cochran-Mantel-Haenszel test without adjustment of strata. The calculations at each visit are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.
**, **, * Statistically significant at the 0.001, 0.01, 0.05 level, respectively.

Program Source Code: /leahyxt/SDA/ABT-494/AD/CSR/M16-045/M/14.2/PCMS_RUN/ml6045-nricl-db.sas

Table 12:Proportion of subjects achieving vIGA-AD of 0 or 1 with at least 2 grade of reduction from baseline ny visit in DB period (NRI-C) (PP M Population)

Proportion of Subjects Achieving vIGA-AD of 0 or 1 with at Least 2 Grades of Reduction from Baseline by Visit in DB Period (NRI-C)
(PP M Population)

Time Point Strata Treatment	N	Responder n (%) [95% CI]&	Missing Due to COVID-19 n	Response Rate Diff Compared to Placebo Diff(%)	Adjusted Diff(%)	[95% CI]#	P-value@	Breslow-Day P-value
Week 16								
All								
Placebo	271	23 (8.6) [5.2, 11.9]	3					
UPA 15 mg QD	266	133 (50.0) [44.0, 56.0]	0	41.4	41.6	[34.9, 48.4]	<0.001***	0.111
UPA 30 mg QD	271	168 (62.0) [56.2, 67.8]	1	53.4	53.5	[46.9, 60.0]	<0.001***	0.522
vIGA-AD 3 (Moderate)								
Placebo	151	14 (9.3) [4.6, 13.9]	2					
UPA 15 mg QD	146	85 (58.2) [50.2, 66.2]	0	48.9		[39.7, 58.2]	<0.001***	
UPA 30 mg QD	145	100 (69.0) [61.4, 76.5]	0	59.7		[50.9, 68.5]	<0.001***	
vIGA-AD 4 (Severe)								
Placebo	120	9 (7.7) [2.9, 12.6]	1					
UPA 15 mg QD	120	48 (40.0) [31.2, 48.8]	0	32.3		[22.9, 42.3]	<0.001***	
UPA 30 mg QD	126	68 (54.0) [45.3, 62.7]	1	46.3		[36.3, 56.3]	<0.001***	

Note: vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis.
NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
& 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.
# @ Across the strata, 95% CI for adjusted difference and P-value are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (Baseline vIGA-AD categories and age [adolescent vs. adult]) for the comparison of two treatment groups. Within each stratum, 95% CI for difference and P-value are calculated using Cochran-Mantel-Haenszel test without adjustment of strata. The calculations at each visit are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.
***, **, * Statistically significant at the 0.001, 0.01, 0.05 level, respectively.

Program Source Code: /leahyxt/SDA/ABT-494/AD/CSR/M16-045/M/14.2/PCMS_RUN/ml6045-nricl-db.sas

To examine the contribution of TCS on the treatment effect of upadacitinib, post-hoc analyses were performed to evaluate the TCS impact on the efficacy achieved with the upadacitinib 30 mg and 15 mg doses as well as with placebo. A logistic regression model was constructed by integrating data from monotherapy Studies M16-045 and M18-891 and the combination study with TCS, Study M16-047. The results

demonstrated no evidence that TCS contributes additional efficacy in the upadacitinib 30 mg or 15 mg groups.

Table 13: TCS effects on EASI 75 of both UPA doses and placebo at week 16 (ITT_M population in studies M16-045, M16-047 and M18-891) (Post hoc anlaysis)

