Supplementary Online Content

Silverberg JI, Simpson EL, Thyssen JP, et al. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol*. Published online June 3, 2020. doi:10.1001/jamadermatol.2020.1406

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

eMethods. Additional Exclusion Criteria, Sample Size Calculation, Bonferroni-Based Procedure for Testing the Coprimary and Key Secondary End Points, and Additional Statistical Analyses

Additional Exclusion Criteria

Patients with acute or chronic medical or psychiatric conditions (including recent or active suicidal ideation or behavior) that could increase the risk associated with study participation or that could confound the interpretation of results; patients vaccinated or exposed to a live or attenuated vaccine within the 6 weeks before the first study drug dose, or patients expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks after discontinuation of study drug; adolescent patients without documented evidence of having received ≥1 dose of the varicella vaccine or with no prior exposure to varicella zoster virus; patients with history of disseminated herpes zoster or disseminated herpes simplex or a recurrent localized, dermatomal herpes zoster; and patients with active or inadequately treated latent infection with *Mycobacterium tuberculosis* were excluded from the study.

Sample Size Calculation

A sample size of 375 patients (150, 150, and 75 patients randomly assigned to receive 200 mg, 100 mg, and placebo, respectively) was determined to provide ≥95% power to detect ≥20% difference in IGA response rates between either abrocitinib dose and placebo, assuming a placebo response rate of 6% at week 12, and ≥99% power to detect ≥30% difference in EASI-75 response rate between either abrocitinib dose and placebo, assuming a placebo response rate of 15% at week 12.

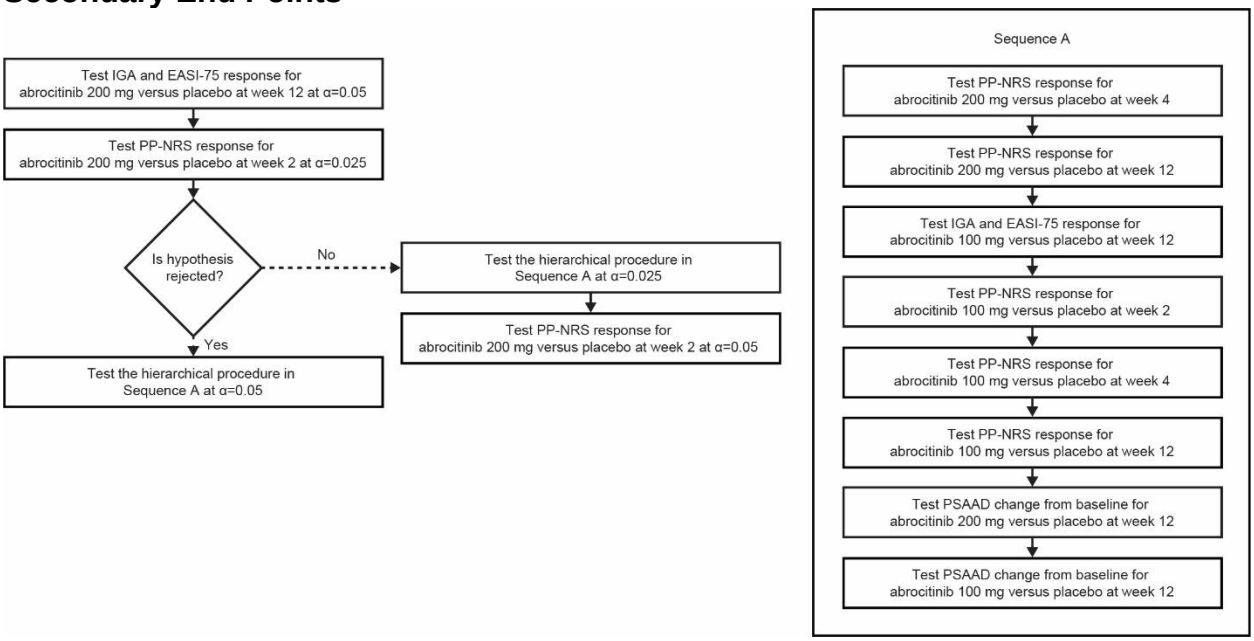
Bonferroni-Based Procedure for Testing the Coprimary and Key Secondary End Points

