SUPPLEMENTAL MATERIALS

Integrated Safety Analysis of Abrocitinib for the Treatment of Moderate-to-Severe Atopic Dermatitis (AD) From the Phase II and Phase III Clinical Trial Program

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Table S1. Summary of clinical trials included in this integrated analysis. Studies in shaded cells were included in placebo-controlled cohort.

Trial Name (ClinicalTrials.gov Identifier)	**Study Design**	**Key Inclusion Criteria**	**Treatment/Duration**	**Number of Patients**
Phase IIb (NCT02780167) (9)	Phase IIb dose-ranging proof-of-concept randomized monotherapy study in adult patients	• Age 18–75 y • Moderate-to-severe chronic AD ≥1 y prior to the study • Inadequate response to topical medications received ≥4 w, or if such treatment otherwise medically inadvisable within 12 m of the study	• Abrocitinib 10 mg QD • Abrocitinib 30 mg QD • Abrocitinib 100 mg QD • Abrocitinib 200 mg QD • Placebo 12 weeks treatment, 4 weeks follow-up	*N* = 269 (randomized 1:1:1:1:1) • 10 mg: 49 • 30 mg: 51 • 100 mg: 56 • 200 mg: 55 • Placebo: 56
JADE MONO-1 (NCT03349060)[a] (11)	Phase III randomized, monotherapy study in adults and adolescents	• Age ≥12 y • Body weight ≥40 kg • Moderate-to-severe chronic AD ≥1 year prior to the study • Recent history (within 6 m of screening) of inadequate response to topical medications for ≥4 w, if such treatment otherwise medically inadvisable, or if systemic therapies were required for control of AD	• Abrocitinib 100 mg QD • Abrocitinib 200 mg QD • Placebo 12 weeks treatment	*N* = 387 (randomized 2:2:1) • 100 mg: 156 • 200 mg: 154 • Placebo: 77
JADE MONO-2 (NCT03575871)[a] (10)	Phase III randomized, monotherapy study in adults and adolescents	• Age ≥12 y • Body weight ≥40 kg • Moderate-to-severe chronic AD ≥1 year prior to the study	• Abrocitinib 100 mg QD • Abrocitinib 200 mg QD • Placebo 12 weeks treatment	*N* = 391 (randomized 2:2:1) • 100 mg: 158 • 200 mg: 155 • Placebo: 78

		• Recent history (within 6 m of screening) of inadequate response to topical medications for ≥4 w, if such treatment otherwise medically inadvisable, or if systemic therapies were required for control of AD		
JADE COMPARE (NCT03720470)[a]	Phase III randomized combination study including a comparator and on background therapy in adult patients	• Age ≥18 y • Moderate-to-severe chronic AD ≥1 year prior to the study • Recent history (within 6 m of screening) of inadequate response to topical medications for ≥4 w, or if systemic therapies were required for control of AD • Inadequate response to twice-daily use of nonmedicated emollient for 7 d prior to the first study day	• Abrocitinib 100 mg QD • Abrocitinib 200 mg QD • Dupilumab 300 mg SC every other week (loading dose of 600 mg at baseline) • Placebo 16 weeks treatment, 4 weeks of follow-up	*N* = 837 (randomized 2:2:2:1) • 100 mg: 238 • 200 mg: 226 • Dupilumab: 242 • Placebo: 131
JADE REGIMEN (NCT03627767)[b,c]	Phase III randomized withdrawal and retreatment study in adults and adolescents	• Age ≥12 y • Body weight ≥40 kg • Moderate-to-severe chronic AD ≥1 year prior to the study • Recent history (within 6 m of screening) of inadequate response to topical medications for ≥4	200 mg QD for 12 weeks open label Responders, based on IGA and EASI-75, were randomized to 200 mg QD, 100 mg QD, or matching placebo up to 52 weeks. Patients with loss of response enter a 12-week rescue treatment period of open-	Open label *N* = ~1370 *N* = ~600 (randomized 1:1:1) • 100 mg: ~200 • 200 mg: ~200 • Placebo: ~200

		w or if systemic therapies were required for control of AD	label 200 mg QD with or without topical therapy Treatment duration is up to 64 weeks	
JADE EXTEND (NCT03422822; ongoing)[c]	Phase III long-term extension study in adults and adolescents	• Age ≥12 y • Body weight ≥40 kg • Must have completed the full treatment period of qualifying phase III study OR must have completed the full rescue treatment period of a qualifying phase III study (if applicable) OR must have completed the full OL run in period in JADE EXTEND and did not meet the protocol-specified response criteria at w 12	Patients previously allocated to abrocitinib 200 mg or 100 mg QD in the qualifying parent study were allocated to the same dose Patients previously randomized to active control drug or placebo only in a qualifying parent study were randomized to double blind treatment, either abrocitinib 200 mg or 100 mg QC when enrolled into JADE EXTEND	*N* = ~3000

EASI Eczema Area and Severity Index, *d* day, *IGA* Investigator's Global Assessment *m* month, *OL* open-label, *QD* once daily, *w* week, *y* year.

