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Sponsor: Pfizer Global Research & Development

Investigational Product: CP-690,550 (tofacitinib)

Clinical Study Report Synopsis: Protocol A3921116

Protocol Title: A Phase 2a, Multi-Site, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Pilot Efficacy, Safety, and Pharmacokinetics of 2 Ointment Formulations of CP-690,550 in Subjects With Mild to Moderate Chronic Plaque Psoriasis

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* Did not randomize subjects

Study Centers: A total of 4 centers in Canada and 6 centers in the United States enrolled subjects in the study.

Publications Based on the Study: None.

Study Initiation and Completion Dates: 16 February 2011 to 29 November 2011.

Date of Report: 16 August 2012

Phase of Development: Phase 2a

Study Objectives: The objective of the study was to characterize and compare the efficacy, local tolerability, systemic safety, and systemic pharmacokinetics (PK) of 2 ointment formulations of 2% CP-690,550 administered topically twice daily (BID) for 4 weeks in subjects with mild to moderate chronic plaque psoriasis (psoriasis vulgaris).

METHODS

Study Design: This Phase 2a, multicenter, randomized, double-blind, vehicle (placebo)-controlled, 4-arm, parallel-group study was designed to characterize the efficacy, local tolerability, systemic safety, and systemic PK of 2 topical formulations of 2% CP-690,550 (tofacitinib) administered BID for 4 weeks in subjects with mild to moderate chronic plaque psoriasis. Screening was to take place no more than 4 weeks before Baseline (Day 1 of treatment). Visits were to occur weekly for 4 weeks, and there was to be a Follow-up visit 1 week (7 to 10 days) after the end of the 4-week treatment period. Subjects were randomized to receive either 2% CP-690,550 (Ointment 1 or Ointment 2) BID or placebo (Vehicle 1 or Vehicle 2) BID.

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Diagnosis and Main Criteria for Inclusion: Male and female subjects at least 18 years of age who had been diagnosed with chronic plaque psoriasis (psoriasis vulgaris) at least 6 months before the start of study treatment were included. At Baseline, subjects were required to have plaque psoriasis meeting the following criteria: overall psoriasis affecting ≤10% of body surface area (BSA) and rated mild or moderate on the Physician's Global Assessment (PGA); and a target psoriasis plaque with Total Plaque Severity Score (TPSS) ≥5 (induration component ≥2) and Target Plaque Area (TPA) ≥9 cm^2. Plaques that were intertriginous or were on the hands, feet, neck, face, elbows, knees, below the knees, or scalp were not eligible to be target plaques or to be included in the treatment area.

Study Treatment: Subjects were randomized to 1 of 4 treatment groups in the ratio of 2:1:2:1 (2% CP-690,550 Ointment 1: Vehicle 1: 2% CP-690,550 Ointment 2: Vehicle 2). Subjects were instructed to apply study drug topically BID (in the morning and evening approximately 12 hours apart, at approximately the same times each day) to a single fixed 300 cm^2 treatment area (application dose of approximately 900 mg of ointment and application coverage of approximately 3 mg/cm^2). During the 4-week treatment period subjects applied the study drug at home except on the study visit days.

Table S1 presents the study drug lot and dosage material numbers.

Table S1. Lot and Dosage Material Numbers

Study Drug	Lot Number	Dosage Material Number	Potency	Formulation
vehicle (placebo) for CP-690,550 topical ointment	10-083605	D0904843	N/A	ointment
CP-690,550 20 mg/g topical ointment	10-083604	D0904844	20 mg/g[a]	ointment
CP-690,550 20 mg/g topical ointment	10-085241	D1005084	20 mg/g[a]	ointment
vehicle (placebo) for CP-690,550 topical ointment	10-085242	D1005085	N/A	ointment

Abbreviation: N/A=not applicable
[a]Potency of 20 mg/g=2%.

Efficacy Evaluations: The primary efficacy endpoint was the percent change from Baseline at Week 4 in TPSS (Full Analysis Set [FAS]). The target plaque was scored at each study visit for signs of erythema, induration, and scaling, each of which was scored separately according to a 5-point severity scale, where 0=none, 1=slight, 2=moderate, 3=marked, and 4=very marked. The severity scores were summed to yield the TPSS. The TPSS can vary in

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increments of 1 and range from 0 to 12, with higher scores representing greater severity of psoriasis.

Secondary efficacy endpoints were:

- Proportion of subjects with Treatment Area Overall Severity of Psoriasis response of "clear" (0) or "almost clear" (1) at Weeks 1, 2, 3, and 4. Treatment Area Overall Severity of Psoriasis was scored at each study visit on a 5-point scale, reflecting a global consideration of the erythema, induration, and scaling across all psoriatic plaques that fell within the treatment area. Erythema, induration, and scaling were scored separately over the treatment area according to a 5-point severity scale, where 0=no involvement, 1=slight, 2=moderate, 3=marked, and 4=very marked. The severity scores were summed and averaged, after which the total average was rounded to the nearest whole number score to determine the Treatment Area Overall Severity of Psoriasis score, where 0=clear, 1=almost clear, 2=mild, 3=moderate, and 4=severe;

- Proportion of subjects with a decrease from Baseline of ≥2 points in Treatment Area Overall Severity of Psoriasis score at Weeks 1, 2, 3, and 4;

- Percent change from Baseline at Weeks 1, 2, 3, and 4 in TPA. The TPA was calculated at each study visit by tracing the target plaque;

- Change from Baseline at Weeks 1, 2, 3, and 4 in TPSS subscores for erythema, induration, and scaling;

- Percent change from Baseline in TPSS at Weeks 1, 2, and 3.