The Bonferroni-based procedure used in this study to test the coprimary and key secondary end points is depicted in eTable 1. Briefly, abrocitinib 200 mg and 100 mg were determined to be superior to placebo if the null hypothesis of no difference between either dose versus placebo for both coprimary end points was rejected at the 5% significance level. The procedure first tested the coprimary end points at week 12 for abrocitinib 200 mg versus placebo at a 5% significance level. No further testing was conducted if this hypothesis was not rejected. If this hypothesis was rejected, testing continued on 2 paths depending on the results of the test of PP-NRS response at week 2 for abrocitinib 200 mg versus placebo at a 2.5% significance level. If this hypothesis was rejected, the unused alpha level of 2.5% was passed onto a series of testing in Sequence A at a 5% significance level. If any hypothesis in this sequence was not rejected, the procedure stopped. If the hypothesis was not rejected, the series of testing in Sequence A was tested at a 2.5% significance level. If any hypothesis in this sequence was not rejected, the procedure stopped. If all hypotheses in this sequence were rejected, the unused alpha level of 2.5% was passed on to the testing of hypotheses for PP-NRS response at week 2 for abrocitinib 200 mg versus placebo at a 5% significance level.

Additional Statistical Analyses

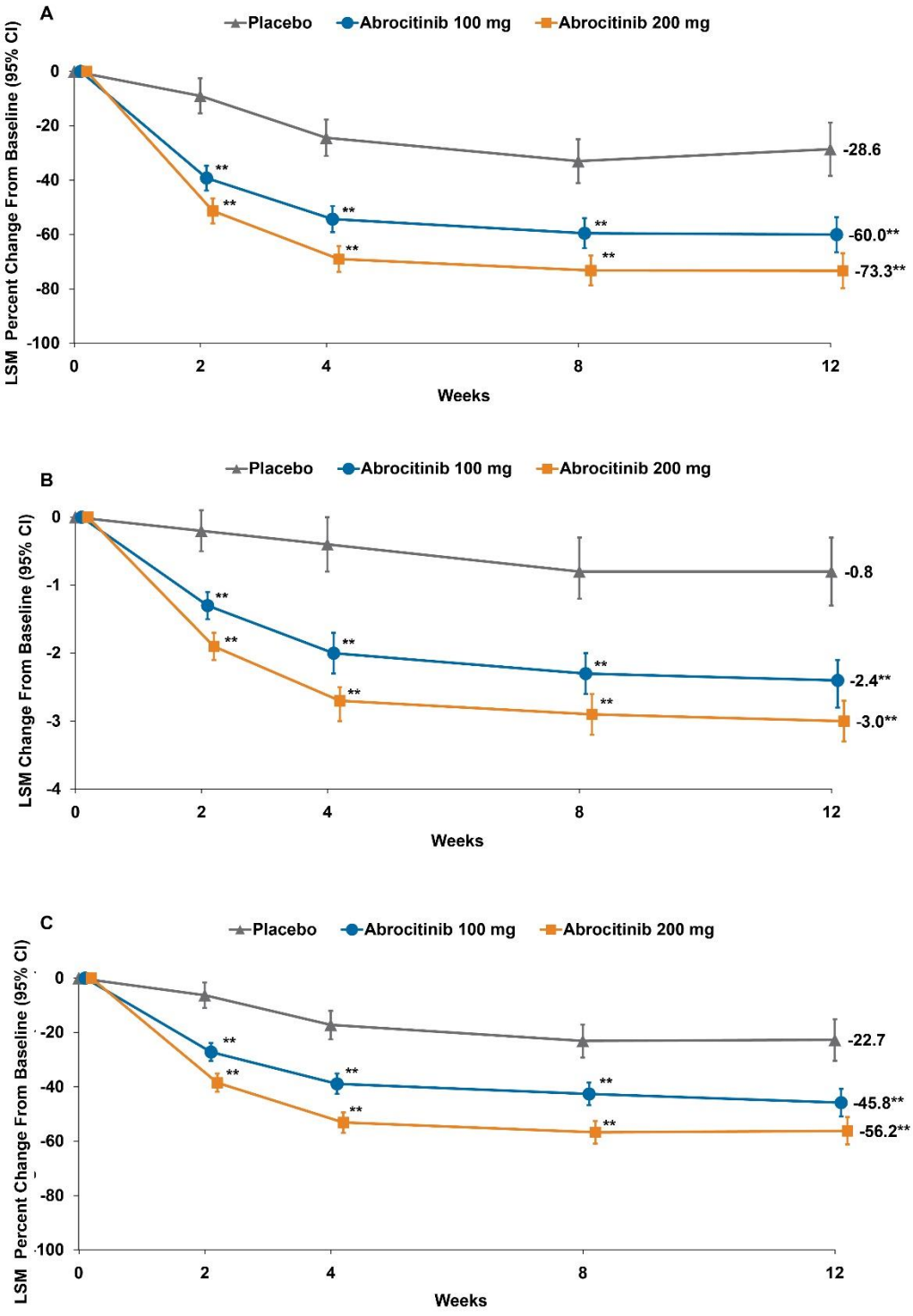
The primary analysis population for efficacy data was the full analysis set, defined as all patients randomly assigned to receive treatment who received ≥1 dose of study medication. Coprimary, key secondary, and other binary end points were analyzed using the Cochran-Mantel-Haenszel test, adjusted by randomization strata. Missing responses for patients who permanently discontinued the study were defined as nonresponders at all subsequent visits. All continuous end points were analyzed using a mixed-effects model with repeated measures (MMRM) based on all observed data. The model included fixed effects for treatment group, randomization strata, visit, treatment-by-visit interaction, and relevant baseline value. To assess the robustness of the findings from the primary analysis under various assumptions about the missing data mechanism, coprimary end points were also analyzed using the per-protocol analysis set (excluded patients with major protocol violations and who had missing responses for coprimary end points) and a tipping point analysis based on the full analysis set (imputed all missing responses). Safety was assessed in the safety analysis set, defined as all patients who received ≥1 dose of study drug. All safety data were summarized using descriptive statistics.