[a]Patients randomized to placebo contributed to exposure to all-abrocitinib cohort starting at the time they were randomized to either dose of abrocitinib in JADE EXTEND; [b]Patients were included in all-abrocitinib cohort if they participated in the initial open-label period of the study prior to the randomized withdrawal period; [c]Cut-off date was April 22, 2020.

Table S2. Adverse event definitions

	Definition
Investigators assessment of adverse event intensity	
Mild	Does not interfere with patient's usual function
Moderate	Interferes to some extent with patient's usual function
Severe[a]	Interferes significantly with patient's usual function
Definition of serious adverse event	
Serious	Results in death, is life-threatening (immediate risk of death), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions), results in congenital anomaly/birth defect, and is an important medical event based on investigator's judgment

[a]A severe adverse event is not necessarily a serious adverse event as a severe adverse event must meet a criterion of seriousness to be a serious adverse event.

Table S3. Demographic and baseline characteristics by treatment group within the (**a)** placebo-controlled cohort and (**b)** all-abrocitinib cohort.

(a)

	Placebo ***N*** **= 342**	**Abrocitinib 100 mg** ***N*** **= 608**	**Abrocitinib 200 mg** ***N*** **= 590**
Age, median (IQR), y	33.0 (24.0, 46.0)	34.0 (24.0, 47.0)	32.0 (23.0, 46.0)
Age group, *n* (%)			
<18 years	25 (7.3)	51 (8.4)	48 (8.1)
18–64 years	300 (87.7)	521 (85.7)	501 (84.9)
≥65 years	17 (5.0)	36 (5.9)	41 (6.9)
Female, *n* (%)	148 (43.3)	273 (44.9)	289 (49.0)
Race, *n* (%)			
White	229 (67.0)	436 (71.7)	393 (66.6)
Black or African American	28 (8.2)	37 (6.1)	39 (6.6)
Asian	70 (20.5)	128 (21.1)	138 (23.4)
Other	15 (4.4)	7 (1.2)	20 (3.4)
Hispanic or Latino, *n* (%)	27 (7.9)	49 (8.1)	48 (8.1)
Weight (kg), median (IQR)	74.0 (62.8, 84.2)	73.5 (63.0, 87.0)	73.2 (62.3, 85.5)
Body mass index (kg/m^2), median (IQR)	24.7 (22.1, 28.7)	25.7 (22.5, 29.4)	25.4 (22.5, 29.2)
IGA moderate/severe, %	64.6/35.4	62.8/37.2	62.5/37.5
Prior topical agents only	193 (56.4)	329 (54.1)	323 (54.7)
Prior systemic therapy, *n* (%)	144 (42.1)	271 (44.6)	261 (44.2)
Dupilumab	11 (3.2)	20 (3.3)	14 (2.4)

IGA Investigator's Global Assessment, *IQR* interquartile range.

(b)

	Abrocitinib 100 mg N = 885	**Abrocitinib 200 mg N = 1971**
Age, median (IQR), y	33.0 (24.0, 47.0)	29.0 (21.0, 43.0)
Age group, *n* (%)		
<18 years	64 (7.2)	300 (15.2)
18–64 years	770 (87.0)	1577 (80.0)
≥65 years	51 (5.8)	94 (4.8)
Female, *n* (%)	396 (44.7)	907 (46.0)
Race, *n* (%)		
White	637 (72.0)	1426 (72.3)
Black or African American	49 (5.5)	121 (6.1)
Asian	187 (21.1)	366 (18.6)
Other	12 (1.4)	58 (2.9)
Hispanic or Latino, *n* (%)	78 (8.8)	316 (16.0)
Weight (kg), median (IQR)	73.6 (63.0, 87.0)	72.0 (60.3, 85.0)
Body mass index (kg/m^2), median (IQR)	25.4 (22.4, 29.3)	24.9 (21.8, 28.9)
IGA moderate/severe, %	63.7/36.3	60.3/39.7
Prior topical agents only	485 (54.8)	897 (45.5)
Prior systemic therapy, *n* (%)	391 (44.2)	1063 (53.9)
Dupilumab	26 (2.9)	82 (4.2)

IGA Investigator's Global Assessment, *IQR* interquartile range.

