Synopsis

Clinical Report Synopsis for Protocol 271-102-00002

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd.

Name of Investigational Medicinal Product: OPA-15406

Protocol Title: A Multicenter, Randomized, Double-blind, Vehicle-controlled, Parallel-group Trial to Assess the Safety and Efficacy of 0.3% and 1% OPA-15406 Ointments When Administered for 4 Weeks in Pediatric Patients With Atopic Dermatitis

Coordinating Investigator and Trial Centers:

[redacted]

Publications: None to date.

Trial Period:

Date of first signed informed consent: 19 Jan 2017

Date of last trial observation: 12 Jun 2017

Clinical Development Phase: 2

Trial Interruption: There was no planned trial interruption.

Scientific Background and Explanation of Rationale:

Atopic dermatitis (AD) is defined as a disease with repeated exacerbations/remissions of which the main lesion is eczema with pruritus. Topical agents such as steroids and calcineurin inhibitors (immunosuppressors) are used for the treatment of inflammation, topical moisturizers and protective agents for skin care to treat abnormal physiological functions, and oral antihistamines and antiallergic agents for pruritus as adjuvant treatment. Elimination of as many aggravating factors as possible has been established by current consensus as a basic therapy for AD. Inflammation can be generally suppressed by topical steroids. However, long-term use of topical steroids may induce adverse drug reactions (eg, skin atrophy, hairiness); therefore, drugs with long-term safety have been anticipated.

OPA-15406 is a phosphodiesterase 4 inhibitor. In a mouse chronic contact hypersensitivity model, OPA-15406 ointment demonstrated its efficacy in improving of the condition of dermatitis. Therefore, development of OPA-15406 ointment was started with the expectation of efficacy for AD. In Japanese healthy adult subjects and AD patients, OPA-15406 ointment showed no clinically relevant safety issues and good tolerability. Also, in the phase 2 trial outside Japan, 1% OPA-15406 ointment

demonstrated the efficacy on AD. Based on these results, the present trial was designed to assess the safety, efficacy, and pharmacokinetics of OPA-15406 ointment in Japanese pediatric AD patients.
The phase 2 trial (Study 271-15-001) was conducted to assess the efficacy and safety of OPA-15406 ointments in Japanese adult AD patients.

Objectives:
Primary Objective:

- To evaluate the safety of 0.3% and 1% OPA-15406 ointments in pediatric patients with AD when administered twice daily for 4 weeks

Secondary Objective:

- To evaluate the efficacy (dose response) and pharmacokinetics of 0.3% and 1% OPA-15406 ointments in pediatric patients with AD when administered twice daily for 4 weeks

Methodology:
This was a phase 2, multicenter, randomized, double-blind, vehicle-controlled, parallel-group trial designed to evaluate the safety, efficacy, and pharmacokinetics of OPA-15406 ointment in pediatric AD patients. The trial consisted of a 2- to 30-day screening period, a 4-week assessment period, and a 2-week post-treatment observation period.
Subjects received topically the 0.3% or 1% formulation or the vehicle of OPA-15406 ointment. These investigational medicinal products (IMPs) were administered twice daily (approximately 12 hours apart between morning and night administration) for 4 weeks.

Number of Subjects:
Planned: Total 60 subjects
0.3% OPA-15406 group: 20 subjects
1% OPA-15406 group: 20 subjects
Vehicle group: 20 subjects

Enrolled: Total 73 subjects
0.3% OPA-15406 group: 24 subjects
1% OPA-15406 group: 25 subjects
Vehicle group: 24 subjects

Diagnosis and Main Criteria for Inclusion:
At the screening examination:

1) Sex: Either male or female
2) Hospitalization status: Outpatient
3) Age: 2 to 14 years, inclusive (at the time of obtaining informed consent)
4) Diagnosis of AD based on the criteria of Hanifin and Rajka
5) Subjects whose legal guardian was able to provide written informed consent prior to participation in the trial

At the screening and baseline examinations:

6) AD affecting ≥ 5% to ≤ 40% of body surface area (BSA)
7) Investigator's global assessment (IGA) score of 2 (mild) or 3 (moderate)

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot No.(s.):
Investigational medicinal products were 0.3% OPA-15406 ointment (Lot No. 100614), 1% OPA-15406 ointment (Lot No. 100202) and vehicle of OPA-15406 ointment (Lot No. 101266). The amount of IMP per dose was determined based on the subject's BSA calculated from height and body weight at the screening examination. The IMPs were administered topically at the determined dose.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot No.(s.): Not applicable

Duration of Treatment:
Subjects received the 0.3% or 1% formulation or the vehicle of OPA-15406 ointment twice daily for 4 weeks.