EASI 75 Response Rate

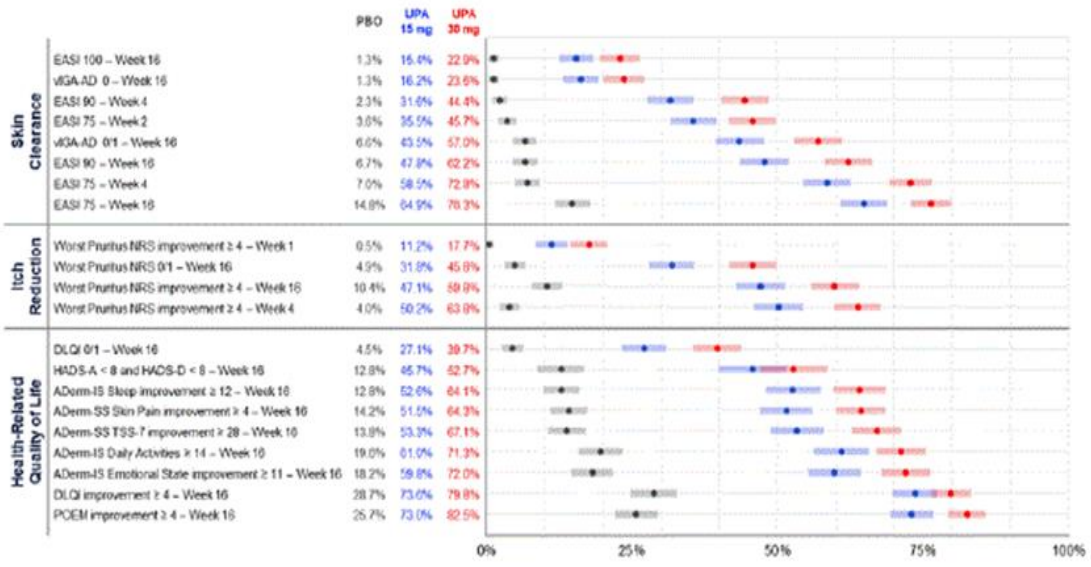
	Response Rate %
Placebo Monotherapy	14.5
Placebo + TCS	26.3
UPA 15 mg QD Monotherapy	64.0
UPA 15 mg QD + TCS	64.3
UPA 30 mg QD Monotherapy	75.7
UPA 30 mg QD + TCS	76.8

Note: EASI = Eczema Area and Severity Index.
Logistic model with TCS effect on UPA 15 mg QD (TCS_15), TCS effect on UPA 30 mg QD (TCS_30), TCS effect on Placebo (TCS_0), UPA 15 mg QD treatment, UPA 30 mg QD treatment, age (adolescent vs adult) and Baseline vIGA score (moderate vs severe) in the model.

Program Source Code: /leahynt/SDA/ABT-494/AD/Integrated_Summaries/ISE/1.2/PGMS_RUN/ise-tcs-eff2.sas

Furthermore, they performed post hoc analysis to examine the treatment effect between 15 mg group and 30 mg group and the results showed Upadacitinib's efficacy was dose-dependent, with higher efficacy observed with 30 mg versus 15 mg across all outcome measures of disease activity in all three studies.

Figure 5: Efficacy of upadacitinib 30 mg and 15 mg across AD domains in the PBO-controlled period (integrated phase 3 monotherapy studies, NRI-C)



3.2.3 Clinical Safety

They assessed the safety of upadacitinib in the Atopic dermatitis clinical studies by integrated subject data into three analysis sets:

- PBO-controlled AD Analysis Set (short-term safety through 16 weeks of upadacitinib 15 mg QD and upadacitinib 30 mg versus placebo)
- Long-term Upadacitinib Phase 3 AD Analysis Set (long-term safety of upadacitinib from the 3 pivotal Phase 3 studies)
- All Upadacitinib AD Analysis Set (a supplemental analysis set that was used to provide counts of rare events and AEs of special interest in the entire AD program, including regional studies).

3.2.3.1 Patient exposure

Table 14 : Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (ALL Upadacitinib Anlaysis Set)

	Overall			
Days	UPA 15 mg QD[a] (N = 1371) n (%)	UPA 30 mg QD[a] (N = 1378) n (%)	Phase 2 All Doses[b] (N = 144) n (%)	Total (N = 2893) n (%)
≥ 4 weeks	1361 (99.3)	1370 (99.4)	140 (97.2)	2871 (99.2)
≥ 12 weeks	1279 (93.3)	1286 (93.3)	130 (90.3)	2695 (93.2)
≥ 24 weeks	1076 (78.5)	1084 (78.7)	106 (73.6)	2266 (78.3)
≥ 36 weeks	640 (46.7)	666 (48.3)	102 (70.8)	1408 (48.7)
≥ 48 weeks	329 (24.0)	346 (25.1)	98 (68.1)	773 (26.7)
≥ 52 weeks	253 (18.5)	267 (19.4)	94 (65.3)	614 (21.2)
≥ 72 weeks	41 (3.0)	42 (3.0)	78 (54.2)	161 (5.6)
≥ 104 weeks	0	0	0	0
≥ 130 weeks	0	0	0	0
Mean duration (days)	254.4	258.2	422.0	264.6