Pharmacokinetic, Pharmacogenomic, and Other Evaluations:

Patient-Reported Outcomes (PRO)

Secondary PRO endpoints were:

- Actual and change from Baseline on the treatment area Itch Severity Item (ISI) at Weeks 1, 2, 3 and 4. The severity of itching (pruritus) due to psoriasis within the treatment area was assessed using a single item PRO. At all study visits, subjects were asked to assess their worst itching due to psoriasis within the treatment area during the previous 24 hours on a numeric rating scale from 0 (no itching) to 10 (worst possible itching);

- Proportion of subjects in each Patient Satisfaction with Study Medication (PSSM) response category at Week 4. The PSSM survey was a single, 7-point item that evaluated overall subject satisfaction with the study drug at Week 4. Response options ranged from "very dissatisfied" to "very satisfied".

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Pharmacokinetics

Plasma samples for PK analysis were collected at Week 4. Study drug application occurred at the study site and PK samples were collected postdose at predefined intervals. If a subject had been off study drug for more than 1 day at the time of the Week 4 visit or upon early termination, only a single PK blood sample was collected. The secondary PK endpoint was plasma CP-690,550 concentrations from blood sampling at Week 4 (Day 29).

Pharmacogenomics and Skin Biopsy Evaluations

This study included an additional research component involving the collection of biological samples for de-identified exploratory pharmacogenomic (PG) and biomarker analysis. Subjects were not required to participate in the PG component. Molecular profiling sampling included collection of blood samples and target plaque skin biopsies (which were also used to generate skin biomarker and CP-690,550 concentration data). For consenting subjects, the skin biopsy was performed after the 4-9 hour PK sample was obtained at Week 4, or upon early termination. Separate bioanalytical reports detailing PG may be produced at a later time. Separate reports on skin biomarker and CP-690,550 concentration data will be produced at a later time.

Safety Evaluations: Subject safety was assessed through physical examinations, laboratory evaluations, vital signs measurements (blood pressure [BP] and pulse rate), electrocardiograms (ECGs), and adverse event (AE) assessment.

Secondary local tolerability endpoints were:

- Incidence, nature, and severity of observed and reported administration site AEs over 4 weeks of treatment. All application site (treatment area) reactions were to be recorded as AEs on the case report form (CRF), including the severity, duration, and outcome of the reaction;

- Incidence and severity of burning/stinging of psoriatic or perilesional skin in the treatment area over 4 weeks of treatment. Treatment area burning/stinging symptoms were queried of the subject and scored by the investigator using a 4-point scale (none, mild, moderate, and severe);

- Incidence and severity of reactions of perilesional skin in the treatment area as measured by Draize scoring over 4 weeks of treatment. Perilesional skin (if any) within the treatment area was assessed using Draize scoring for erythema (on a 5-point scale from 0=no reaction visible to 4=strong to severe reaction) and the presence or absence of other signs and symptoms. Psoriatic skin within the treatment area was not evaluated using Draize scoring. Draize scoring of burning/stinging/itching did not necessarily agree with the treatment area burning/stinging score. In cases where a treated plaque decreased in size, the current lesion perimeter was used to define the border for perilesional skin.

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Scores for erythema, edema, papules, and vesicles were judged to be present only if they involved ≥25% of the perilesional skin within the treatment area.

Statistical Methods:

Data Sets Analyzed

The FAS included all subjects who were randomized to the study and received at least 1 dose of the investigational drug (CP-690,550 or vehicle) as randomized. This was the primary analysis population for the study. In order to be included in longitudinal modeling for any of the efficacy parameters, subjects were required to have at least 1 postbaseline measurement. For the analyses based on the random effects model of repeated measures, all available windowed measurements over time were used.

The Per Protocol Analysis Set (PP) was a subset of subjects from the FAS; subjects who had a protocol deviation thought to affect the efficacy analysis were excluded from the PP set.

The Safety Analysis Set (SAS) consisted of all subjects who received at least 1 dose of study drug (CP-690,550 or vehicle).

The PK Analysis Set (PKAS) consisted of all subjects treated with CP-690,550 Ointment 1 or Ointment 2 who had at least 1 plasma concentration value at or above the lower limit of quantification (LLOQ).

Efficacy Analyses

Analyses of the primary endpoint were conducted using both the FAS and PP. Analyses of all secondary endpoints were conducted using the FAS. Safety analyses were conducted using the SAS.

The primary comparisons of interest were between each of the active treatment groups and the corresponding vehicle group. The following contrasts were the primary comparisons:

- Contrast 1: (Treatment Group A [CP-690,550 Ointment 1] – Treatment Group B [Vehicle 1])
- Contrast 2: (Treatment Group C [CP-690,550 Ointment 2] – Treatment Group D [Vehicle 2]).

Contrast 1 and Contrast 2 were the primary comparisons and were evaluated for all study endpoints. Upper and lower 1-sided 90% confidence limits (CLs; corresponding to 2-sided 80% confidence intervals [CIs]) for the difference and p-values were presented. Additional, secondary comparisons were made.

The primary endpoint for this study was the percent change from Baseline in TPSS at Week 4 (FAS). The primary comparisons of interest were the differences between the active

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treatment groups and the corresponding vehicle groups (CP-690,550 minus vehicle) (Contrast 1 and Contrast 2). A negative value (<0) in this difference represented a favorable treatment effect due to CP-690,550.

The percent change from Baseline in TPSS was analyzed using a random effects model for repeated measures. The model included fixed effects for treatment group, time (Weeks 1, 2, 3, and 4), treatment group by time interaction, and a random effect of subject (nested within treatment group). Least squares (LS) means, standard errors (SEs), and 1-sided upper and lower 90% CLs (80% CIs) were provided for each treatment group at Weeks 1, 2, 3, and 4 and Follow-up. For contrasts in the primary comparisons, differences in LS means between each CP-690,550 group and the corresponding vehicle group were derived, along with SEs, 1-sided upper and lower 90% CLs (80% CIs); associated p-values were provided. Statistical significance was claimed if the upper limit of the 1-sided 90% CL was less than 0. No adjustment for multiple comparisons was made, since there was only 1 primary endpoint (2 independent comparisons).