Trial Assessments:

- *Safety*: Adverse events (AEs), physical examination, vital signs (blood pressure, pulse rate, body temperature, and body weight), 12-lead electrocardiogram (ECG) (if possible for children aged 2 to 6 years), and clinical laboratory tests (hematology, serum chemistry, and qualitative urinalysis)
- *Efficacy*: IGA, Eczema area and severity index (EASI), Visual analogue scale (VAS) for pruritus (only for patients aged 7 to 14 years), Verbal rating scale (VRS) for pruritus (only for patients aged 7 to 14 years), and Patient-oriented eczema measure (POEM), affected BSA
- *Pharmacokinetics*: Plasma concentration of OPA-15406

Criteria for Evaluation:
Primary Endpoint:

- The number and percentage of subjects experiencing AEs

Secondary Endpoints:

- Incidence of success in IGA at Week 4, change from baseline in EASI, VAS for pruritus, VRS for pruritus, POEM, affected BSA at Week 4
- Plasma concentration of OPA-15406 (the trough concentration at Week 1 and Week 4)

Pharmacokinetic Methods:

- *Bioanalytical*: Plasma samples were analyzed for OPA-15406 using liquid chromatography with tandem mass spectrometry.
- *Pharmacokinetics*: The plasma concentration of OPA-15406 (trough concentration at Week 1 and Week 4) was measured.

Statistical Methods:

Determination of Sample size:

The sample size of 20 subjects for each group, a total of 60 subjects, had been established in consideration of the feasibility of the trial and the number of subjects needed to evaluate efficacy and safety. Assuming that the probabilities of success in IGA for each group were the same as those in the phase 2 trial outside Japan (271-12-205), the expected incidence of success in the 1% OPA-15406 group, the 0.3% OPA-15406 group, and the vehicle group was 20.93%, 14.63%, and 2.7%, respectively. In that case, the probability of the 1% group > the vehicle group, the 0.3% group > the vehicle group, and the 1% group minus the vehicle group > 10% in the point estimate of incidence of success was 96.2%, 88.3%, and 71.5%, respectively. Also, the probability of the 1% group > the 0.3% group ≥ the vehicle group in point estimate of incidence of success was 60.6%.

Subject Samples:

- Safety Analysis Set: The safety analysis set consisted of all subjects who had received the IMP at least once.
- Efficacy Analysis Set: The efficacy analysis set consisted of all subjects who had received the IMP at least once and whose efficacy data had been obtained after the start of IMP administration.
- Pharmacokinetic (PK) Analysis Set: The PK analysis set consisted of all subjects whose the IMP had received at least once and plasma drug concentration had been measured.

Primary Endpoint:

- The number and percentage of subjects experiencing AEs were calculated for each treatment group.

Secondary Endpoints:

- For the incidence of success in IGA at Week 4, the incidence of success of each treatment group and its 95% confidence interval (CI) were calculated. The difference between the vehicle group and each treatment group in the incidence of success and its 95% CI were calculated. Incidence of success in IGA was defined as the rate of subjects whose IGA score was 0 (clear) or 1 (almost clear) and had improved by at least 2 grades (responders) from baseline. Based on the Cochran-Mantel-Haenszel method, the difference in incidence of success adjusted by the severity of baseline IGA and its CI were calculated as the primary analysis. For reference, the Cochran-Mantel-Haenszel method was performed using baseline IGA (mild or moderate) as a stratification factor, and the p-value was calculated. A multiplicity adjustment was not conducted.
- The incidence of success in IGA at Week 1 and Week 2 was calculated, in the same manner as the incidence of success in IGA at Week 4.
- For the change from baseline in IGA at Weeks 1, 2, and 4, mixed model repeated measure (MMRM) analysis with factors of treatment (0.3% or 1% OPA-15406 groups, and vehicle group), time point, baseline IGA (mild or moderate), and interaction between treatment and time point were applied with an unstructured variance covariance structure to the change from baseline up to Week 4 based on observed case (OC) dataset. Kenward-Roger method was used to calculate the