3.2.3.2 Adverse events

Serious adverse events and deaths

Serious adverse events

- During PBO-controlled Analysis Set, 26 (2.9%) subjects in placebo group and 19 (2.1%) subjects in UPA 15 mg/ 30 mg group had SAE.
- During the long-term Upadacitinib Phase 3 AD Analysis Set**,** 62 (7.1%) subjects in UPA 15 mg group and 57 (8.4) subjects in UPA 30 mg group had SAE.
- During the All Upadacitinib AD Analysis Set**,** 66 (6.9) subjects in the UPA 15 mg group and 78 (8.0) subjects in the UPA 30mg group had SAE. The types of SAEs reported were consistent with that observed in the Long-term Upadacitinib Phase 3 AD Analysis Set.

The most serious adverse events were pneumonia, acne, and opportunistic infection, including tuberculosis (TB), herpes simplex, and herpes zoster.

The most commonly reported adverse drug reactions are upper respiratory tract infections (13.5%), nausea (3.5%), increased blood creatine phosphokinase (2.5%), and cough (2.2%).

Deaths

- There were no deaths reported during the placebo-controlled period and Long-term Upadacitinib Phase 3 AD Analysis Set.
- Through All Upadacitinib AD Analysis Set, two deaths were reported in the Phase 2b study in 2 subjects on upadacitinib 30 mg. The treatment-emergent death was in a subject with a history of hypertension and asthma who received the treatment sequence upadacitinib 30 mg/placebo/rescue upadacitinib 30 mg; the subject experienced cardiopulmonary arrest and died at home 2 days after the last dose of upadacitinib (no further information was available).

  The frequency of a few existing adverse drug reactions (ADRs) was changed compared to what was observed in the RA clinical program. Increased frequency: herpes simplex and herpes zoster occurred at rates which were common (≥ 1% – < 10%) rather than uncommon (< 1%). Decreased frequency: hypercholesterolemia, increasing alanine aminotransaminase (ALT), and aspartate aminotransferase (AST) occurred at uncommon rates.

Laboratory findings

Upadacitinib treatment was associated with dose-related increases in total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, ALT and AST, and creatine phosphokinase (CPK) Levels.
Upadacitinib treatment was associated with a dose-related decrease in total neutrophil counts, lymphocyte counts, and hemoglobin level.

Safety in special populations

Pregnancy

- There are no or limited data on the use of upadacitinib in pregnant women. Studies in animals have shown reproductive toxicity. Upadacitinib was teratogenic in rats and rabbits with effects in bones in rat foetuses and in the heart in rabbit foetuses when exposed in utero.
- Upadacitinib is contraindicated during pregnancy.
- Available data from the pharmacovigilance safety database and postmarketing case reports on use of upadicitinib in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage.

Immunological events

Not available (NA)

Safety related to drug-drug interactions and other interactions

Upadacitinib exposure increased when co-administered with strong Cytochrome P450 3A isoform subfamily (CYP3A4) inhibitors.
Upadacitinib exposure decreased when co-administered with strong CYP3A4 inducers.

Discontinuation due to AEs

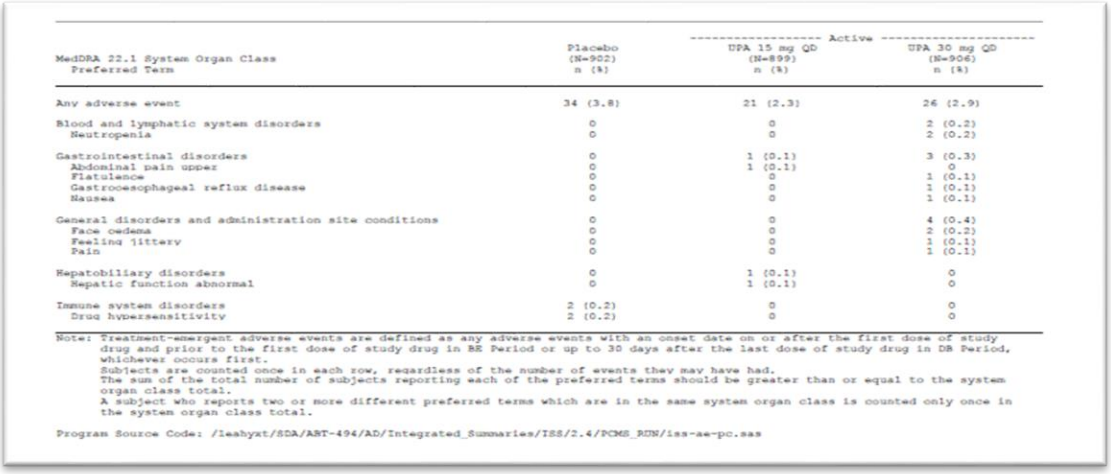
During PBO-controlled Analysis Set, 34 (3.8%) subjects in the placebo group, 21 (2.3%) subjects in the UPA 15 mg group and 26 (2.9%) subjects in the UPA 30 mg group discontinued the treatment due to adverse events / due to an adverse event.