For the analysis of continuous variables, such as percent change from Baseline in TPSS at Weeks 1, 2, or 3, the statistical method for random effects model for repeated measures similar to that described for the primary endpoint was used.

For the analysis of binary variables, such as proportion of subjects with Treatment Area Overall Severity of Psoriasis response of "clear" (0) or "almost clear" (1) at Weeks 1, 2, 3, and 4, the differences in proportions between the CP-690,550 and vehicle groups were obtained and the CIs of the differences were estimated by the exact methods approach.

For the ISI, descriptive statistics of the absolute scores and change from Baseline (prior to the first application of study drug on Visit 1) to each of the specified assessment visits were calculated and tabulated for the active (CP-690,550) treatment groups and the vehicle groups. Mean changes from Baseline at each assessed time point for the active treatment groups and the vehicle groups were compared and analyzed for statistical significance (using the same criteria as those for the primary endpoint).

For the PSSM (administered at Week 4 only), descriptive statistics were calculated for the active (CP-690,550) treatment groups and the vehicle groups. Categorical analyses comparing the proportion of subjects in each response category were performed.

Safety Analyses

Safety data were summarized in accordance with the Sponsor's data standards and included: AEs; safety events that led to withdrawal of a subject; clinical laboratory data; changes in physical examination from Screening; changes in vital signs; and changes in ECG parameters.

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Local Tolerability Analyses

For local tolerability (burning/stinging and Draize scores), descriptive statistics were used to summarize the findings. For incidence data, the number and proportion of subjects with events were presented. For continuous data, the mean, standard deviation (SD), median, quartiles, and range were presented.

PK Analyses

The objective of the analyses was to characterize the systemic PK data for CP-690,550 in subjects following topical application of Ointment 1 and Ointment 2 for 4 weeks. PK data were summarized through appropriate data tabulations and descriptive statistics.

The following CP-690,550 PK parameters were calculated for each subject for each formulation using noncompartmental analysis of concentration-time data (Table S2). Actual sample collection times were used for the PK analyses. Samples below LLOQ were set to 0.00 ng/mL for analysis. Area under the plasma concentration-time profile from time zero to 12 hours (AUCτ) for the 12-hour dosing interval was calculated from PK data at Week 4 by assuming the 12-hour concentration to be the same as measured predose (0 hour) concentrations.

Analysis was also done by setting <LLOQ samples to the LLOQ (0.100 ng/mL) ("adjusted analyses"). These values are reported as $C_{max(adj)}$ (maximum plasma concentration adjusted) and $AUC_{\tau\,(adj)}$ (AUC_{τ} adjusted). These "adjusted" parameter values were used as a conservative estimate of exposure to compare with systemic exposures expected from subjects with psoriasis receiving oral CP-690,550. The PKAS for the adjusted analyses consisted of all subjects treated with CP-690,550 Ointment 1 or Ointment 2, irrespective of the plasma concentration value (<LLOQ or ≥LLOQ).

Table S2. Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observed directly from data; <LLOQ samples were set to 0.00 ng/mL.
$C_{max\,(adj)}$	C_{max} adjusted	Observed directly from data; <LLOQ samples were set to 0.100 ng/mL.
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence.
AUC_{τ}	Area under the plasma concentration-time profile from time zero to 12 hours	Linear/Log trapezoidal method by setting <LLOQ samples to 0.00 ng/mL.
$AUC_{\tau\,(adj)}$	AUC_{τ} adjusted	Linear/Log trapezoidal method by setting <LLOQ samples to 0.100 ng/mL.

Pharmacokinetic parameter values were calculated using internally validated software, eNCA version 2.2.3.
Abbreviations: LLOQ=lower limit of quantification; adj=adjusted

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RESULTS

Subject Disposition and Demography: A total of 120 subjects were screened, and 71 subjects were assigned to study treatment and treated (23 in the CP-690,550 Ointment 1 group, 13 in the Vehicle 1 group, 25 in the CP-690,550 Ointment 2 group, and 10 in the Vehicle 2 group; Table S3). A total of 3 (4.2%) subjects were discontinued from the study before completion: 1 subject in the CP-690,550 Ointment 1 group was no longer willing to participate in the study, 1 subject in the CP-690,550 Ointment 2 group was withdrawn due to a protocol violation for noncompliance with study drug dosing, and 1 subject in the Vehicle 2 group was lost to follow-up.

All 71 subjects enrolled received study drug and were analyzed for safety (Table S3). All 71 subjects enrolled were included in the FAS at Baseline and in the primary analysis of the TPSS; 67 subjects had observed TPSS values at the primary analysis time point, Week 4 (3 subjects were withdrawn early and did not have a Week 4 visit; a fourth subject completed the study but did not have a Week 4 visit in the time window required for inclusion in the analyses). Twelve subjects were excluded from the PP set. A total of 43 subjects (20 in the CP-690,550 Ointment 1 group and 23 in the CP-690,550 Ointment 2 group) were analyzed for PK.