eFigure 1. Bonferroni-Based Procedure for Testing the Coprimary and Key Secondary End Points



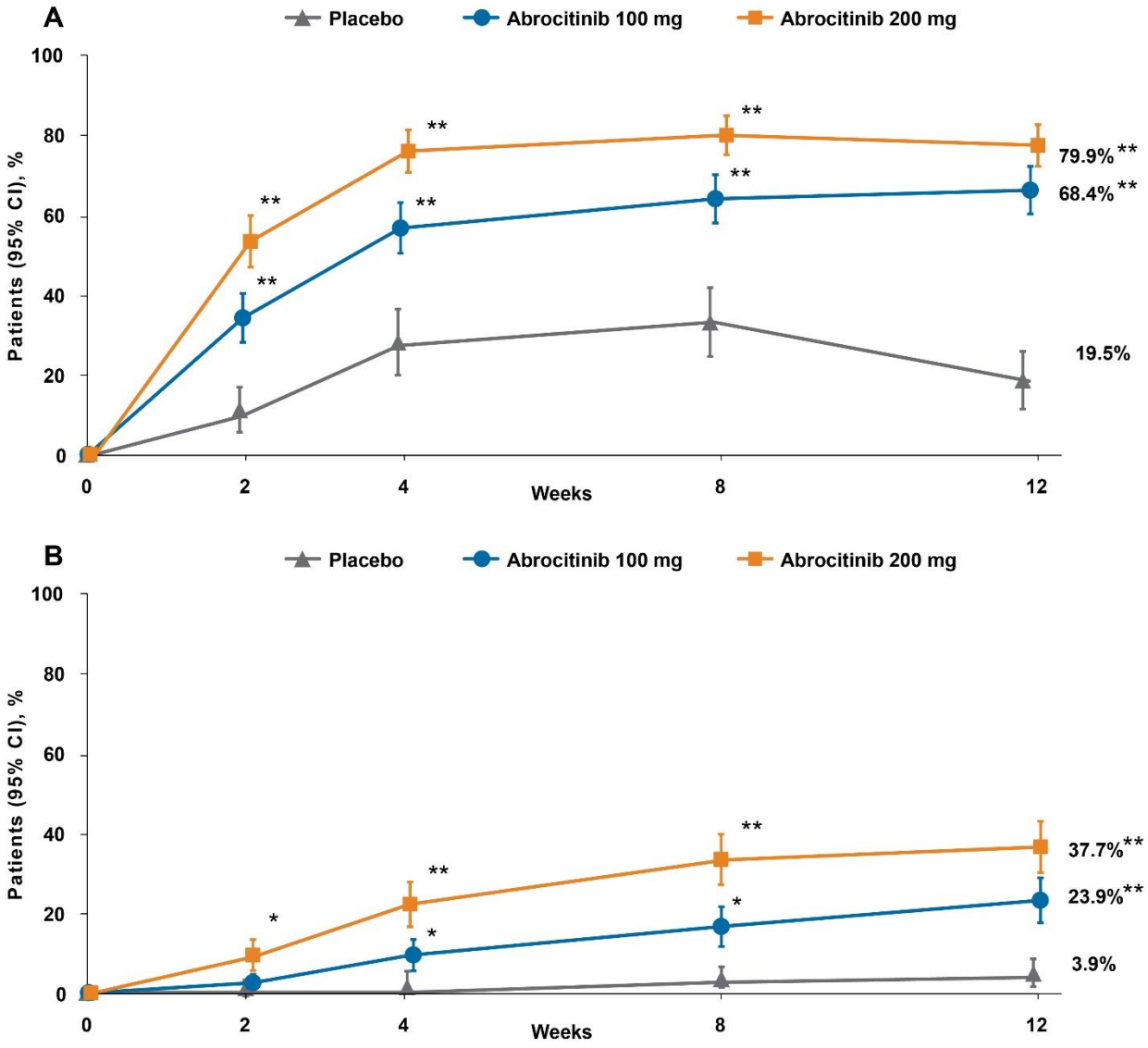
EASI-75, ≥75% improvement in Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis.
IGA response defined as clear (0) or almost clear (1) with ≥2-grade improvement from baseline.
Solid arrows indicate statistical significance has to be achieved to test the subsequent hypothesis.