standard error of fixed effects and degree of freedom. The least square (LS) mean of each treatment group was calculated by time point. Also, the difference in the LS means between the vehicle group and each OPA-15406 group, and the two-sided 95% CI and p-value were calculated at Weeks 1, 2, and 4. Analysis of covariance (ANCOVA) with factors of treatment (0.3% or 1% OPA-15406 groups, vehicle group), and baseline IGA (mild or moderate) were applied to the change from baseline up to each time point based on OC and last observation carried forward (LOCF) datasets. The LS mean of each treatment group was calculated by time point. Also, the difference in the LS means between the vehicle group and each OPA-15406 group, and the two-sided 95% CI and p-value were calculated at Weeks 1, 2, and 4. Using the OC and LOCF data sets, the descriptive statistics were calculated for measured values and changes from baseline by treatment group for each time point.

- The change from baseline in EASI, VAS for pruritus, POEM, and affected BSA were calculated in the same manner as the change from baseline in IGA. Except for baseline, the same MMRM and ANCOVA models as those used in the analysis of IGA were used. For baseline, the baseline values of the respective variables were used.
- Change from baseline in VRS for pruritus up to 7 days after the first administration was calculated. Using the OC and LOCF datasets up to 7 days after the first administration, ANCOVA with factors of treatment (0.3% or 1% OPA-15406 groups, vehicle group), and baseline value were applied to the change from baseline up to each time point. The LS mean of each treatment group was calculated by time point. Also, the difference in the LS means between the vehicle group and each OPA-15406 group, and the two-sided 95% CI and p-value were calculated. Using the OC and LOCF datasets, the descriptive statistics were calculated for measured values and changes from baseline by treatment group for each time point. The data was collected at 4, 8, and 12 hours after the start of administration, 1 day after the start of administration (morning and night), and thereafter in the same manner up to 7 days after the first administration (morning).
- For time to response in IGA and VRS for pruritus, Kaplan-Meier plots were generated for each treatment group and vehicle group. For IGA, subjects with an IGA score was 0 (clear) or 1 (almost clear) with an improvement by at least 2 grades from the baseline were defined as responders. For VRS for pruritus, subjects with VRS score of 0 (none) or 1 (mild) with an improvement by at least 1 grade from the baseline were defined as responders.
- The descriptive statistics (number of subjects, arithmetic mean, standard deviation [SD], coefficient of variation, minimum value, median value, and maximum value) of plasma OPA-15406 concentrations were calculated by treatment group and by time point.
- The descriptive statistics (number of subjects, arithmetic mean, SD, coefficient of variation, minimum value, median value, and maximum value) of plasma OPA-15406 concentrations adjusted for affected BSA at baseline evaluation were calculated by treatment group and by time point.
- The descriptive statistics (number of subjects, arithmetic mean, SD, coefficient of variation, minimum value, median value, and maximum value) of plasma OPA-15406

concentrations were calculated by treatment group, by time point, and by affected BSA at baseline examination (5% to < 10%, ≥ 10% to < 30%, and ≥ 30%).

- The descriptive statistics (number of subjects, arithmetic mean, SD, coefficient of variation, minimum value, median value, and maximum value) of age, affected BSA at baseline (%), and amount of administration (g) by affected BSA were calculated.

Summary of Results:

Disposition, Demographics, and Baseline Characteristics:

A total of 74 subjects were screened. Of those subjects, 73 were randomized and treated with IMP. Of the 73 subjects, 63 subjects (86.3%) completed and 10 subjects (13.7%) discontinued the trial. The discontinuation rates for the OPA-15406 0.3%, OPA-15406 1%, and vehicle groups were 8.3% (2/24), 4.0% (1/25), and 29.2% (7/24), respectively. The frequently reported reasons for discontinuation were AEs (6/73 subjects [8.2%]) and withdrew by parent/guardian (2/73 subjects [2.7%]). The majority of the subjects was males (52/73 subjects [71.2%]).

Efficacy Results:

- The OPA-15406 0.3% (success rate, 37.50%) and OPA-15406 1% (success rate, 40.00%) groups had higher success rate in IGA score in comparison with the vehicle (success rate, 8.33%) group at Week 4. This analysis for IGA was confirmed by sensitivity analyses.
- The OPA-15406 0.3% (success rate, 4.17% and 33.33%) and OPA-15406 1% (success rate, 16.0% and 32.00%) groups had higher success rate in IGA score in comparison with the vehicle (success rate, 0% and 4.17%) group at Weeks 1 and 2.
- The OPA-15406 0.3% and OPA-15406 1% groups had greater LS mean decreases from baseline in IGA score, EASI score, VAS score, POEM score, and affected BSA in comparison with the vehicle group over the 4-week trial.
- The OPA-15406 0.3% and OPA-15406 1% groups had greater LS mean decreases from baseline in VRS score in comparison with the vehicle group at 12 hours after the first treatment of IMP and the greater decreases were continued approximately up to 168 hours.
- The exploratory analysis of the 50%, 75%, and 90% success rate for EASI scores showed similar trends to the analysis of the total EASI score that both OPA-15406 groups had greater decrease from baseline in EASI score in comparison with the vehicle group at most visits.
- There were no notable differences between the results for the efficacy analyses using the MMRM, LOCF and OC datasets.
- These results suggest that OPA-15406 (0.3% and 1%) ointment is an effective treatment for pediatric AD in the studied population.

Pharmacokinetic Results:

- The mean OPA-15406 plasma trough concentrations after topical administration of 0.3% and 1% OPA-15406 ointment (median total treatment area [%] range: 12.0% to 20.0%) were respectively 0.842 and 2.90 ng/mL at Week 1 and 0.946 and 2.21 ng/mL at Week 4.
- The mean normalized OPA-15406 plasma trough concentrations by dose derived from %BSA treated were similar at Week 1 and Week 4, indicating no accumulation.

Safety Results:

- There were no deaths, serious AEs (SAEs), or severe AEs reported in this trial. Six subjects were discontinued from the trial due to Treatment-emergent AEs (TEAEs). The number of subjects who discontinued IMP due to TEAEs by treatment group were 1 of 24 subjects (4.2%), 1 of 25 subjects (4.0%), and 4 of 24 subjects (16.7%) for the OPA-15406 0.3%, OPA-15406 1%, and vehicle groups, respectively.
- Treatment-emergent AEs experienced by 37 of 73 subjects (50.7%) were mild to moderate in severity and the most of TEAEs resolved.
- Treatment-emergent AEs that occurred at an incidence ≥ 5% of overall subjects were upper respiratory tract inflammation (9/73 [12.3%]) and atopic dermatitis (7/73 [9.6%]).
- The most frequently observed TEAEs related to the IMP was atopic dermatitis (5/73 [6.8%]).
- No clinically relevant trends in abnormalities were reported from the results of clinical laboratory assessments, vital signs assessments, or ECGs.
- Treatment with OPA-15406 (0.3% and 1%) ointment twice daily for up to 4 weeks was safe and well tolerated in both groups of pediatric subjects with AD.

Conclusions:

- The success rate of IGA score in the OPA-15406 (0.3% and 1%) group was numerically larger than the vehicle group over the 4-week trial.
- The change from baseline in IGA score, EASI score, VAS score, POEM score, and affected BSA in the OPA-15406 (0.3% and 1%) group showed greater improvement (indicated by negative score) than the vehicle group over the 4-week trial.
- No accumulation of OPA-15406 plasma trough concentration was observed at 4 weeks of multiple administration.
- There were no deaths, SAEs, or severe AEs reported in this trial. Two subjects were discontinued from the trial due to TEAEs in the OPA-15406 groups. All of the TEAEs that had induced discontinuation of IMP were moderate in severity and resolved. All TEAEs were mild to moderate and most of these resolved.
- No clinically relevant trends in abnormalities were reported from the results of clinical laboratory assessments, vital signs assessments, or ECGs.

- Treatment with OPA-15406 (0.3% and 1%) ointment twice daily for up to 4 weeks is safe and effective for AD.