Table S3. Subject Disposition and Evaluation Groups

No. of Subjects	2% CP-690,550 Ointment 1 BID	Vehicle 1 BID	2% CP-690,550 Ointment 2 BID	Vehicle 2 BID
Screened: 120				
Assigned to study treatment: 71	23	13	25	10
Treated	23	13	25	10
Completed	22	13	24	9
Discontinued	1	0	1	1
Lost to follow-up	0	0	0	1
No longer willing to participate in study	1	0	0	0
Protocol violation	0	0	1	0
Analyzed for efficacy				
Full Analysis Set (FAS)	23	13	25	10
Per Protocol Analysis Set (PP)	20	12	18	9
Analyzed for pharmacokinetics	20	N/A	23	N/A
Analyzed for safety				
Adverse events	23	13	25	10
Laboratory data	22	13	25	9

Abbreviations: BID=twice daily; No.=number; N/A=not applicable

Baseline characteristics were comparable across the treatment groups. The majority of subjects were male (43/71, 60.6%) and white (67/71, 94.4%). The mean age was 50.6 years (range 24 years to 80 years). The mean weight was 92.3 kg (range 58.1 kg to 175.0 kg), and the mean body mass index (BMI) was 31.0 kg/m^2 (range 18.6 kg/m^2 to 63.1 kg/m^2).

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The mean duration of time since diagnosis with psoriasis was 16.7 years and ranged from 10.5 years to 19.1 years across the treatment groups (overall subject range 0.6 years to 58.4 years). The mean total Psoriasis Area and Severity Index (PASI) score at Baseline ranged from 5.1 to 6.7 across the treatment groups (possible PASI scores range from 0.0 to 72.0, with higher scores representing greater severity of psoriasis). The minimum total PASI score at Baseline across all subjects was 1.5 and the maximum total score was 13.8. The majority of subjects (38/71, 53.5%) had a total PASI score at Baseline in the 5.0 to 9.9 range. The mean total BSA affected at Baseline was 4.3% (mean BSA ranged from 3.3% to 5.4% across the treatment groups). The minimum total BSA affected at Baseline across all subjects was 0.6%, and the maximum total BSA affected was 10.0%. The mean TPSS total score at Baseline was 7.09 overall and ranged from 6.80 to 7.31 across the treatment groups (possible TPSS scores range from 0 to 12, with higher scores representing greater severity of psoriasis). The mean TPA at Baseline was 36.07 cm^2 overall and ranged from 30.72 cm^2 to 44.08 cm^2 across the treatment groups. The majority of subjects (42/71, 59.2%) had a PGA of mild at Baseline. The majority of subjects (46/71, 64.8%) had a Treatment Area Overall Severity of Psoriasis rating of mild at Baseline. The mean ISI at Baseline ranged from 4.09 to 6.20 across the treatment groups (possible ISI scores range from 0=no itching to 10=worst possible itching). The most frequent location of treated target plaques was on the arms (28/71 [39.4%] subjects).

Efficacy Results:

Primary Endpoint

Descriptive statistics for the TPSS at Baseline and Week 4 for the FAS are presented in Table S4. Mean TPSS scores for the FAS across the treatment groups ranged from 6.80 (CP-690,550 Ointment 2) to 7.31 (Vehicle 1) at Baseline and from 3.55 (CP-690,550 Ointment 1) to 5.89 (Vehicle 2) at Week 4. Among the 4 treatment groups, CP-690,550 Ointment 1 had the largest mean and mean percent decreases from Baseline (changes of -3.73 and -53.97%, respectively), while Vehicle 2 had the smallest mean and mean percent decreases from Baseline (changes of -1.22 and -17.24%, respectively).

The primary analysis was the LS mean difference between CP-690,550 and vehicle (ie, CP-690,550 Ointment 1 vs Vehicle 1 [Contrast 1] and CP-690,550 Ointment 2 vs Vehicle 2 [Contrast 2]) for the percent change from Baseline in TPSS at Week 4 for the FAS (Table S5). The LS mean difference for Contrast 1 (CP-690,550 Ointment 1 minus Vehicle 1) was -12.87%, and the 1-sided 90% upper CL was -0.71% (significant). The LS mean difference for Contrast 2 (CP-690,550 Ointment 2 minus Vehicle 2) was -6.97%, and the 1-sided 90% upper CL was 6.62% (nonsignificant).

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Table S4. Summary of Descriptive Statistics for TPSS at Baseline and Week 4 (FAS, No Imputation)

	2% CP-690,550 Ointment 1 BID	Vehicle 1 BID	2% CP-690,550 Ointment 2 BID	Vehicle 2 BID
Baseline				
N	23	13	25	10
Mean (SD)	7.22 (1.51)	7.31 (1.38)	6.80 (1.19)	7.20 (1.40)
Range (Min-Max)	5.0-10.0	5.0-9.0	5.0-9.0	5.0-9.0
Week 4				
N	22[a]	13	23[b]	9[a]
Mean (SD)	3.55 (2.67)	4.23 (1.48)	5.09 (2.48)	5.89 (1.96)
Range (Min-Max)	0.0-11.0	2.0-7.0	0.0-12.0	2.0-8.0
Mean chg (SD)	-3.73 (1.98)	-3.08 (1.75)	-1.65 (2.37)	-1.22 (1.56)
Mean % chg (SD)	-53.97 (29.93)	-41.01 (20.29)	-24.26 (33.43)	-17.24 (25.40)

Abbreviations: BID=twice daily; N=number of subjects providing data; SD=standard deviation; Mean chg=mean change from Baseline; Mean % chg=mean percent change from Baseline; TPSS=Target Plaque Severity Score; FAS=Full Analysis Set; Min=minimum; Max=maximum

The TPSS can vary in increments of 1 and range from 0 to 12, with higher scores representing greater severity of psoriasis.

[a]One subject in this treatment group did not complete the study and had a TPSS score at Baseline only.

[b]One subject in this treatment group did not complete the study and had TPSS scores through Week 2 only. Another subject did not have a Week 4 visit in the time window required for inclusion in the TPSS analysis.