Table S4. Summary of abrocitinib exposure for all-abrocitinib cohort

Cumulative exposure, *n* (%)	**Abrocitinib 100 mg *N* = 885**	**Abrocitinib 200 mg *N* = 1971**	**All Abrocitinib *N* = 2856**
≥24 weeks	553 (62.5)	695 (35.3)	1248 (43.7)
≥36 weeks	414 (46.8)	581 (29.5)	995 (34.8)
≥48 weeks	265 (29.9)	341 (17.3)	606 (21.2)
≥72 weeks	80 (9.0)	118 (6.0)	198 (6.9)

Table S5. Factors associated with statistically higher risk of herpes zosters infections in the all-abrocitinib cohort

Comparison	**Hazard Ratio (95% CI)**
Study treatment	
Abrocitinib 200 mg QD vs 100 mg QD	2.25 (1.15–4.38)
Age at baseline (years)	
≥65 vs 18–<65	3.65 (1.37–9.71)
≥65 vs <18	5.84 (1.55–21.98)
18<65 vs <18	1.60 (0.60–4.26)
Baseline disease severity	
Severe vs moderate	1.91 (1.11–3.28)

ALC absolute lymphocyte count, *eGFR* estimated glomerular filtration rate, *QD* once daily.

Hazard ratios and associated confidence intervals were estimated from a Cox regression model including fixed effects of treatment, study (parent), categorical variables of baseline age, sex, ethnicity, baseline body weight, body mass index, geographic region, baseline disease severity, prior systemic therapy and baseline eGFR, and time-dependent variable of confirmed ALC prior to the event (≥ 1.0 or < 1.0 $10^3/mm^3$). The results for the fixed effects shown statistical significance ($P < 0.05$, 2-sided) are displayed on this table.

Table S6. Hazard ratios of risk factors associated with eczema herpeticum or herpes simplex in all-abrocitinib cohort

Comparison	**Hazard Ratio (95% CI)**	***P* value**
Study treatment		0.7454
Abrocitinib 200mg QD vs 100 mg QD	0.94 (0.66–1.34)	
Baseline age (years)		0.6296
≥65 vs 18–<65	0.84 (0.30–2.39)	
≥65 vs <18	1.06 (0.34–3.31)	
18–<65 vs 18–<65	1.26 (0.77–2.06)	
Baseline disease severity		0.4625
Severe vs moderate	0.89 (0.66–1.21)	
Sex		0.0591
Female vs male	1.34 (0.99–1.81)	
Ethnicity		0.3075
Hispanic or Latino vs Not Hispanic or Latino	0.59 (0.21–1.62)	
Baseline body weight (kg)		0.3503
≤100 vs >100	0.72 (0.36–1.44)	
BMI (kg/m^2)		0.2339
25–<30 vs <25	1.01 (0.72–1.40)	
25–<30 vs ≥30	1.64 (0.91–2.94)	
<25 vs ≥30	1.63 (0.91–2.92)	
Geographic region		<0.0001
Asia vs Eastern Europe/Russia	0.97 (0.62–1.54)	
Asia vs Latin America	0.56 (0.17–1.81)	
Asia vs US/Canada/Australia	2.41 (1.39–4.16)	
Asia vs Western Europe	0.74 (0.45–1.22)	
Eastern Europe/Russia vs Latin America	0.57 (0.18–1.79)	

Eastern Europe/Russia vs US/Canada/Australia	2.47 (1.59–3.85)	
Eastern Europe/Russia vs Western Europe	0.76 (0.51–1.13)	
Latin America vs US/Canada/Australia	4.31 (1.40–13.20)	
Latin America vs Western Europe	1.33 (0.43–4.07)	
US/Canada/Australia vs Western Europe	0.31 (0.19–0.49)	
Prior systemic therapy		0.3428
No vs yes	0.86 (0.64–1.17)	
Baseline eGFR (mL/min)		0.0389
60–<90 vs <60	1.40 (0.18–10.88)	
60–<90 vs ≥90	0.62 (0.42–0.90)	
<60 vs ≥90	0.44 (0.06–3.41)	
Confirmed ALC <1.0 (10^3/mm^3) prior to event	0.69 (0.32–1.50)	0.3502
Medical history		<0.0001
No vs yes	0.16 (0.11–0.23)	

ALC absolute lymphocyte count, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *QD* once daily.

Table S7. Proportion of patient with eczema herpeticum by IGA category

	Abrocitinib 100 mg ***N* = 885**	**Abrocitinib 200 mg** ***N* = 1971**
n (%)[a] of patients with events	15 (1.7)	8 (0.4)
IGA,[b,c] *n* (%)		
0	0	0
1	2 (13.3)	0
2	5 (33.3)	4 (50.0)
3	7 (46.7)	2 (25.0)
4	1 (6.7)	2 (25.0)

IGA Investigator's Global Assessment.