eFigure 2. Change From Baseline in (A) EASI, (B) PSAAD, and (C) SCORAD



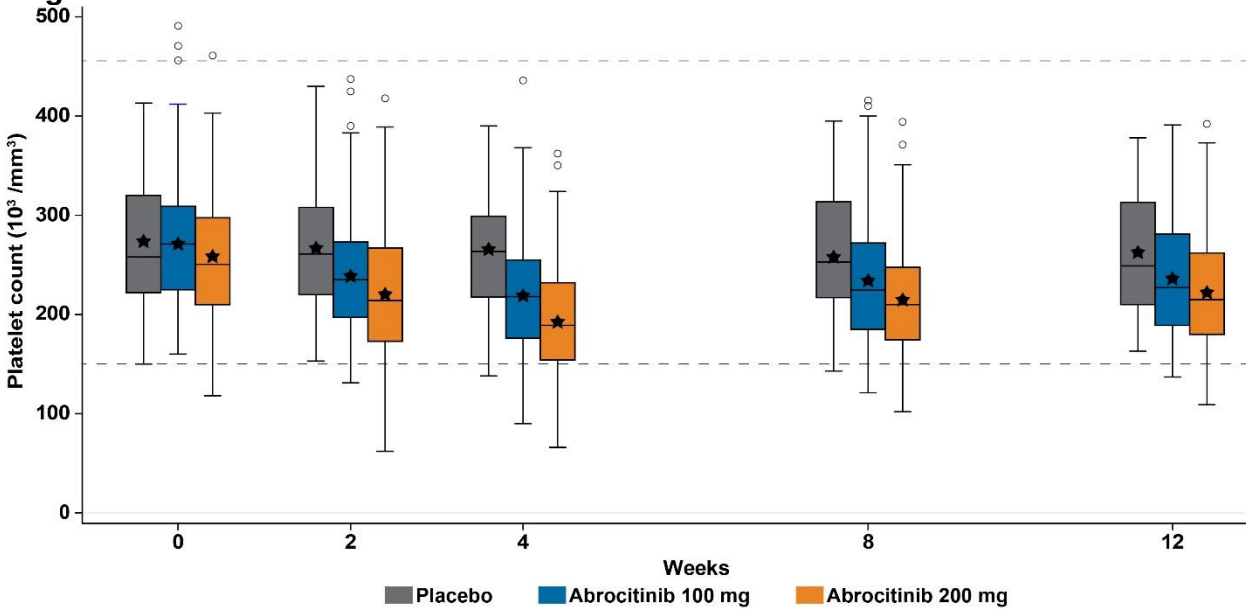
CI, confidence interval; EASI, Eczema Area and Severity Index; LSM, least-squares mean; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; SCORAD, SCORing Scoring of Atopic Dermatitis.
***P*<.0001 versus placebo. Conclusion of statistical significance was not controlled for multiplicity at any time point.

eFigure 3. Proportions of Patients Achieving (A) EASI-50 and (B) EASI-90 Responses



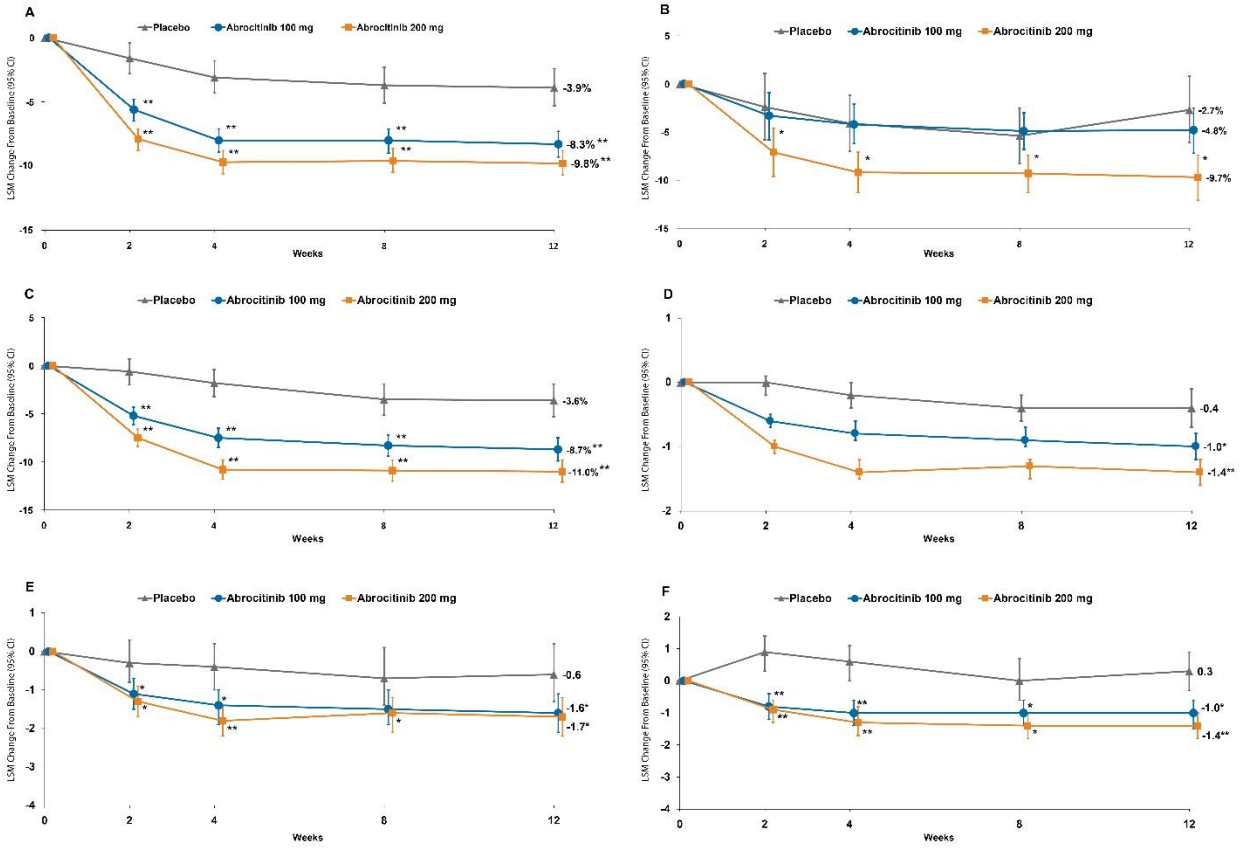
CI, confidence interval; EASI-50, ≥50% improvement in Eczema Area and Severity Index; EASI-90, ≥90% improvement in Eczema Area and Severity Index.
*P<.05 versus placebo, **P≤.0001 versus placebo. Conclusion of statistical significance was not controlled for multiplicity at any time point.

eFigure 4. Median Absolute Platelet Count



Horizontal lines represent median; stars, mean; bars, interquartile range; whiskers, 1.5-times interquartile range, circles represent outlier data for individual patients. Gray dashed lines represent the normal platelet count range (150,000/mm^3-450,000/mm^3).

eFigure 5. Patient-Reported Outcomes



Least-squares mean change from baseline in (A) DLQI, (B) CDLQI, (C) POEM, (D) PtGA, (E) HADS anxiety, and (F) HADS depression
CDLQI, Children's Dermatology Life Quality Index; CI, confidence interval; DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; LSM, least-squares mean; POEM, Patient-Oriented Eczema Measure; PtGA, Patient Global Assessment.
*P<.05, **P≤.0001 versus placebo. Conclusion of statistical significance was not controlled for multiplicity.

eTable 1. Summary of Efficacy End Points and Patient-Reported Outcomes

End Point		Placebo	Abrocitinib	
			100 mg	200 mg
Coprimary end points				
IGA response				
Week 12	Responders, n/N (%)	7/77 (9.1)	44/155 (28.4)	59/155 (38.1)
	Difference from placebo (95% CI), %	–	19.3 (9.6-29.0)	28.7 (18.6-38.8)
	P value	–	0.0008	<.0001
EASI-75 response				
Week 12	Responders, n/N (%)	8/77 (10.4)	69/155 (44.5)	94/154 (61.0)
	Difference from placebo (95% CI), %	–	33.9 (23.3-44.4)	50.5 (40.0-60.9)
	P value	–	<.0001	<.0001
Key secondary end points				
PP-NRS response (≥4-point improvement from baseline)				
Week 2	Responders, n/N (%)	3/76 (3.9)	36/156 (23.1)	54/153 (35.3)
	Difference from placebo (95% CI), %	–	19.2 (11.0-27.4)	31.2 (22.3-40.2)
	P value	–	0.0002	<0.0001
Week 4	Responders, n/N (%)	3/76 (4.0)	52/156 (33.4)	81/153 (52.8)
	Difference from placebo (95% CI), %	–	29.5 (20.5-38.4)	48.8 (39.5-58.2)
	P value	–	<.0001	<.0001
Week 12	Responders, %	9/76 (11.5)	71/156 (45.2)	85/153 (55.3)
	Difference from placebo (95% CI), %	–	33.7 (22.8-44.7)	43.9 (32.9-55.0)
	P value	–	<.0001	<.0001
PSAAD change from baseline				
Week 12	N	77	156	155
	LSM change from baseline (95% CI)	−0.8 (−1.3 to −0.3)	−2.4 (−2.8 to −2.1)	−3.0 (−3.3 to −2.7)

	LSM difference from placebo (95% CI)	–	−1.7 (−2.3 to −1.1)	−2.2 (−2.8 to −1.6)
	P value	–	<0.0001	<0.0001
Other secondary end points				
EASI-90 response				
Week 12	Responders, n/N (%)	3/77 (3.9)	37/155 (23.9)	58/154 (37.7)
	Difference from placebo (95% CI), %	–	20.1 (11.9-28.3)	33.5 (24.6-42.5)
EASI-50 response				
Week 12	Responders, n/N (%)	15/77 (19.5)	106/155 (68.4)	123/154 (79.9)
	Difference from placebo (95% CI), %	–	48.7 (37.2-60.1)	60.1 (49.1-71.0)
PP-NRS response (≥4-point improvement from baseline)				
Week 8	Responders, n/N (%)	9/76 (12.0)	63/156 (40.4)	83/153 (54.4)
	Difference from placebo (95% CI), %	–	28.5 (17.8-39.3)	42.4 (31.4-53.4)
DLQI change from baseline				
Week 12	N	70	140	139
	LSM change from baseline (95% CI)	−3.9 (−5.3 to −2.4)	−8.3 (−9.3 to −7.3)	−9.8 (−10.7 to −8.8)
	LSM difference from placebo (95% CI)	–	−4.4 (−6.2 to −2.7)	−5.9 (−7.7 to −4.2)
CDLQI change from baseline				
Week 12	N	8	16	15
	LSM change from baseline (95% CI)	−2.7 (−6.1 to 0.8)	−4.8 (−7.2 to −2.5)	−9.7 (−12.1 to −7.4)
	LSM difference from placebo (95% CI)	–	−2.2 (−6.3 to 2.0)	−7.1 (−11.2 to −2.9)
POEM change from baseline				
Week 12	N	78	156	154
	LSM change from baseline (95% CI)	−3.6 (−5.3 to −1.9)	−8.7 (−9.9 to −7.5)	−11.0 (−12.1 to −9.8)
	LSM difference from placebo (95% CI)	–	−5.1 (−7.2 to −3.1)	−7.4 (−9.5 to −5.3)