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Table S5. Statistical Analysis of Percent Change From Baseline in TPSS at Week 4 (Longitudinal Model), Contrast 1 (A–B) and Contrast 2 (C–D) (FAS, No Imputation)

Treatment	LS Mean (SE)	Difference From Vehicle[a]		
		Diff (SE)[b]	1-Sided 90% Confidence Limit[c]	
			Lower Limit	Upper Limit
(A) 2% CP-690,550 Ointment 1 BID	-54.40 (5.75)	-12.87 (9.42)	-25.03	-0.71*
(B) Vehicle 1 BID	-41.53 (7.48)			
(C) 2% CP-690,550 Ointment 2 BID	-24.19 (5.51)	-6.97 (10.53)	-20.57	6.62
(D) Vehicle 2 BID	-17.21 (8.98)			

Abbreviations: BID=twice daily; SE=standard error; TPSS=Target Plaque Severity Score; FAS=Full Analysis Set; LS=least squares; Diff=difference
Results were obtained from a longitudinal mixed-effect model with percent change from Baseline as the response.
The effects of treatment, week, and treatment-by-week interaction were included as fixed effects, along with subject as a random effect and Baseline as a covariate.
*Statistically significant.
[a]Contrast 1: (A-B)=2% CP-690,550 Ointment 1 BID minus Vehicle 1.
Contrast 2: (C-D)=2% CP-690,550 Ointment 2 BID minus Vehicle 2.
[b]Difference=(CP-690,550 Ointment – Vehicle).
[c]One-sided 90% lower and upper confidence limits represent 2-sided 80% confidence interval. Efficacy was declared if 1-sided 90% upper confidence limit <0.

Secondary Endpoints

TPSS at Weeks 1 through 3: A time-course response in mean percent change from Baseline in TPSS over Weeks 1 through 3 of both the CP,690,550-treated and vehicle-treated target plaques was apparent for all treatment groups.

TPSS Subscores: A time-course response in mean change from Baseline in TPSS-Erythema over Weeks 1 through 4 of both the CP-690,550-treated and vehicle-treated target plaques was apparent for all treatment groups except for Vehicle 2 at Week 4. For changes from Baseline in TPSS-Erythema, all 90% upper CLs for the CP-690,550 ointment groups vs vehicle were >0. A time-course response in mean change from Baseline in TPSS-Induration over Weeks 1 through 4 of both the CP-690,550-treated and vehicle-treated target plaques was apparent for all treatment groups except for CP-690,550 Ointment 2 and Vehicle 2 at Week 4. At Weeks 2, 3, and 4, the 90% upper CLs for the changes from Baseline in TPSS-Induration for CP-690,550 Ointment 1 vs Vehicle 1 were <0; the 90% upper CLs for the changes from Baseline for CP-690,550 Ointment 2 vs Vehicle 2 were >0 at all 4 weeks. A time-course response in mean change from Baseline in TPSS-Scaling over Weeks 1 through 4 of both the CP-690,550-treated and vehicle-treated target plaques was apparent for all treatment groups except for CP-690,550 Ointment 2 at Weeks 2 and 4 and Vehicle 2 at

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Week 4. At Weeks 2 and 3, the 90% upper CLs for the changes from Baseline in TPSS-Scaling for CP-690,550 Ointment 1 vs Vehicle 1 were <0; the 90% upper CLs for the changes from Baseline for CP-690,550 Ointment 2 vs Vehicle 2 were >0 at all 4 weeks.

Treatment Area Overall Severity of Psoriasis: The proportions of subjects with a response of "clear" or "almost clear" in Treatment Area Overall Severity of Psoriasis in the CP-690,550 Ointment 1 and Ointment 2 groups increased from Weeks 1 through 4. CIs of the between-treatment group differences were estimated by the exact methods approach with no imputation. At Week 3, the CI for the CP-690,550 Ointment 1 group compared to the Vehicle 1 group did not include 0% (response rates of 59.09% vs 23.08% for the CP-690,550 Ointment 1 and Vehicle 1 groups, respectively); at all 4 weeks, the CI for the CP-690,550 Ointment 2 group compared to the Vehicle 2 group included 0%.

The proportion of subjects with a decrease from Baseline of ≥2 points in Treatment Area Overall Severity of Psoriasis score in the CP-690,550 Ointment 1 group increased from Weeks 1 through 4. CIs of the between-treatment group differences were estimated by the exact methods approach with no imputation. At Week 1, the CI for the CP-690,550 Ointment 1 group compared to the Vehicle 1 group did not include 0% (response rates of 15.79% vs 0% for the CP-690,550 Ointment 1 and Vehicle 1 groups, respectively); at all 4 weeks, the CI for the CP-690,550 Ointment 2 group compared to the Vehicle 2 group included 0%. All subjects with a decrease from Baseline of ≥2 points also had a response of "clear" (score=0) or "almost clear" (score=1).

TPA: The mean TPA values at Baseline were higher in the vehicle groups (means 43.73 cm^2 and 44.08 cm^2 for Vehicle 1 and Vehicle 2, respectively) than in the CP-690,550 ointment groups (means 34.06 cm^2 and 30.72 cm^2 for CP-690,550 Ointment 1 and Ointment 2, respectively). All 4 treatment groups had mean and mean percent decreases from Baseline in the TPA at Weeks 1 through 4 as well as at Follow-up (except for the CP-690,550 Ointment 2 group at Week 1). At Week 3, the LS mean difference for Contrast 1 (CP-690,550 Ointment 1 minus Vehicle 1) was -20.34%, and the 1-sided 90% upper CL was -3.97%; at Week 4, the LS mean difference for Contrast 1 (CP-690,550 Ointment 1 minus Vehicle 1) was -19.04%, and the 1-sided 90% upper CL was -2.75%. The 90% upper CLs for the changes from Baseline for Contrast 2 (CP-690,550 Ointment 2 vs Vehicle 2) were >0 at all 4 weeks.