During the Long-term Upadacitinib Phase 3 AD Analysis Set**,** 47 (5.4%) subjects in the UPA 15 mg group and 62 (6.9%) subjects in the UPA 30 mg group discontinued the treatment due to adverse events.
During the All Upadacitinib AD Analysis Set, 51 (5.3%) subjects in the UPA 15 mg group and 63 (6.5%) subjects in the UPA 30 mg group discontinued the treatment due to adverse events.

Table 15: Treatment- Emergent Adverse Events Leading to Discontinuation of Study Drug Reported in ≥ 0.2 Events Per 100 Patient year (PY) in any Treatment Group by Decreasing Frequency Overall (Long-term Upadacitinib Phase 3 AD Analysis Set)

System Organ Class MedDRA 22.1 Preferred Term	Overall		Adolescent	
	UPA 15 mg QD (Phase 3 only) (N = 1238) (PY = 872.2)	UPA 30 mg QD (Phase 3 only) (N = 1242) (PY = 892.7)	UPA 15 mg QD (Phase 3 only) (N = 167) (PY = 122.6)	UPA 30 mg QD (Phase 3 only) (N = 166) (PY = 125.5)
	E (E/100 PY)			
Any Adverse Event	47 (5.4)	62 (6.9)	7 (5.7)	9 (7.2)
Dermatitis atopic	13 (1.5)	4 (0.4)	1 (0.8)	1 (0.8)
Herpes simplex	0	3 (0.3)	0	0
Pruritus	2 (0.2)	0	1 (0.8)	0
Asthma	2 (0.2)	0	1 (0.8)	0
Eczema	0	2 (0.2)	0	0
Neutropenia	0	2 (0.2)	0	0
Alanine aminotransferase increased	0	2 (0.2)	0	0
Aspartate aminotransferase increased	0	2 (0.2)	0	0
Haemoglobin decreased	0	2 (0.2)	0	0
Pyrexia			1 (0.8)	0
Hepatic functional abnormal			1 (0.8)	0
Osteomyelitis			0	1 (0.8)
Pharyngotonsillitis			1 (0.8)	0
Pneumonia			0	1 (0.8)
Pyoderma			0	1 (0.8)
Sepsis			0	1 (0.8)
Staphylococcal sepsis			0	1 (0.8)

Table 16: Number and Percentage of subjects with treatment –Emergent Adverse Events Leading to Discontinuation of Study Drug



MedDRA 22.1 System Organ Class Preferred Term	Placebo (N=902) n (%)	Active UPA 15 mg QD (N=899) n (%)	Active UPA 30 mg QD (N=906) n (%)
Any adverse event	34 (3.8)	21 (2.3)	26 (2.9)
Blood and lymphatic system disorders	0	0	2 (0.2)
Neutropenia	0	0	2 (0.2)
Gastrointestinal disorders	0	1 (0.1)	3 (0.3)
Abdominal pain upper	0	1 (0.1)	0
Flatulence	0	0	1 (0.1)
Gastrooesophageal reflux disease	0	0	1 (0.1)
Nausea	0	0	1 (0.1)
General disorders and administration site conditions	0	0	4 (0.4)
Face oedema	0	0	2 (0.2)
Feeling litterv	0	0	1 (0.1)
Pain	0	0	1 (0.1)
Hepatobiliary disorders	0	1 (0.1)	0
Hepatic function abnormal	0	1 (0.1)	0
Immune system disorders	2 (0.2)	0	0
Drug hypersensitivity	2 (0.2)	0	0

Note: Treatment-emergent adverse events are defined as any adverse events with an onset date on or after the first dose of study drug and prior to the first dose of study drug in BE Period or up to 30 days after the last dose of study drug in DB Period, whichever occurs first.
Subjects are counted once in each row, regardless of the number of events they may have had.
The sum of the total number of subjects reporting each of the preferred terms should be greater than or equal to the system organ class total.
A subject who reports two or more different preferred terms which are in the same system organ class is counted only once in the system organ class total.