PtGA change from baseline				
Week 12	N	78	157	154
	LSM change from baseline (95% CI)	−0.4 (−0.7 to −0.1)	−1.0 (−1.2 to −0.8)	−1.4 (−1.6 to −1.2)
	LSM difference from placebo (95% CI)	–	−0.6 (−0.9 to −0.3)	−1.0 (−1.3 to −0.7)
HADS anxiety change from baseline				
Week 12	N	78	156	153
	LSM change from baseline (95% CI)	−0.6 (−1.3 to 0.2)	−1.6 (−2.1 to −1.1)	−1.7 (−2.2 to −1.2)
	LSM difference from placebo (95% CI)	–	−1.0 (−1.9 to −0.1)	−1.1 (−2.0 to −0.2)
HADS depression change from baseline				
Week 12	N	78	156	153
	LSM change from baseline (95% CI)	0.3 (−0.3 to 0.9)	−1.0 (−1.5 to −0.6)	−1.4 (−1.8 to -1.0)
	LSM difference from placebo (95% CI)	–	−1.3 (−2.1 to −0.6)	−1.7 (−2.5 to −0.9)

CDLQI, Children's Dermatology Life Quality Index; CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; LSM, least squares mean; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA, Patient Global Assessment.

P values for coprimary and key secondary efficacy controlled for multiplicity; statistical testing of other secondary end points not controlled for multiplicity and P values not provided. For PP-NRS response, estimated number of responders, response rates, and 95% CIs are based on a multiple-imputation procedure accounting for any other missing data that was not already handled by nonresponder imputation.

eTable 2. Sensitivity Analysis Using the Per-Protocol Analysis Set for Coprimary End Points

		Placebo	Abrocitinib	
			100 mg	200 mg
Proportion of patients achieving IGA response at week 12				
FAS	Responders (95% CI), %	9.1 (2.7-15.5)	28.4 (21.3-35.5)	38.1 (30.4-45.7)
	Difference from placebo (95% CI), %	–	19.3 (9.6-29.0)	28.7 (18.6-38.8)
PPAS	Responders (95% CI), %	11.5 (2.9-20.2)	30.5 (22.5-38.4)	38.5 (30.1-46.8)
	Difference from placebo (95% CI), %	–	18.8 (6.8-30.8)	26.7 (14.4-38.9)
Proportion of patients achieving EASI-75 response at week 12				
FAS	Responders (95% CI), %	10.4 (3.6-17.2)	44.5 (36.7-52.3)	61.0 (53.3-68.7)
	Difference from placebo (95% CI), %	–	33.9 (23.3-44.4)	50.5 (40.0-60.9)
PPAS	Responders (95% CI), %	13.5 (4.2-22.7)	49.2 (40.6-57.9)	62.3 (54.0-70.6)
	Difference from placebo (95% CI), %	–	35.6 (22.6-48.5)	48.7 (35.9-61.4)

CI, confidence interval; EASI, Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment; PPAS, per-protocol analysis set.

eTable 3. Sensitivity Analysis Using Tipping Point Analysis for Coprimary End Points

Weight for Placebo Response Probability		Placebo	Abrocitinib	
			100 mg	200 mg
Estimated IGA response rate at week 12				
0.00	Estimated response (95% CI), %	13.0 (4.3-21.7)	31.3 (23.7-38.9)	39.7 (31.8-47.5)
	Difference from placebo (95% CI), %		18.3 (6.7-29.9)	26.5 (14.6-38.3)
0.25	Estimated response (95% CI), %		30.8 (23.2-38.3)	39.3 (31.5-47.2)
	Difference from placebo (95% CI), %		17.8 (6.3-29.3)	26.1 (14.3-38.0)
0.50	Estimated response (95% CI), %		30.3 (22.8-37.7)	39.1 (31.2-46.9)
	Difference from placebo (95% CI), %		17.3 (5.9-28.7)	25.9 (14.1-37.6)
0.75	Estimated response (95% CI), %		29.8 (22.4-37.1)	38.8 (31.0-46.5)
	Difference from placebo (95% CI), %		16.8 (5.5-28.1)	25.6 (13.9-37.2)
1.00	Estimated response (95% CI), %		29.3 (21.9-36.6)	38.4 (30.7-46.2)
	Difference from placebo (95% CI), %		16.3 (5.0-27.5)	25.2 (13.6-36.8)
Estimated EASI-75 response rate at week 12				
0.00	Estimated response (95% CI), %	13.6 (4.9-22.2)	49.5 (41.4-57.6)	64.0 (56.2-71.7)
	Difference from placebo (95% CI), %		35.8 (23.9-47.8)	50.2 (38.5-61.9)
0.25	Estimated response (95% CI), %		48.5 (40.4-56.7)	63.2 (55.4-71.0)
	Difference from placebo (95% CI), %		34.9 (23.0-46.7)	49.5 (37.8-61.1)
0.50	Estimated response (95% CI), %		47.5 (39.4-55.7)	62.5 (54.7-70.3)
	Difference from placebo (95% CI), %		33.9 (22.0-45.7)	48.7 (37.1-60.4)
0.75	Estimated response (95% CI), %		46.5 (38.4-54.6)	61.7 (54.0-69.5)
	Difference from placebo (95% CI), %		32.9 (21.1-44.6)	48.0 (36.3-59.6)
1.00	Estimated response (95% CI), %		45.5 (37.5-53.6)	61.0 (53.3-68.7)
	Difference from placebo (95% CI), %		31.9 (20.1-43.6)	47.2 (35.6-58.9)

CI, confidence interval; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment.

eTable 4. Proportion of Patients Achieving Coprimary End Points by Age Group

			Placebo	Abrocitinib	
				100 mg	200 mg
Proportion of patients achieving IGA response at week 12					
<18 years	Responders (95% CI), %		0.0 (0.0-41.0)	12.5 (0.0-28.7)	40.0 (15.2-64.8)
	Difference from placebo (95% CI), %		–	12.5 (-11.7 to 36.7)	40.0 (9.4-70.6)
≥18 years	Responders (95% CI), %		10.0 (3.0-17.0)	30.2 (22.6-37.8)	37.9 (29.8-45.9)
	Difference from placebo (95% CI), %		–	20.2 (9.8-30.6)	27.9 (17.2-38.5)
Proportion of patients achieving EASI-75 response at week 12					
<18 years	Responders (95% CI), %		0.0 (0.0-41.0)	43.8 (19.4-68.1)	60.0 (35.2-84.8)
	Difference from placebo (95% CI), %		–	43.8 (13.5-74.0)	60.0 (29.4-90.6)
≥18 years	Responders (95% CI), %		11.4 (4.0-18.9)	44.6 (36.3-52.9)	61.2 (53.0-69.3)
	Difference from placebo (95% CI), %		–	33.2 (22.0-44.3)	49.7 (38.7-60.7)

CI, confidence interval; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment.

eTable 5. Serious Adverse Events of Any Causality

No. (%)	Placebo N = 78	Abrocitinib	
		100 mg N = 158	200 mg N = 155
Sudden death	0	1 (0.6)	0
Anaphylactic shock	0	0	1 (0.6)
Eczema herpeticum	1 (1.3)[a]	0	0
Herpangina	0	1 (0.6)[a]	0
Osteomyelitis bacterial	0	1 (0.6)	0
Pneumonia	0	1 (0.6)[a]	0
Staphylococcal bacteremia	0	1 (0.6)	0
Staphylococcal infection	1 (1.3)[a]	0	0
Femoral neck fracture	0	0	1 (0.6)
Dermatitis atopic	0	1 (0.6)	0

[a]Adverse event considered related to treatment.