[a]Percentage is based on total number of patients in each treatment group.

[b]IGA is assessed on or prior to first onset date of the treatment-emergent adverse event, or within 7 days of the first onset date, whichever is closer to the first onset date. If equal distance, then the later one was chosen.

[c]Percentage is based on number of patients with event in each treatment group.

Table S8. Details of patients who reported serious adverse events adjudicated as pulmonary embolism

Baseline Age	**Race**	**Sex**	**Start Day**	**End Day**	**Risk factors**	**Platelets (10^3/mm^3)**
68	White	Female	98	102	Older age, estrogen use for 10 years	• BL: 378 • Day 30: 242 • Day 85: 262 • Day 94: 203
16	Black	Male	565	574	Obesity (BMI 44.1) and family history: PE in brother (at age 18), paternal grandmother (PE), maternal aunt (PE and recurrent thromboembolisms beginning in her 30s), and maternal great-grandmother (VTE)	• BL: 314 • Day 31:126 • Day 508: 202 • Day 592: 461
54	White	Male	80	155	None identified	BL: 157 Day 29: 107 Day 57:131 Day 86: 176

BL baseline, *BMI* body mass index, *PE* pulmonary embolism, *VTE* venous thromboembolism.

Table S9. Shift table of patients in LDL-C categories by visit in the placebo-controlled cohort

Analysis Visit	Post-Baseline	Placebo *N* = 342 *n* (%)				Abrocitinib 100 mg *N* = 608 *n* (%)				Abrocitinib 200 mg *N* = 590 *n* (%)			
		<130	**≥130–<160**	**≥160–<190**	**≥190**	**<130**	**≥130–<160**	**≥160–<190**	**≥190**	**<130**	**≥130–<160**	**≥160–<190**	**≥190**
Week 4	<130	201 (79.8)	16 (6.3)	1 (0.4)	0	350 (71.3)	13 (2.6)	4 (0.8)	0	351 (73.1)	13 (2.7)	3 (0.6)	0
	≥130–<160	10 (4.0)	13 (5.2)	1 (0.4)	0	46 (9.4)	31 (6.3)	7 (1.4)	1 (0.2)	49 (10.2)	13 (2.7)	3 (0.6)	1 (0.2)
	≥160–<190	2 (0.8)	0	4 (1.6)	2 (0.8)	7 (1.4)	16 (3.3)	6 (1.2)	0	10 (2.1)	12 (2.5)	4 (0.8)	0
	≥190	0	1 (0.4)	0	1 (0.4)	1 (0.2)	3 (0.6)	3 (0.6)	3 (0.6)	3 (0.6)	8 (1.7)	6 (1.3)	4 (0.8)
Week 12	<130	107 (77.5)	8 (5.8)	1 (0.7)	0	192 (67.1)	12 (4.2)	2 (0.7)	1 (0.3)	224 (76.7)	4 (1.4)	0	0
	≥130–<160	6 (4.3)	12 (8.7)	1 (0.7)	0	28 (9.8)	20 (7.0)	4 (1.4)	0	26 (8.9)	10 (3.4)	3 (1.0)	1 (0.3)
	≥160–<190	0	2 (1.4)	0	1 (0.7)	4 (1.4)	10 (3.5)	6 (2.1)	0	8 (2.7)	5 (1.7)	6 (2.1)	0
	≥190	0	0	0	0	1 (0.3)	3 (1.0)	2 (0.7)	1 (0.3)	0	1 (0.3)	1 (0.3)	3 (1.0)
Week 16	<130	99 (76.7)	8 (6.2)	1 (0.8)	0	162 (69.8)	8 (3.4)	0	0	162 (69.8)	7 (3.0)	0	0
	≥130–<160	7 (5.4)	7 (5.4)	2 (1.6)	0	24 (10.3)	9 (3.9)	5 (2.2)	0	29 (12.5)	7 (3.0)	2 (0.9)	0
	≥160–<190	0	2 (1.6)	2 (1.6)	0	4 (1.7)	9 (3.9)	7 (3.0)	1 (0.4)	7 (3.0)	6 (2.6)	3 (1.3)	1 (0.4)
	≥190	0	0	0	1 (0.8)	0	3 (1.3)	0	0	2 (0.9)	3 (1.3)	3 (1.3)	0

LDL low-density lipoprotein.

N = number of patients in Safety Analysis Set population (all patients who received ≥1 dose of abrocitinib).

Baseline was defined as the last measurement prior to first dosing (day 1). Patients missing baseline were excluded. Percentage used number of patients with non-missing LDL cholesterol results and baseline in each analysis visit as denominator.