Pharmacokinetic and Other Results:

Patient Reported Outcomes (PRO)

Mean ISI scores at Baseline ranged from 4.09 in the CP-690,550 Ointment 1 group to 6.20 in the Vehicle 2 group (possible ISI scores range from 0=no itching to 10=worst possible itching). The CP-690,550 ointment groups had lower Baseline mean ISI scores than the vehicle groups. All 4 treatment groups had lower mean ISI scores at all time points during the study compared to Baseline; the scores at Week 4 ranged from 1.55 in the CP-690,550 Ointment 1 group to 4.44 in the Vehicle 2 group, and the scores at Follow-up ranged from

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1.61 in the CP-690,550 Ointment 1 group to 4.82 in the Vehicle 1 group. The CP-690,550 Ointment 1 group had the largest LS mean decreases from Baseline at each time point.

One-half (50.0%) of subjects in the CP-690,550 Ointment 1 group had PSSM responses at Week 4 of "very satisfied," compared with 32.0% of subjects in the CP-690,550 Ointment 2 group and 23.1% and 0.0% of subjects in the Vehicle 1 and Vehicle 2 groups, respectively. The proportions of subjects with responses of "very satisfied" or "somewhat satisfied" on the PSSM were similar in the CP-690,550 Ointment 1 and Vehicle 1 groups (15/22, 68.2% and 8/13, 61.5% subjects, respectively). More than one-half (52.0%) of subjects in the CP-690,550 Ointment 2 group had responses of "very satisfied" or "somewhat satisfied," compared to 11.1% of subjects in the Vehicle 2 group.

Pharmacokinetics

The PK parameters are defined in Table S2.

PK samples were collected from 44 CP-690,550-treated subjects (21 in the CP-690,550 Ointment 1 group and 23 in the CP-690,550 Ointment 2 group). The plasma PK samples for 1 subject in the CP-690,550 Ointment 1 group were received by the central laboratory at ambient temperature; although this subject's plasma samples were analyzed, the resulting PK data were excluded from parameter calculations and concentration summaries. Therefore, valid PK data were available for 20 subjects in the CP-690,550 Ointment 1 group.

In the CP-690,550 Ointment 1 group, 12/20 (60%) subjects had a systemic concentration at or above the LLOQ for at least 1 time point, compared to 6/23 (26%) subjects in the CP-690,550 Ointment 2 group.

Following the application of topical 2% CP-690,550, the median T_{max} values were 0.5 and 2 hours, respectively, for Ointment 1 and Ointment 2 (Table S6). By setting all samples <LLOQ to 0.00 ng/mL and performing noncompartmental analyses (the standard analyses), the median AUC_{τ} values in the CP-690,550 Ointment 1 and Ointment 2 groups were 1.08 ng•hr/mL and 0.00 ng•hr/mL, respectively. The median C_{max} values in the CP-690,550 Ointment 1 and Ointment 2 groups were 0.16 ng/mL and 0.00 ng/mL, respectively.

By setting all samples <LLOQ to 0.100 ng/mL and performing noncompartmental analyses (the adjusted analyses), the geometric mean $AUC_{\tau(adj)}$ in the CP-690,550 Ointment 1 group (1.92 ng•hr/mL) was approximately 40% higher compared with the geometric mean $AUC_{\tau(adj)}$ in the CP-690,550 Ointment 2 group (1.38 ng•hr/mL). Similarly, the geometric mean $C_{max(adj)}$ in the CP-690,550 Ointment 1 group (0.19 ng/mL) was approximately 55% higher compared with the geometric mean $C_{max(adj)}$ in the CP-690,550 Ointment 2 group (0.12 ng/mL).

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Table S6. Summary of Plasma CP-690,550 Pharmacokinetic Parameters by Treatment Group

Parameter	2% CP-690,550 Ointment 1 (N=20)	2% CP-690,550 Ointment 2 (N=23)
T_{max}, hr	0.50 (0.00, 4.75)	2.01 (0.00, 3.98)
Parameters, standard[a]		
AUC_{τ}, ng•hr/mL	1.08 (124)	0 (228)
C_{max}, ng/mL	0.16 (118)	0 (227)
Parameters, adjusted[a]		
$AUC_{\tau\ (adj)}$, ng•hr/mL	1.92 (61)	1.38 (36)
$C_{max\ (adj)}$, ng/mL	0.19 (75)	0.12 (47)

Abbreviations: hr=hour; CV=coefficient of variation; adj=adjusted; LLOQ=lower limit of quantification
N=number of subjects providing data (except for T_{max}).
Median (range) presented for T_{max}. Median (%CV) presented for C_{max} and AUC_{τ}.
Geometric mean (%CV) presented for $C_{max(adj)}$ and $AUC_{\tau(adj)}$.
[a] Standard parameters calculated by setting concentrations <LLOQ to 0.00 ng/mL.
Adjusted parameters calculated by setting concentrations <LLOQ to 0.100 ng/mL
Parameters are defined in Table S2.

Safety Results: Overall, 25/71 (35.2%) subjects experienced a treatment-emergent AE (all causalities); the rates of subjects experiencing AEs were highest in the CP-690,550 ointment groups and lowest in the vehicle groups (Table S7). Five subjects (7.0%), all in the CP-690,550 ointment groups, experienced a treatment-related treatment-emergent AE. There were no serious AEs (SAEs) during the study, and no subjects withdrew from the study due to AEs or had their study drug temporarily discontinued due to AEs.

Table S7. Overview of Treatment-Emergent Adverse Events (All Causalities)

No. of Subjects	2% CP-690,550 Ointment 1 BID	Vehicle 1 BID	2% CP-690,550 Ointment 2 BID	Vehicle 2 BID
Number of subjects evaluable for AEs	23	13	25	10
Number of AEs	17	3	12	5
Subjects with AEs	10	3	9	3
Subjects with SAEs	0	0	0	0
Subjects with severe AEs	0	0	0	0
Subjects with AEs that led to Discontinuation	0	0	0	0
Subjects with dose reductions or temporary discontinuations due to AEs	0	0	0	0

Abbreviations: BID=twice daily; AE=adverse event; SAE=serious adverse event; No.=number
Except for the number of AEs, subjects were counted only once per treatment in each row.
SAEs – according to the investigator's assessment.

The most frequently reported treatment-emergent AEs (all causalities) by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) overall were infections and

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infestations (12/71, 16.9% subjects). No treatment-related AE occurred in more than 1 subject in any SOC. The only AEs (all causalities) to occur in more than 1 subject overall were nasopharyngitis (4 subjects) and urinary tract infection (2 subjects). All of the AEs were mild or moderate in intensity.

Infection AEs

A total of 13 subjects (10 in the CP-690,550 ointment groups and 3 in the vehicle groups) experienced a total of 14 treatment-emergent infection AEs (all causalities). The most frequent infection AEs overall were nasopharyngitis (4 subjects) and urinary tract infection (2 subjects). All of the infection AEs except for 2 (1 moderate AE of [redacted] in the CP-690,550 Ointment 1 group and 1 moderate AE of tooth abscess in the CP-690,550 Ointment 2 group) were mild in intensity. One infection AE (upper respiratory tract infection), in the CP-690,550 Ointment 2 group, was considered treatment-related.

Study Drug Application Site AEs

A total of 3 subjects (2 in the CP-690,550 Ointment 1 group and 1 in the CP-690,550 Ointment 2 group) experienced treatment-emergent study drug application site AEs (1 AE each of application site erythema [CP-690,550 Ointment 1 group], wound dehiscence [CP-690,550 Ointment 1 group], and pruritus [CP-690,550 Ointment 2 group]). All 3 AEs were considered of mild intensity and all resolved by the end of the Follow-up period; both of the AEs in the CP-690,550 Ointment 1 group were considered treatment-related. No action was taken with study drug for any of the AEs, and all 3 subjects completed the study.

Laboratory Tests

Among subjects with normal Baselines, the laboratory abnormalities occurring in ≥2 subjects in any treatment group were elevated urine specific gravity, decreased bicarbonate, elevated urine blood hemoglobin, elevated urine leukocyte esterase, elevated urine white blood cells (WBCs), and elevated urine red blood cells (RBCs).

One subject, in the CP-690,550 Ointment 1 group, experienced AEs of aspartate aminotransferase (AST) increased and alanine aminotransferase (ALT) increased that began after the subject's last day of treatment; the AEs were considered of mild intensity and not treatment-related. The subject's AST and ALT values were elevated at Screening and within normal limits at Baseline and during the 4 weeks of treatment. At the Follow-up visit on Day 36, the subject's AST and ALT values were both >2×upper limit of normal (ULN); at repeat testing 1 week later the values had both returned to within normal limits, and the AEs were considered resolved. No subject met Hy's Law criteria for drug-induced liver injury.

One subject, in the CP-690,550 Ointment 2 group, met the absolute neutrophil count protocol safety monitoring criterion (neutrophil count $<1.2\times10^3/mm^3$) 1 week after completing 4 weeks of study treatment; the subject's neutrophil value returned to normal upon further testing.

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In general, changes from Baseline in laboratory parameters of interest (hematological parameters, serum lipids, creatinine, and liver function parameters) were small, and few differences were observed in the CP-690,550 ointment groups compared to the vehicle groups.

Vital Signs

There were no clinically meaningful median changes from Baseline in BP, pulse rate, temperature, or weight in any of the treatment groups through Follow-up. A total of 5 subjects had postbaseline vital signs of potential clinical concern. Two subjects had findings related to sitting systolic blood pressure (SBP): 1 subject in the Vehicle 1 group had an SBP <90 mm Hg and 1 subject in the CP-690,550 Ointment 1 group had a maximum increase from Baseline in SBP ≥30 mm Hg. Three subjects (1 subject each in the CP-690,550 Ointment 1, CP-690,550 Ointment 2, and Vehicle 2 groups) had maximum decreases from Baseline in sitting diastolic blood pressure (DBP) ≥20 mm Hg. None of these subjects had vital sign-related AEs during the study.

ECGs

There were no clinically meaningful mean changes from Baseline in ECG parameters in any of the treatment groups through Follow-up. Seven subjects (1 each in the CP-690,550 Ointment 1, Vehicle 1, and Vehicle 2 groups, and 4 subjects in the CP-690,550 Ointment 2 group) had a postbaseline maximum QTcB (in ECG output, the time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate [Bazett's correction]) value between 450 and 480 msec. Three subjects, in the CP-690,550 Ointment 2 group, had a postbaseline maximum QTcF (QTc [Fridericia's correction]) value between 450 and 480 msec. One subject each in the CP-690,550 Ointment 1 and Ointment 2 groups had a maximum decrease from Baseline in QTcB between 30 and 60 msec. One subject, in the CP-690,550 Ointment 2 group, had an increase from Baseline in PR interval (in ECG output, interval between the end of the P wave and the start of the QRS complex, corresponding to the time between the end of atrial depolarization and onset of ventricular depolarization) ≥50%. A total of 7 subjects (3 in the CP-690,550 Ointment 1 group and 2 each in the CP-690,550 Ointment 2 and Vehicle 2 groups) had an increase from Baseline in maximum QTcB between 30 and 60 msec, and 1 subject, in the CP-690,550 Ointment 2 group, had an increase from Baseline in maximum QTcB ≥60 msec. Four subjects in the CP-690,550 Ointment 2 group had an increase from Baseline in maximum QTcF between 30 and 60 msec. One subject, in the CP-690,550 Ointment 2 group, experienced a mild treatment-related AE of electrocardiogram t-wave inversion that began on the subject's last day of treatment and resolved approximately 1 month later.

Physical Examinations

Four subjects had findings on postbaseline physical examination reported as AEs. In the CP-690,550 Ointment 1 group, 1 AE each of wound dehiscence, edema, and [redacted] (investigator term "[redacted]") were observed on physical

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examination. In the CP-690,550 Ointment 2 group, an AE of mouth ulceration was observed on physical examination.

Local Tolerability Assessments

Overall, the number of subjects reporting burning/stinging at the study drug application site was small, and no subject experienced severe burning/stinging postapplication. In general, burning/stinging occurred more frequently at Weeks 1 and 2 and less frequently at Weeks 3 and 4. During Weeks 1 to 4, no more than 1 subject in either of the CP-690,550 ointment groups experienced either immediate (within 5 minutes) or persistent (beyond 5 minutes) burning/stinging at any time point. Three subjects in the Vehicle 1 group at Week 1 and 3 subjects in the Vehicle 2 group at Week 2 experienced mild or moderate immediate burning/stinging. One subject in the Vehicle 1 group and 2 subjects in the Vehicle 2 group experienced mild or moderate persistent burning/stinging at 1 or more windowed time points. Two subjects, in the CP-690,550 Ointment 2 group, reported mild burning/stinging at Follow-up.

Subjects' perilesional skin was assessed by Draize scoring after study drug application at the study center throughout the study. Two subjects, both in the CP-690,550 Ointment 2 group, reported numerical scores of erythema >0 at least 1 time during the study. Letter grades and superficial observations were recorded infrequently. The only letter grade finding reported during the study was burning/stinging/itching, reported postbaseline in 1 subject each in the CP-690,550 Ointment 1 and Vehicle 1 groups and in 2 subjects in the CP-690,550 Ointment 2 group. Superficial observations reported postbaseline were hyperpigmentation (reported twice by 1 subject in the CP-690,550 Ointment 1 group), scaling-flaking of skin (reported once or more by 2 subjects in the CP-690,550 Ointment 2 group), and peeling (reported once by 1 subject in the CP-690,550 Ointment 1 group). Only 1 Draize score was reported as an AE, erythema for 1 subject in the CP-690,550 Ointment 1 group.

Conclusions:

- CP-690,550 Ointment 1 showed statistically significant efficacy over the corresponding vehicle based on analysis of percent change from Baseline in TPSS at Week 4 (the primary endpoint). CP-690,550 Ointment 2 did not achieve statistical significance compared to its vehicle.

- A time-course response in mean percent change from Baseline in TPSS over Weeks 1 through 3 in the CP-690,550-treated and vehicle-treated target plaques was observed.

- A time-course response in mean percent change from Baseline in TPSS-Erythema, TPSS-Induration, and TPSS-Scaling over Weeks 1 through 4 in the CP-690,550-treated and vehicle-treated target plaques was observed.

- CP-690,550 Ointment 1 showed efficacy over the corresponding vehicle based on analysis of the proportion of subjects with Treatment Area Overall Severity of Psoriasis

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response of "clear" or "almost clear" at Week 3 only. CP-690,550 Ointment 2 did not show efficacy over the corresponding vehicle based on analysis of the proportion of subjects with Treatment Area Overall Severity of Psoriasis response of "clear" or "almost clear" at any of the 4 weekly time points.

- CP-690,550 Ointment 1 showed efficacy over the corresponding vehicle based on analysis of the proportion of subjects with decrease from Baseline of ≥2 points for the Treatment Area Overall Severity of Psoriasis at Week 1 only. CP-690,550 Ointment 2 did not show efficacy over the corresponding vehicle based on analysis of the proportion of subjects with decrease from Baseline of ≥2 points for the Treatment Area Overall Severity of Psoriasis at any of the 4 weekly time points. All subjects with a decrease from Baseline of ≥2 points also had a response of "clear" or "almost clear" for the Treatment Area Overall Severity of Psoriasis.

- All 4 treatment groups had mean and percent mean decreases from Baseline in the TPA at Weeks 1 through 4. CP-690,550 Ointment 1 showed efficacy over the corresponding vehicle based on analysis of percent change from Baseline in TPA at Weeks 3 and 4. CP-690,550 Ointment 2 did not show efficacy over the corresponding vehicle based on analysis of percent change from Baseline in TPA at any of the 4 weekly time points.

- All treatment groups showed decreases from Baseline in the ISI at Weeks 1 through 4. CP-690,550 Ointment 1 showed efficacy over the corresponding vehicle based on analysis of change from Baseline in ISI at Weeks 1 and 4. CP-690,550 Ointment 2 did not show efficacy over the corresponding vehicle based on analysis of change from Baseline in ISI at any of the 4 weekly time points.

- The proportion of subjects reporting that they were "very satisfied" on the PSSM at Week 4 was greatest for the CP-690,550 Ointment 1 group (50.0%), compared with 32.0% of subjects in the CP-690,550 Ointment 2 group and 23.1% and 0.0% of subjects in the Vehicle 1 and Vehicle 2 groups, respectively.

- There were no deaths, SAEs, or AEs leading to withdrawal during the study.

- Topical 2% CP-690,550 (Ointment 1 and Ointment 2) was well-tolerated and comparable to vehicle as determined by systemic safety. No clinically significant safety signals were identified in the study.

- Local tolerability of the topical formulations (Ointment 1, Ointment 2, Vehicle 1, and Vehicle 2) as determined from incidence and severity of administration site AEs was satisfactory; burning/stinging was reported infrequently at both CP-690,550- and vehicle-treated target plaques.

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- The results of pharmacokinetic analyses indicated that systemic exposures in the CP-690,550 Ointment 1 group were higher than those in the CP-690,550 Ointment 2 group.