Program Source Code: /leahyxt/SDA/ABT-494/AD/Integrated_Summaries/ISS/2.4/PCMS_RUN/iss-ae-pc.sas

Post-marketing experience

The overall safety of upadacitinib 15 mg QD therapy was evaluated through a review of post-marketing reports (spontaneous, solicited, literature) received from 16 August 2019 through 15 August 2020. A search of the AbbVie global safety database retrieved 13,239 reports.

Overall, 91% of the reports were considered non-serious, and 97% were from solicited sources. A review of the post-marketing safety data reported for upadacitinib up to date demonstrated a similar safety profile as observed in the clinical studies for RA.

The most frequently reported AEs were in the standard of care SOC of general disorders and administration site conditions and Musculoskeletal and connective tissue disorders. The most commonly reported serious infection was Pneumonia.

3.2.3.3 Overall conclusion on clinical safety

The data presented in this application provide evidence that upadacitinib 15 mg QD has an acceptable safety profile with manageable risks for treating patients with moderate to severe atopic dermatitis using the two dose regimens of 15 and 30mg for the adults and 15mg for the adolescents. In the short-term PBO-controlled AD analysis set, the rates of SAEs and Treatment-emergent adverse event (TEAEs) leading to study drug discontinuation were similar across upadacitinib groups. In adolescent subjects, the rates of SAEs and TEAEs leading to study drug discontinuation were similar between the upadacitinib 15 mg and placebo groups, while the rate of severe TEAEs was higher in the upadacitinib 15 mg group than in the placebo group. In the 30 mg group, no SAEs or

TEAEs led to discontinuation. In the all upadacitinib AD analysis set, SAEs and TEAEs were higher in the 30 mg than in the 15 mg group. In the PBO-controlled analysis set, the percentage of patients with serious infections was similar between the active and placebo groups. Subgroup analysis did not show a trend of difference between adults and adolescents. The safety of the combination therapy was similar to that of monotherapy.

3.2.4 Discussion on clinical efficacy and safety aspects

The overall clinical development program showed the efficacy of Rinvoq for atopic dermatitis with an acceptable safety profile. The combination trial of upadacitinib and topical corticosteroids did not show an additional efficacy response for this indication. The safety also was the same with or without topical corticosteroids. Nevertheless, the option of adding corticosteroids in case of insufficient response with monotherapy is reasonable in light of the accepted safety profile.

The efficacy and safety department recommends approval for Rinvoq for the treatment of moderate to severe atopic dermatitis.

4. Risk Management Plan

4.1 Artwork and Trade Name assessment (Artwork available in appendix)

Proposed trade Name	Dosage Form
Rinvoq	Prolonged-Release Tablet

Look –alike/Sound-alike (LA/SA) Error Risk Potential:

Rinvoq name LA/SA confusion risk potential has been assessed based on the evaluation of LA/SA similarities from our data sources (SFDA registered Drug List, Martindale, ISMP Confused Drug Name List, INN International Nonproprietary Names and USAN United States Adopted Names STEM) and the pharmaceutical characteristic of the product:

LA/SA for Product name	SFDA	Shared File/ Excel Sheet	Martindale	Stem Book 2018
Rinvoq	NO	NO	NO	NO

Trade Name Recommendation:

Based on the submitted data, the proposed name Rinvoq is accepted.

Outer and Inner Package:

Based on the submitted data, the proposed artwork is accepted.

5. Overall Conclusion

Based on a review of data on quality, safety, and efficacy, SFDA considered that the benefit/risk profile of Rinvoq was favorable and decided to grant the marketing authorization of Rinvoq for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy for Rinvoq.

6. Appendix

The date of revision of this text corresponds to that of the Saudi PAR. New information concerning the authorized medicinal product in question will not be incorporated into the Saudi PAR. New findings that could impair the medicinal product's quality, efficacy, or safety are recorded and published at (SDI or Summary Saudi-PAR report).

For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa