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Sponsor: Pfizer Inc.

Investigational Product: PF-04965842 (Abrocitinib)

Clinical Study Report Synopsis: Protocol B7451036

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Investigating the Efficacy and Safety of PF-04965842 Co-Administered With Background Medicated Topical Therapy in Adolescent Participants 12 to <18 Years of Age With Moderate-to-Severe Atopic Dermatitis

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Centers: Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: None.

Study Initiation Date: 18 February 2019

Study Completion Date: 08 April 2020

Report Date: 10 September 2020

Previous Report Date(s): Not Applicable

Phase of Development: Phase 3

Primary and Secondary Study Objectives and Endpoints:

Table S1. Study Objectives and Endpoints

Type	Objectives	Endpoints
Primary		
Efficacy	To assess the efficacy of PF-04965842 compared with placebo when co-administered with background medicated topical therapy in adolescent participants 12 to <18 years of age with moderate-to-severe atopic dermatitis (AD).	Co-primary endpoints: • Response based on the Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 12; • Response based on the Eczema Area and Severity Index (EASI) ≥75% improvement from baseline (EASI-75) at Week 12.
Secondary		
Efficacy	To evaluate the effect of PF-04965842 co-administered with background medicated topical therapy on additional efficacy endpoints and patient reported outcomes (PRO) over time in adolescent participants	Key Secondary Endpoints: • Response based on at least 4 points improvement in the Peak Pruritis Numerical Rating Scale (PP-NRS) from baseline at Weeks 2, 4, and 12; • Change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD)

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Table S1. Study Objectives and Endpoints

Type	Objectives	Endpoints
	12 to <18 years of age with moderate-to-severe AD.	total score at Week 12.
		Secondary Efficacy Endpoints: • Response based on at least 4 points improvement in the PP-NRS from baseline at all scheduled time points other than Weeks 2, 4 and 12; • Time to achieve at least 4 points improvement in the PP-NRS from baseline; • Response based on the EASI-75 at all scheduled time points except Week 12; • Response based on the IGA of clear (0) or almost clear (1) and 2-point reduction from baseline at all scheduled time points except Week 12.
		Other Efficacy Endpoints: • Response based on a ≥50%, ≥90% and 100% improvement in the EASI total score (EASI-50, EASI-90 and EASI-100) at all scheduled time points; • Change from baseline and percent change from baseline in the percentage body surface area (BSA) affected at all scheduled time points; • Response based on affected BSA <5% at Week 12; • Response based on a ≥50% and ≥75% improvement in Scoring Atopic Dermatitis (SCORAD50, SCORAD75) from baseline at all scheduled time points; • Percent change from baseline in EASI at all scheduled time points; • Change from baseline and percent change from baseline at all scheduled time points in SCORAD total score and subjective assessments of sleep loss; • Percent change from baseline in PP-NRS at all scheduled time points; • Week 12 corticosteroid-free days.
PROs		• Change from baseline at Week 12 in Children's Dermatology Life Quality Index (CDLQI) and at all other scheduled time points; • Change from baseline at Week 12 in Hospital Anxiety and Depression Scale (HADS) and at all other scheduled time points; • Change from baseline at Week 12 in Patient-Oriented Eczema Measure (POEM) and at all other scheduled time points; • Change from baseline at Week 12 in Dermatitis Family Impact (DFI) questionnaire;

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Table S1. Study Objectives and Endpoints

Type	Objectives	Endpoints
		• Change from baseline of Patient Global Assessment (PtGA) at Week 12 and at all other scheduled time points; • Change from baseline of EuroQol Quality of Life 5 Dimension Youth Scale (EQ-5D-Y) at Week 12 and at all other scheduled time points; • Change from baseline of Pediatric Functional Assessment of Chronic Illness Therapy Fatigue Scale (Peds-FACIT-F) at Week 12 and at all other scheduled time points; • Response based on achieving ≥2.5-point improvement from baseline in the CDLQI score at all scheduled time points; • Response based on the PtGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at all scheduled time points.
Safety Objective and Endpoints		
Safety	To evaluate the safety and tolerability of PF-04965842 co-administered with background medicated topical therapy in adolescent participants 12 to <18 years of age with moderate-to-severe AD.	• Incidence of treatment-emergent adverse event (TEAEs); • Incidence of serious adverse event (SAEs); • Incidence of adverse event (AEs) leading to discontinuation; • The incidence of clinical abnormalities and change from baseline in clinical laboratory values, electrocardiogram (ECG) measurements, and vital signs.
Immunogenicity Sub-Study Objective and Endpoints		

Immunogenicity	To evaluate the effect of PF-04965842 on the immunogenicity to Tdap vaccine in adolescent participants 12 to <18 years of age with moderate-to-severe AD.	• Fold increase from baseline at 4 weeks post-vaccination in concentration of immunoglobulin G (IgG) against:
		  • Tetanus toxoid;
		  • Diphtheria toxoid;
		  • Pertussis toxoid;
		  • Pertactin (PRN);
		  • Filamentous hemagglutinin (FHA);
		  • Fimbriae types 2 and 3 (FIM).

Pharmacokinetic (PK) Objective and Endpoints		
PK	To evaluate the PK of PF-04965842 in adolescent participants 12 to <18 years of age with moderate-to-severe AD.	• Plasma concentrations of PF-04965842 in adolescent participants 12 to <18 years of age with moderate-to-severe AD.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, parallel-group,

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Phase 3 study to evaluate the efficacy and safety of abrocitinib in adolescent participants 12 to <18 years of age with moderate-to-severe AD. Participants were screened within 28 days prior to the first dose of study intervention to confirm study eligibility. A total of 287 participants were randomized globally from 99 sites in a 1:1:1 ratio to receive abrocitinib once daily (QD) at 200 mg, 100 mg, or placebo for 12 weeks.

Diagnosis and Main Criteria for Inclusion: Participants who met the following criteria were enrolled in this study:

- Confirmed diagnosis of AD at the screening and baseline visits according to Hanafin and Rajka criteria for AD.
- Documentation of any of the following:
  - Inadequate response to treatment with medicated topical therapy for AD for at least 4 consecutive weeks, within 6 months before the screening visit; or
  - Treatment with systemic therapy for AD within 6 months before the screening visit; or
  - Participant was a candidate for systemic therapy for AD.

  NOTE: Medicated topical therapy was defined as a topical product that contained an active pharmaceutical ingredient indicated for the treatment of AD (irrespective of whether it was an over-the-counter [OTC] or prescribed product).
- Moderate-to-severe AD (must have fulfilled all of the following criteria: affected BSA ≥10%, IGA ≥3, EASI ≥16, and PP-NRS ≥4 at the baseline visit).
- During the last 7 days prior to Day 1, for the treatment of AD, the participant must have used only non-medicated topical therapy (ie, emollient) at least twice daily, without other active ingredients indicated to treat AD, or other additives which could have affected AD (eg, hyaluronic acid, urea, ceramide or filaggrin degradation products), with response to treatment remaining inadequate at baseline.
- Body weight ≥25 kg.

Study Treatment: Abrocitinib was administered orally at doses of 100 mg or 200 mg given QD for 12 weeks based on treatment assignment. In addition, one treatment group was assigned to receive abrocitinib-matching placebo. Study drug information is provided in Table S2.

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Table S2. Study Drug Information

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
Placebo for PF-04965842 Round White Film Coated Tablet (9 mm)	N/A	17-004645	0 mg	Tablet
PF-04965842 100 mg Round White Film Coated Tablet (DC)	N/A	18-001885	100 mg	Tablet
Placebo for PF-04965842 Round White Film Coated Tablet (9 mm)	N/A	17-003139	0 mg	Tablet
PF-04965842 100 mg Round White Film Coated Tablet (DC)	N/A	18-002731	100 mg	Tablet
PF-04965842 100 mg Round White Film Coated Tablet (DC)	N/A	18-001886	100 mg	Tablet
Placebo for PF-04965842 Round White Film Coated Tablet (9 mm)	19-DP-00021	19-001255	0 mg	Tablet

Efficacy Evaluations:

The primary endpoints are:

- IGA response: Response based on the IGA score of clear (0) or almost clear (1); and a reduction from baseline of ≥2 points at Week 12.
- EASI-75 response: Response based on the EASI ≥75% improvement from baseline (EASI-75) at Week 12.

The key secondary efficacy endpoints are:

- Response based on ≥4 points improvement from baseline in the PP-NRS from baseline at Weeks 2, 4, and 12.
- Change from baseline in PSAAD total score at Week 12.

The secondary efficacy endpoints are:

- Response based on at least 4 points improvement in the PP-NRS from baseline at all scheduled time points other than Weeks 2, 4 and 12.
- Time to achieve at least 4 points improvement in the PP-NRS from baseline.
- Response based on the EASI-75 at all scheduled time points except Week 12.
- Response based on the IGA of clear (0) or almost clear (1) and 2-point reduction from baseline at all scheduled time points except Week 12.

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- Response based on a ≥50%, ≥90% and 100% improvement in the EASI total score (EASI-50, EASI-90 and EASI-100) at all scheduled time points.
- Change from baseline and percent change from baseline in the percentage BSA affected at all scheduled time points.
- Response based on BSA <5% at Week 12.
- Response based on a ≥50% and ≥75% improvement in SCORAD (SCORAD50, SCORAD75) from baseline at all scheduled time points.
- Percent change from baseline in EASI at all scheduled time points.
- Change from baseline and percent change from baseline at all scheduled time points in SCORAD total score and subjective assessments of sleep loss.
- Percent change from baseline in PP-NRS at all scheduled time points.
- Week 12 corticosteroid-free days.

The PRO secondary endpoints are:

- Change from baseline at Week 12 in CDLQI and at all other scheduled time points.
- Change from baseline at Week 12 in HADS and at all other scheduled time points.
- Change from baseline at Week 12 in POEM and at all other scheduled time points.
- Change from baseline at Week 12 in DFI questionnaire.
- Change from baseline of PtGA at Week 12 and at all other scheduled time points.
- Change from baseline of EQ-5D-Y at Week 12 and at all other scheduled time points.
- Change from baseline of Peds-FACIT-F at Week 12 and at all other scheduled time points.
- Response based on achieving ≥2.5-point improvement from baseline in the CDLQI score at all scheduled time points.
- Response based on the PtGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at all scheduled time points.

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Pharmacokinetic and Immunogenicity Sub-Study Evaluations:

PK: Blood samples (3 mL) to provide minimum 1 mL of plasma for PK analysis were collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) at Day 57 pre-dose and Day 85 post-dose. PK plasma specimens were assayed for abrocitinib using validated analytical methods.

Immunogenicity Sub-Study: This sub-study was to evaluate the effect of abrocitinib on immunogenicity to Tdap vaccine in adolescent participants.

Safety Evaluations: Safety evaluations included incidences of TEAEs, SAEs, AEs leading to discontinuation, clinical abnormalities, ECG measurements, and vital signs.

Statistical Methods:

Efficacy: Abrocitinib 200 mg QD was declared superior to placebo if the null hypothesis of no difference between abrocitinib 200 mg QD versus placebo for both co-primary endpoints was rejected at the 5% significance level. Similarly, abrocitinib 100 mg QD was declared superior to placebo if the null hypothesis of no difference between abrocitinib 100 mg QD versus placebo for both co-primary endpoints was rejected at the significance level specified below.

The familywise Type-I error rate for assessing the co-primary and key secondary endpoints was strongly controlled at 5% (2-sided) using a sequential, Bonferroni-based iterative multiple testing procedure.

The procedure first assessed the co-primary endpoints (IGA and EASI-75 at Week 12 for 200 mg QD versus placebo) at the 5% level. If this hypothesis was not rejected, then all subsequent hypotheses was not considered statistically significant. If this hypothesis was rejected, then assessing for statistical significance continued as follows:

- The hypothesis for severity of pruritus (PP-NRS4) 200 mg QD versus placebo at Week 2 was assessed at the 2.5% level. If this hypothesis was rejected, then the unused alpha level of 2.5% was passed on to the assessment for the key secondary endpoints and the co-primary endpoints for 100 mg QD versus placebo, in the order specified in Sequence A at a 5% significance level. All subsequent hypotheses from any point where a hypothesis cannot be rejected were not considered statistically significant.

- If the hypothesis for severity of pruritus (PP-NRS4) 200 mg QD versus placebo at Week 2) was not rejected at the 2.5% level, then the hypotheses for the key secondary endpoints and the co-primary endpoints for 100 mg QD versus placebo, in the order specified in Sequence A were assessed at a 2.5% significance level. If all hypotheses in this sequence were rejected, then the unused alpha level of 2.5% was passed on to the assessment of the hypothesis for severity of pruritus (200 mg QD versus placebo)

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at Week 2 at the 5% level. All subsequent hypotheses from any point where a hypothesis cannot be rejected were not considered statistically significant.

Estimates of the pairwise differences along with its 2-sided 95% confidence interval (CI) were provided among the active treatment groups, abrocitinib 200 mg QD, abrocitinib 100 mg QD, and placebo.

PK: Plasma concentration data for abrocitinib were summarized through appropriate data tabulations, descriptive statistics and graphical presentation.

Immunogenicity Sub-Study: For the fold increase 4 weeks post-vaccination the ratio of concentration values was calculated. Ratio values were logarithmically transformed for analysis purposes. The geometric mean fold rise (GMFR) of these fold rises was calculated for each treatment arm.

Safety: All safety data were summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations.

RESULTS

Subject Disposition and Demography:

A total of 408 participants were screened, and 287 subjects were randomized. There were 2 participants who randomized to the abrocitinib 200 mg group were not treated.

The disposition events summary, including reasons for discontinuation, are presented in Table S3. Most participants completed Week 12 of the study; discontinuations were low at 3.2% to 6.3% across the treatment groups with highest proportion in the placebo group.

One participant lost to follow-up as a result of Corona Virus Disease 2019 (COVID-19) impact.

Table S3. Disposition Events Summary - Safety Analysis Set

Number (%) of Subjects	Placebo (N=96) n (%)	PF-04965842 100mg QD (N=95) n (%)	PF-04965842 200mg QD (N=94) n (%)
Discontinued	6 (6.3)	3 (3.2)	3 (3.2)
Adverse Event	2 (2.1)	1 (1.1)	2 (2.1)
Lost to Follow-Up	2 (2.1)	1 (1.1)	0
Protocol Deviation	0	0	1 (1.1)

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Table S3. Disposition Events Summary - Safety Analysis Set

Number (%) of Subjects	Placebo (N=96) n (%)	PF-04965842 100mg QD (N=95) n (%)	PF-04965842 200mg QD (N=94) n (%)
Withdrawal By Parent/Guardian	1 (1.0)	1 (1.1)	0
Other	1 (1.0)	0	0
Completed	90 (93.8)	92 (96.8)	91 (96.8)

Completed means completed 12 weeks treatment.
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2020 (11:13) Source Data: adds Output File: ./nda1_cdisc/B7451036/adds_s001 Date of Generation: 18MAY2020 (23:38)
Table 14.1.1.2.1 is for Pfizer internal use.

Baseline demographic characteristics were balanced across treatment groups. The median age was 15.0 years and there were 50.9% males. Majority of the participants were White (56.1%) and Asian (33.0%).

Baseline disease characteristics were balanced across treatment groups. Randomized participants were representative of the moderate (61.4%) or severe (38.6%) AD population at baseline per the IGA score; also, the median EASI was 25.6 and median %BSA was 45.5%.

The baseline PRO values were representative of a high burden of disease and impact on QoL. Median CDLQI values were similar across groups, ranging from 13.0 to 14.0. Median POEM values were also similar across groups, ranging from 20.0 to 21.0.

Efficacy Results:

Co-Primary Efficacy Endpoints:

The study met both co-primary endpoints of IGA and EASI-75 responses at Week 12, demonstrating that both abrocitinib 100 mg and 200 mg treatment groups were superior to the placebo group:

- Statistically significantly higher proportion of participants achieved IGA responses for abrocitinib 100 mg (p=0.0147) and 200 mg (p=0.0030) treatment groups compared with the placebo group (Table S4).
- Statistically significantly higher proportion of participants achieved EASI-75 responses for abrocitinib 100 mg (p=0.0002) and 200 mg (p<0.0001) treatment groups compared with the placebo group (Table S5).

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Table S4. Proportion of Subjects Achieving Investigator's Global Assessment (IGA) Response of 'Clear' or 'Almost Clear' and >=2 Points Improvement from Baseline at Week 12 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
N	94	89	93
n (%)	23 (24.5)	37 (41.6)	43 (46.2)
95% CI	(15.8, 33.2)	(31.3, 51.8)	(36.1, 56.4)
Active - Placebo [1]			
Estimate (%)		16.7	20.6
95% CI		(3.5, 29.9)	(7.3, 33.9)
Two-sided P-value [2]		0.0147	0.0030
200 mg QD - 100 mg QD [1]			
Estimate (%)			3.9
95% CI			(-10.4, 18.2)

Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication.
Baseline was defined as the measurement collected on or prior to Day 1.
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; N = number of subjects in the analysis set with NRI at the specified visit; n (%) = number of subjects with response (percentage based on N); NRI = non-responder imputation.
[1] The estimate and confidence interval (CI) for difference were calculated based on the weighted average of difference for each randomization stratum using the
normal approximation of binomial proportions. The confidence interval for the response rate was based on normal approximation (or the Clopper-Pearson exact method when there were no or if all were responders).
[2] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) method adjusted by randomization strata (baseline disease severity).
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2020 (11:16) Source Data: adad Output
File: ./nda1_cdisc/B7451036/adad_s102 Date of Generation: 18MAY2020 (22:18)
Table 14.2.1.1.1.1 is for Pfizer internal use.

Table S5. Proportion of Subjects Achieving Eczema Area and Severity Index (EASI) Response >= 75% Improvement from Baseline at Week 12 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
N	94	89	93

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Table S5. Proportion of Subjects Achieving Eczema Area and Severity Index (EASI) Response >= 75% Improvement from Baseline at Week 12 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
n (%)	39 (41.5)	61 (68.5)	67 (72.0)
95% CI	(31.5, 51.4)	(58.9, 78.2)	(62.9, 81.2)
Active - Placebo [1]			
Estimate (%)		26.5	29.4
95% CI		(13.1, 39.8)	(16.3, 42.5)
Two-sided P-value [2]		0.0002	<.0001
200 mg QD - 100 mg QD [1]			
Estimate (%)			3.1
95% CI			(-9.9, 16.2)

Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication.
Baseline was defined as the measurement collected on or prior to Day 1.
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; N = number of subjects in the analysis set with NRI at the specified visit; n (%) = number of subjects with response (percentage based on N); NRI = non-responder imputation.
[1] The estimate and confidence interval (CI) for difference were calculated based on the weighted average of difference for each randomization stratum using the
normal approximation of binomial proportions. The confidence interval for the response rate was based on normal approximation (or the Clopper-Pearson exact method when there were no or if all were responders).
[2] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) method adjusted by randomization strata (baseline disease severity).
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2020 (23:29) Source Data: adea Output
File: ./nda1_cdisc/B7451036/adea_s104 Date of Generation: 18MAY2020 (23:09)
Table 14.2.1.1.3.1 is for Pfizer internal use.

Key Secondary Efficacy Endpoints:

All subsequent hypotheses (after the comparison of PP-NRS4 for abrocitinib 100 mg versus placebo at Week 4) were not considered statistically significant. Thus hypotheses (a) comparison of PP-NRS4 for abrocitinib 100 mg versus placebo at Week 12; and (b) comparison of change from baseline in the total PSAAD score for both abrocitinib doses versus placebo at Week 12 were not considered statistically significant.

Abrocitinib 200 mg group had statistically significantly greater proportion of PP-NRS4 responders compared with the placebo group at Weeks 2, 4, and 12 (Table S6). Abrocitinib 100 mg group had statistically significantly greater proportion of PP-NRS4 responders compared with the placebo group at Week 2, but not at Week 4 (Table S6).

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Table S6. Proportion of Subjects with >=4 Points at Baseline and Achieving >=4 Points Improvement from Baseline in Numeric Rating Scale for Severity of Pruritus at Weeks 2, 4, 8 and 12 - CMH (FAS, NRI)

		Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
Week 2	N	95	92	88
	n (%)	12 (12.6)	25 (27.2)	34 (38.6)
	95% CI	(6.0, 19.3)	(18.1, 36.3)	(28.5, 48.8)
	Active - Placebo [1]			
	Estimate (%)		14.7	26.1
	95% CI		(3.5, 25.9)	(13.9, 38.3)
	Two-sided P-value [2]		0.0119	<.0001
	200 mg QD - 100 mg QD [1]			
	Estimate (%)			11.7
	95% CI			(-1.8, 25.2)
Week 4	N	92	89	84
	n (%)	19 (20.7)	28 (31.5)	42 (50.0)
	95% CI	(12.4, 28.9)	(21.8, 41.1)	(39.3, 60.7)
	Active - Placebo [1]			
	Estimate (%)		10.9	29.4
	95% CI		(-1.8, 23.6)	(16.0, 42.9)
	Two-sided P-value [2]		0.0971	<.0001
	200 mg QD - 100 mg QD [1]			
	Estimate (%)			18.4
	95% CI			(4.1, 32.7)
Week 8	N	92	87	85
	n (%)	29 (31.5)	36 (41.4)	48 (56.5)
	95% CI	(22.0, 41.0)	(31.0, 51.7)	(45.9, 67.0)
	Active - Placebo [1]			
	Estimate (%)		9.9	24.9
	95% CI		(-4.1, 23.9)	(10.8, 39.0)
	Two-sided P-value [2]		0.1723	0.0009
	200 mg QD - 100 mg QD [1]			
	Estimate (%)			15.1
	95% CI			(0.4, 29.9)
Week 12	N	84	76	74
	n (%)	25 (29.8)	40 (52.6)	41 (55.4)
	95% CI	(20.0, 39.5)	(41.4, 63.9)	(44.1, 66.7)

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Table S6. Proportion of Subjects with >=4 Points at Baseline and Achieving >=4 Points Improvement from Baseline in Numeric Rating Scale for Severity of Pruritus at Weeks 2, 4, 8 and 12 - CMH (FAS, NRI)

	Placebo	PF-04965842 100mg QD	PF-04965842 200mg QD
Active - Placebo [1]			
Estimate (%)		22.8	25.6
95% CI		(8.0, 37.7)	(10.6, 40.6)
Two-sided P-value [2]		0.0035	0.0013
200 mg QD - 100 mg QD [1]			
Estimate (%)			2.6
95% CI			(-13.4, 18.7)

Full Analysis Set (FAS) was defined as all randomized subjects who received at least one dose of study medication.
Baseline was defined as the measurement collected on or prior to Day 1.
If a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; N = number of subjects in the analysis set with NRI at the specified visit; n (%) = number of subjects with response (percentage based on N); NRI = non-responder imputation.
[1] The estimate and confidence interval (CI) for difference were calculated based on the weighted average of difference for each randomization stratum using the
normal approximation of binomial proportions. The confidence interval for the response rate was based on normal approximation (or the Clopper-Pearson exact method when there were no or if all were responders).
[2] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) method adjusted by randomization strata (baseline disease severity).
PFIZER CONFIDENTIAL SDTM Creation: 12MAY2020 (11:17) Source Data: adnr2 Output File: ./nda1_cdisc/B7451036/adnr_s201 Date of Generation: 18JUN2020 (22:02)
Table 14.2.3.2.1.1 is for Pfizer internal use.

Other Secondary Efficacy Endpoints:

Remaining secondary efficacy endpoints (not multiplicity controlled) showed similar pattern of efficacy as the primary and key efficacy endpoints. Efficacy with both abrocitinib groups was statistically significantly better (not controlled for multiplicity) than placebo for all secondary endpoints.

PP-NRS:

The proportions of PP-NRS4 responders at Day 2 to Day 15 and Week 8 were all numerically greater in the abrocitinib 200 mg and 100 mg groups than the placebo group, but the differences did not reach statistical significance at some timepoints.

The Kaplan-Meier analysis to estimate the time to first PP-NRS4 showed the time to response was statistically significantly faster in the abrocitinib 100 mg (p=0.0159) and 200 mg (p=0.0003) groups compared with the placebo group. Since response was assessed

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only at scheduled visits after Week 2, it was unknown whether the actual median time to response was between 2 scheduled visits.

The least square mean (LSM) of percent change from baseline in PP-NRS was statistically significantly improved (lower) in both abrocitinib 100 mg and 200 mg groups compared with the placebo group at all scheduled time points except abrocitinib 200 mg versus placebo at Day 2 and both abrocitinib groups versus placebo at Day 5.

IGA:

At Weeks 4 and 8, both abrocitinib treatment groups showed statistically significantly higher proportions of participants with IGA responses compared with the placebo group. At Week 2, only abrocitinib 200 mg group showed statistically significantly higher proportions of participants with IGA responses compared with the placebo group.

EASI:

Both abrocitinib treatment groups had statistically significantly greater proportion of EASI-75 responders compared with the placebo group at Weeks 2, 4, and 8.

The LSM of percent change from baseline in the total EASI score demonstrated statistically significant decreases in both abrocitinib treatment groups compared with the placebo group at all scheduled time points (Weeks 2, 4, 8, and 12).

Both abrocitinib treatment groups demonstrated statistically significantly greater EASI-50 and EASI-90 responses compared with the placebo group at all scheduled time points (Weeks 2, 4, 8, and 12). At Week 2, only 1 participant from abrocitinib 100 mg group achieved EASI-100 response and none from the placebo or abrocitinib 200 mg group achieved EASI-100 response. Abrocitinib 200 mg group demonstrated statistically significantly greater EASI-100 responses compared with the placebo group only at Weeks 4 and 8.

BSA:

Both abrocitinib treatment groups demonstrated statistically significant decreases from baseline in %BSA compared with the placebo group as early as Week 2 and were maintained at Weeks 4, 8, and 12 ($p \leq 0.0001$ for absolute change and $p \leq 0.0002$ for percent change, based on the MMRM analysis).

Statistically significantly higher proportions of participants achieved %BSA < 5% for both abrocitinib treatment groups compared with the placebo group ($p < 0.05$) except for abrocitinib 200 mg group at Week 12.

SCORAD:

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Both abrocitinib treatment groups demonstrated statistically significantly higher proportions of participants with SCORAD50 responses compared with the placebo group as early as Week 2 ($p \leq 0.0089$) and were maintained at each scheduled time point up to Week 12 ($p < 0.0001$).

Both abrocitinib treatment groups demonstrated statistically significantly higher proportions of participants with SCORAD75 responses compared with the placebo group as early as Week 2 ($p \leq 0.0242$) and were maintained at each scheduled time point up to Week 12, except abrocitinib 100 mg group at Week 8.

Both abrocitinib treatment groups demonstrated statistically significantly greater decreases compared with the placebo group in absolute value ($p < 0.0001$ for both abrocitinib treatment groups) and percent change from baseline ($p \leq 0.0003$) of SCORAD total score, began at Week 2 and were maintained at each scheduled time point up to Week 12, based on the MMRM analysis.

Both abrocitinib treatment groups demonstrated statistically significantly greater decreases compared with the placebo group in absolute value change from baseline in SCORAD Visual Analogue Scale (VAS) of sleep loss, that began at Week 2 and were maintained at each scheduled time point up to Week 12.

Corticosteroid-Free Days:

LSM of number of days up to Week 12 when corticosteroid was not used was statistically significantly higher in the abrocitinib 200 mg group compared with the placebo group ($p=0.0176$).

Patient-Reported Outcomes Endpoints:

CDLQI

The LSM of change from baseline in CDLQI scores was statistically significantly improved (lower than baseline) in both abrocitinib treatment groups compared with the placebo group at Weeks 2, 4, 8, and 12.

Proportion of participants with ≥2.5-point improvement from baseline in the CDLQI score in the abrocitinib 100 mg treatment group showed statistically significant difference from the placebo group at Weeks 8 and 12.

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HADS

The LSM changes from baseline in HADS anxiety subscale did not show statistically significant improvement (lower) for both abrocitinib treatment groups compared with the placebo group at Weeks 2, 4, 8 and 12.

The LSM changes from baseline in HADS depression subscale did not show statistically significant improvement (lower) for both abrocitinib treatment groups compared with the placebo group at Weeks 2, 4, 8 and 12.

POEM

The LSM of change from baseline in POEM scores was statistically significantly improved (lower than baseline) in both abrocitinib treatment groups compared with the placebo group at Weeks 2, 4, 8, and 12 ($p < 0.0001$).

DFI Questionnaire

At Week 12, LSM of change from baseline in DFI score was statistically significantly improved (lower than baseline) in abrocitinib 200 mg group compared with the placebo group.

PtGA

The LSM of change from baseline in PtGA scores was statistically significantly improved (lower) for both abrocitinib treatment groups compared with the placebo group that began at Week 2 and were maintained up to Week 12.

Both abrocitinib treatment groups demonstrated statistically significantly higher proportions of participants with ≥2 points at baseline and achieving ‘Clear’ or ‘Almost Clear’ and ≥2 points improvement from baseline in PtGA compared with the placebo group that began at Week 4 and were maintained up to Week 12.

EQ-5D-Y

The LSM of change from baseline in EQ-5D-Y scores was statistically significantly improved (higher) for abrocitinib 200 mg group compared with the placebo group at Weeks 2, 4, 8 and 12; and for abrocitinib 100 mg group compared with the placebo group at Week 8.

Peds-FACIT-F

The LSM changes from baseline in Peds-FACIT-F at Week 12 did not show statistically significant improvement for both abrocitinib treatment groups compared with the placebo group.

Pharmacokinetic and Immunogenicity Sub-Study Results:

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PK

The mean plasma abrocitinib concentrations observed at 2 hours prior to dosing (Week 8) and at 2 hours post dose (Week 12) appeared to increase in a dose-related manner between the abrocitinib 200 mg and 100 mg QD groups in this study.

Immunogenicity Sub-Study

Immunogenicity sub-study analysis set was defined as participants who had completed 8 weeks of treatment and received Tdap vaccination. All participants (10, 9, 6 participants in the placebo group, abrocitinib 100 mg and 200 mg groups, respectively) in the immunogenicity sub-study completed the 12 weeks treatment.

Greater than 4-fold increase in pertussis toxin IgG and tetanus toxoid IGG antibody was observed in the abrocitinib group. There was no apparent difference on immunogenicity to Tdap vaccine between abrocitinib and placebo.

Safety Results:

No deaths were reported in the study.

The proportion of participants with all-causality TEAEs was higher for the abrocitinib 200 mg group (62.8%) compared to the abrocitinib 100 mg (56.8%) and placebo (52.1%) groups (Table S7). Three participants reported SAEs (2 from the placebo group and 1 from the abrocitinib 200 mg group; Table S7), and no SAEs were treatment-related.

Note: There were 2 TEAEs (hand fracture in the abrocitinib 100 mg group, pustule in the placebo group) missing in Table S7, both TEAEs were not treatment-related and had no substantive impact on efficacy and/or safety interpretation as well as on the statistical conclusions for this study.

The proportion of participants experiencing severe AEs and AEs leading to study discontinuations or temporary discontinuations were low and similar across all treatment groups.

Table S7. Treatment-Emergent Adverse Events (All Causalities, Safety Analysis Set)

Number (%) of Subjects	Placebo n (%)	PF-04965842 100mg QD n (%)	PF-04965842 200mg QD n (%)
Subjects evaluable for adverse events	96	95	94

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Table S7. Treatment-Emergent Adverse Events (All Causalities, Safety Analysis Set)

Number (%) of Subjects	Placebo n (%)	PF-04965842 100mg QD n (%)	PF-04965842 200mg QD n (%)
Number of adverse events	99	134	132
Subjects with adverse events	50 (52.1)	54 (56.8)	59 (62.8)
Subjects with serious adverse events	2 (2.1)	0	1 (1.1)
Subjects with severe adverse events	2 (2.1)	0	2 (2.1)
Subjects discontinued from study due to adverse events [1]	2 (2.1)	1 (1.1)	2 (2.1)
Subjects discontinued study drug due to AE and continue Study [2]	0	0	0
Subjects with temporary discontinuation from study drug due to adverse events	4 (4.2)	4 (4.2)	4 (4.3)

Included data up to 28 days after last dose of study.
Except for the number of adverse events subjects were counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
[1] Subjects who had an AE record that indicated that the AE caused the subject to be discontinued from the study
[2] Subjects who had an AE record that indicated that action taken with study treatment was drug withdrawn but AE did not cause the subject to be discontinued from Study
MedDRA v23.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 13MAY2020 (01:35) Source Data: adae Output
File: ./nda1_cdisc/B7451036/adae_s010 Date of Generation: 20MAY2020 (01:33)
Table 14.3.1.2.1.1 is for Pfizer internal use.

There were no reported serious infections, pulmonary embolism, malignancies, major adverse cardiovascular event (MACE) or venous thromboembolic event (VTE) in this study.

The most frequently reported system organ class (SOC) was Infections and Infestations, with slightly higher proportion of participants reported in the abrocitinib 200 mg (36.2%) and 100 mg (35.8%) groups compared with the placebo group (31.3%).

Only 1 participant in the abrocitinib 100 mg group experienced a Tier-1 event of herpes zoster and the event was mild in severity.

There were no clinically significant hematologic parameters except for platelet which has a dose-dependent decrease in abrocitinib groups with nadir at Week 4; majority of participants remained within the normal range.

No clinically meaningful increases in total cholesterol and low-density lipoprotein (LDL) cholesterol (reached a plateau since Week 4) were observed in this study. There were no clinically meaningful changes in the LDL/high-density lipoprotein (HDL) ratio in any treatment groups at Week 4 or Week 12.

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Compared with the placebo group, there were dose-dependent increases of creatine kinase in abrocitinib treatment groups.

No clinically significant changes or pattern in the abrocitinib treatment groups were observed in vital signs and ECG data.

Conclusions:

Efficacy

Co-Primary Endpoints:

- The study met both co-primary endpoints of IGA and EASI-75 responses at Week 12, demonstrating that both abrocitinib 100 mg and 200 mg treatment groups were superior to the placebo group.
    - Statistically significantly higher proportions of participants achieved IGA responses and EASI-75 responses for both abrocitinib treatment groups compared with the placebo group.
    - Sensitivity analyses of IGA and EASI-75 responses were consistent with the primary analyses.
    - The treatment effects for both IGA response and EASI-75 response were similar across subgroups.

Key Secondary Endpoints:

- Abrocitinib 200 mg group had statistically significantly greater proportions of PP-NRS4 responders compared with the placebo group at Weeks 2, 4, and 12.
- Abrocitinib 100 mg group had statistically significantly greater proportion of PP-NRS4 responders compared with the placebo group at Week 2, but not at Week 4.
- Comparison of PP-NRS4 for abrocitinib 100 mg versus placebo at Week 12, and comparison of change from baseline in the total PSAAD score for both abrocitinib doses versus placebo at Week 12 were not considered statistically significant.

Other Secondary Endpoints:

Additional secondary efficacy endpoints (IGA, EASI, PP-NRS, BSA, SCORAD, and corticosteroid-free days) generally demonstrated improved efficacy in abrocitinib groups compared with the placebo group, especially for the abrocitinib 200 mg group.

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PP-NRS:

- The proportions of PP-NRS4 responders from Day 2 to Day 15 and at Week 8 were all numerically greater in the abrocitinib 200 mg and 100 mg groups than in the placebo group.

- Time to first PP-NRS4 showed the time to response was statistically significantly faster in the abrocitinib 100 mg (p=0.0159) and 200 mg (p=0.0003) groups compared with the placebo group.

- The LSM of percent change from baseline in PP-NRS was statistically significantly improved (lower) in both abrocitinib 100 mg and 200 mg groups compared with the placebo group at all scheduled time points except abrocitinib 200 mg versus placebo at Day 2 and both abrocitinib groups versus placebo at Day 5 and Day 7.

IGA:

- At Weeks 4 and 8, both abrocitinib treatment groups showed statistically significantly higher proportions of participants with IGA responses compared with the placebo group. At Week 2, only abrocitinib 200 mg group showed statistically significantly higher proportions of participants with IGA responses compared with the placebo group.

- Abrocitinib 200 mg group had a greater proportion of IGA responders than the abrocitinib 100 mg group at Weeks 4 and 8.

EASI:

- Statistically significantly greater EASI-50, EASI-75, and EASI-90 responses for both abrocitinib treatment groups compared with the placebo group were observed at all scheduled timepoints (Weeks 2, 4, 8, and 12) except EASI-75 at Week 12.

- The LSM of percent change from baseline in the total EASI score demonstrated statistically significant decreases in both abrocitinib treatment groups compared with the placebo group at Weeks 2, 4, 8, and 12.

- Abrocitinib 200 mg group demonstrated statistically greater EASI-100 responses compared with the placebo group only at Weeks 4 and 8.

BSA:

- Both abrocitinib treatment groups demonstrated statistically significant decreases from baseline in %BSA compared with the placebo group as early as Week 2 and were maintained at Weeks 4, 8 and 12.

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- Statistically significantly higher proportions of participants achieved %BSA < 5% for both abrocitinib treatment groups compared with the placebo group except for abrocitinib 200 mg group at Week 12.

SCORAD:

- Both abrocitinib treatment groups demonstrated statistically significantly higher proportions of participants with SCORAD50 responses compared with the placebo group as early as Week 2 and were maintained at each scheduled time point up to Week 12.

- Both abrocitinib treatment groups demonstrated statistically significantly higher proportions of participants with SCORAD75 responses compared with the placebo group as early as Week 2 and were maintained at each scheduled time point up to Week 12, except abrocitinib 100 mg group at Week 8.

- Both abrocitinib treatment groups demonstrated statistically significantly greater decreases compared with the placebo group in absolute value and percent change from baseline of SCORAD total score, that began at Week 2 and were maintained at each scheduled time point up to Week 12.

- Both abrocitinib treatment groups demonstrated statistically significantly greater decreases compared with the placebo group in absolute value change from baseline in SCORAD VAS of sleep loss, that began at Week 2 and were maintained at each scheduled time point up to Week 12.

Corticosteroid-Free Days:

- Number of days up to Week 12 when corticosteroid was not used was statistically significantly higher in the abrocitinib 200 mg group compared with the placebo group.

Patient-Reported Outcomes:

Favorable and improved differences across most PRO measures (CDLQI, POEM, DFI, PtGA, and EQ-5D-Y) were observed for abrocitinib treatment groups compared with the placebo group, except for HADS and Peds-FACIT-F.

- CDLQI: change from baseline in CDLQI scores was statistically significantly improved (lower than baseline) in both abrocitinib treatment groups compared with the placebo group at Weeks 2, 4, 8, and 12. Participants with ≥ 2.5-point improvement from baseline in the CDLQI score in abrocitinib 100 mg treatment group showed statistically significant difference from the placebo group at Weeks 8 and 12.

- HADS: changes from baseline in HADS anxiety and depression subscales did not show improvement (lower) for either abrocitinib treatment groups compared with the placebo group at Weeks 2, 4, 8, and 12.

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- POEM: change from baseline in POEM scores was statistically significantly improved (lower than baseline) in both abrocitinib treatment groups compared with the placebo group at Weeks 2, 4, 8, and 12.

- DFI Questionnaire: at Week 12, change from baseline in DFI score was statistically significantly improved (lower than baseline) in abrocitinib 200 mg group compared with the placebo group.

- PtGA: changes from baseline in PtGA scores was statistically significantly improved (lower) for both abrocitinib treatment groups compared with the placebo group that began at Week 2 and were maintained up to Week 12.

- EQ-5D-Y: change from baseline in EQ-5D-Y scores was statistically significantly improved (higher) for abrocitinib 200 mg group compared with the placebo group at Weeks 2, 4, 8, and 12.

- Peds-FACIT-F: changes from baseline in Peds-FACIT-F at Week 12 did not show statistically significant improvement for either abrocitinib treatment groups compared with the placebo group.

Pharmacokinetics

- The mean plasma abrocitinib concentrations observed at 2 hours prior to dosing (Week 8) and at 2 hours post-dose (Week 12) appeared to increase in a dose-related manner between the abrocitinib 200 mg and 100 mg QD groups in this study.

Safety

- Abrocitinib was well tolerated. The observed safety events were consistent with those seen in other abrocitinib studies.

- A higher incidence of AEs was reported in the abrocitinib groups, however, the percentage of participants experiencing SAEs, severe AEs and AEs leading to study discontinuation were low and similar across treatment groups.

- No serious infections were reported in this study.

- Infections and Infestations were the most frequently reported AEs across all treatment groups.

- A higher incidence of nausea and herpes simplex infections were observed in the abrocitinib groups. Only 1 event of herpes zoster was reported in the abrocitinib 100 mg group.

- No cases of MACE were observed in the study.

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- No deaths or VTE were reported in the study.
- No participants discontinued treatment due to thrombocytopenia and/or lymphopenia according to protocol-specified discontinuation criteria.
- Dose-dependent decrease in platelets in abrocitinib groups with nadir at Week 4; the majority of participants remained within the normal range.
- No clinically significant changes in hemoglobin, lymphocyte and neutrophil counts.
- No clinically meaningful increases in total cholesterol and LDL cholesterol (reached a plateau since Week 4); LDL:HDL ratios in both abrocitinib groups were unchanged through Week 12.
- Dose-dependent increases in creatine kinase were observed, no rhabdomyolysis was reported.
- No pattern of concern in ECG, vital signs and no unexpected laboratory abnormalities were observed.
- No unique safety signals were noted in the study.

Immunogenicity Sub-Study

- There was no apparent difference on immunogenicity to Tdap vaccine between abrocitinib and placebo. Greater than 4-folder increase in pertussis toxin IgG and tetanus toxoid IGG antibody was observed in the abrocitinib groups. A clinically meaningful conclusion cannot be established because of the small sample size.